Farahnak Assadi

Clinical Decisions in Pediatric Nephrology

A Problem-Solving Approach to Clinical Cases

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This book is dedicated to the individuals who have given meaning to my life:

- *To the memory of my mother whose honesty and fairness served as a model that I have tried to emulate. Her continued love has allowed me to maintain a frame of reference which has assured my happiness*
- *To my father who remains, in his later years, a source of inspiration to three generations of loving progeny*
- *To my wife, Nassrin, for her support, patience, understanding and great sacrifices in order for me to pursue my career*
- *To my children, Ladan and Ramin–and to my grandchildren, Emily, Mathew, Caroline, and Christian–who provide my hope for the future*
- *To all medical students, residents, and fellows who have enriched my life*
- *To all the children for whom I have cared, who always taught me so much*

Preface

Over the last twenty-five years of teaching, I have found the evidence-based medicine approach to be very effective in teaching clinical nephrology to students of health professions at all stages of their training. For this reason, I believe that the time has come to undertake the task of publishing a comprehensive book dealing with common renal disorders as they present in clinical practice**.**

This book is designed to expand the clinical knowledge and experience of residents in training and the practicing clinician. The format of case reports will illuminate the basic principles and pathophysiology of diseases of the kidney and define diagnosis and treatment. The selected case reports focus on the essential aspects of the patient's presentation findings and managements needed to assist in the differential diagnosis. They develop a process of logical questioning from the presentation of the signs and symptoms and laboratory data, and they are presented in the way in which our patients come to us with their signs and symptoms or are referred to us by our colleagues. Each question is followed by a detailed discussion that reviews recent publications and translates emerging areas of science into data that is useful at the bedside. The content is an evidence-based medicine approach, resulting in improved quality, safety, and cost-effectiveness of patient care. An update bibliography will conclude each set of clinical cases. This format will help readers stay abreast of developing areas of clinical nephrology.

I am appreciative of the work of the medical editors of Springer Publishers, Inc., for their contributions to this endeavor and all those persons who have dedicated their skills, intelligence, and work to help make this a book of outstanding editorial quality.

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In the beginning of my career at the University of Illinois, one could hardly have had a better mentor than Professor Ira Rosenthal. After moving to Thomas Jefferson University, I received extraordinary help from Michael Norman. He supported my efforts to establish the core of an outstanding nephrology program at Dupont Hospital for Children. Leading the Division of Nephrology at Rush University Medical Center has been one of the greatest fortunes of my life. Samuel Gotoff and Kenneth Boyer have made it enjoyable to come to work each and every day for the past several years. Our residents at Rush have enriched the clinical experience immensely.

Farahnak Assadi

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Chapter 1
Fluid and Electrolyte Disorders

CASE 1

A 16-year old female is brought into the hospital in a stuporous state. No history is initially obtainable. The physical examination is unremarkable except for the abnormal mental status. There are no obvious signs of volume depletion or expansion. The BP is 100/59 mmHg. Laboratory data reveal serum sodium 102 mEq/l, potassium 2.5 mEq/l, chloride 66 mEq/l, bicarbonate 32mEq/l, BUN 9 mg/dl, and creatinine 0.4 mg/dl. Urine sodium is 130 mEq/l, potassium 61 mEq/l, chloride 107 mEq/l and osmolality 467 mOsml/kg.

What is the most likely diagnosis?

A. Primary hyperaldosteronism
B. Diuretic abuse
C. Bartter's syndrome
D. SIADH
E. Excessive emesis

The correct answer is B. The differential diagnoses of hyponatremia, hypokalemia, and metabolic alkalosis with a high urine sodium and chloride concentrations is highly suggestive of diuretic abuse. Hypokalemia essentially excludes SIADH. Neither hyperaldosteronism nor Bartter's syndrome causes marked hyponatremia. The high urine chloride excludes vomiting, suggesting the patient has surreptitious diuretic abuse. The urine sodium plus potassium is well above that in the plasma; thus, solute is being lost in excess of water, which will directly lower the plasma sodium concentration.

References

Chung HM, Kluge R, Schrier RW, Anderson RJ (1987) Clinical assessment of extracellular fluid volume in hyponatremia 83:905–908
Assadi F (1993) Hyponatremia. Pediatr Nephrol 7:503–505
Fichman MP, Vorherr H, Kleeman CR, et al. (1971) Diuretic-induced hyponatremia. Ann Intern Med 75:853–563

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Can you estimate the urine pH in this patient?

A. Acid pH
B. Alkaline pH

The correct answer is B. The urine pH should be alkaline; the anion gap in the urine is positively charged $[(Na^+ + K^+) > Cl^-]$. This is probably due to bicarbonate excretion in an attempt to correct the metabolic alkalosis.

Reference

Rose BD, Post TW (2001) Clinical pathology of acid-base and electrolyte disorders, 5th ed, McGraw-Hill, New York, pp 699–710

What would your initial therapy be?

A. Administration of hypertonic saline alone
B. Combination therapy with hypertonic saline and potassium chloride
C. Administration of potassium chloride alone
D. Combination therapy with hpertonic saline, potassium chloride and potassium sparing diuretic

The correct answer is C. Potassium chloride alone will correct the hypokalemia and metabolic alkalosis and raise the plasma sodium concentration toward normal; as potassium enters cells, sodium will leave to maintain electroneutrality, thereby correcting the hyponatremia. The administration of large amounts of potassium (4 mEq/kg) over the first 24 hours) can raise the plasma sodium concentration by 10 mEq/l over the first day, which is the maximum desired rate of correction of the hyponatremaia. If this were ignored and hypertonic saline also given, overly rapid correction would ensue.

References

Berl T, Linas SL, Aisenbrey GA, Anderson RJ (1977) On the mechanism of polyuria in potassium depletion: The role of polydipsia. J Clin Invest 60:620–625
Robertson GL, Shelton RL, Athar S (1976) The osmoregulation of vasopressin. Kidney Int 10:25–37

CASE 2

A 10-year old female presents with 5 days of severe vomiting. She has no prior history of gastrointestinal or renal disease. Physical examination reveals a mild decrease in skin turgor and an orthostatic fall in BP of 7 mmHg.

Laboratory studies show sodium 136 mEq/l, potassium 3.0 mEq/l, chloride 89 mEq/l, bicarbonate 35 mEq/l, BUN 30 mg/dl, creatinine 1.2 mg/dl, and arterial

pH 7.55. The urine sodium is 42 mEq/l, potassium 12 mEq/l, and chloride 68 mEq/l. The fractional excretion of chloride was 0.08%.

What is the most likely diagnosis?

A. Hyperaldosteronism
B. Liddle's syndrome
C. Vomiting
D. Bartter's syndrome

The correct answer is C. The history suggests simple vomiting, but the high urine chloride concentration suggests diuretic use, Bartter's syndrome, or some form of hyperaldosteronism. However, it is important to appreciate that the urine chloride concentration is determined by the urine volume as well as tubular reabsorption of chloride. Thus, a hypovolemic patient could have very little chloride in the urine, but a relatively high chloride concentration due to marked water avidity. Measurement of fractional excretion of chloride which eliminates the contribution of water can differentiate the low urine chloride metabolic alkalosis (ECF volume contraction) from the high urine chloride excretion (adrenal disorders). In this patient, the fractional excretion of chloride was extremely low at 0.08%, consistent with vomiting and underlying volume contraction.

Reference

Rose BD, Post TW (2001) Clinical pathology of acid-base and electrolyte disorders, 5th ed, McGraw-Hill, New York, pp 699–710

CASE 3

A 13-year old patient with a history of seizures is admitted with right-sided abdominal pain. He denies vomiting, diarrhea, fever, chills, or a history of kidney disease. Medications include phenytoin and phenobarbital. Physical examination is unremarkable. BP is 114/78 mmHg. Laboratory studies are as follows: sodium 140 mEq/l, potassium 5.0 mEq/l, chloride 109 mEq/l, bicarbonate 34 mEq/l, BUN 17 mg/dl, creatinine 0.9 mg/dl, arterial pH 7.43, and pCO2 49 mmHg. The urine sodium is 198 mEq/l, potassium 138 mEq/l, and chloride 194 mEq/l.

How can you explain the electrolytes abnormalities that are present?

A. Diuretic abuse
B. Chronic vomiting
C. Eccessive Gatorade intake
D. Hyperaldosteronism
E. Glucocorticoid deficiency

The correct answer is C. The major findings in this case are a high plasma bicarbonate concentration, a high-normal arterial pH, and a high-normal plasma potassium concentration. The relative hyperkalemia that occurs does so despite normal renal function, no obvious cause, and a high rate of urinary potassium excretion. The urine also shows a positive anion gap of approximately 100 mEq/l (presumably bicarbonate), which is an appropriate response to the metabolic alkalosis that is present, suggesting exogenous intake as a cause. Upon closer questioning, it is determined that he drinks extremely large quantities of Gatorade fluid, which contains sodium, potassium, and alkaline anions.

Reference

Rose BD, Post TW (2001) Clinical pathology of acid-base and electrolyte disorders, 5th ed. McGraw-Hill, New York, pp 699–710

CASE 4

A five-year old boy in septic shock is hypotensive and oliguric after high doses of norepinephrine administration. An intern suggests an infusion of vasopressin at the rate of 0.01 U/hour.

Which ONE of the following would be a valid response to the suggestion?

A. The vasopressin infusion will be ineffective because vasopressin levels should already be high.
B. The vasopressin infusion will be ineffective because the presser effects of vasopressin and norepinephrin are mediated by the same receptors.
C. If vasopressin is infused, his BP will fall further because of the activation of V_2 receptors.
D. If vasopressin is infused, urine output is likely to increase.
E. If vasopressin is infused, urine output is likely to fall even more.

The correct answer is D. Vassopressin is increasingly being used for hemodynamic support of septic shock and vasodilatoey shock due to systemic inflammatory response syndrome (SIRS). Vasopressin is both a vasopressor and an antidiuretic hormone. Its vasopressor effect is caused by vasoconstriction, by activating V1-receptors on vascular smooth muscle. The antiduretic effect is caused by activation of V2-receptors in the collecting duct and diminishes the urine volume. At low plasma concentrations, vasopressin mediates vasodilatation in the coronary, cerebral, and pulmonary arterial circulations. Initially, septic shock is associated with a moderate increase in plasma vasopressin levels. With more prolonged septic shock, vasopressin levels are very low in comparison to the levels found in other cases of hypotension with different causes. Infusion of 0.01 to 0.04 U/min of vasopressin in patients with septic shock increases plasma levels of the hormone to those observed

in carcinogenic shock and decreases the dose requirements for other vasopressores. Paradoxically, urinary output may increase when patients with septic shock are treated with vasopressin, presumably because of improved renal perfusion.

References

Landry DW, Levin HR, Gallant EM, et al. (1997) Vasopressin deficiency the vasodilatation of septic shock. Circulation 95: 1122–1225

Holmes CL, Patel BM, Russell JA, et al. (2001) Physiology of vasopressin on hemodynamics and renal function in severe septic shock. Chest 120:989–1002

Agus ZS, Goldberg M (1971) Role of vasopressin in the antidiuresis of anterior pituitary insufficiency. J Clin Invest 50:1478–1489

CASE 5

A 10-year old boy is found to be hypertensive and hypokalemic. A medical student taking a careful history discovers that the patient is extremely fond of licorice.

Which of the following genetic defects produces a similar syndrome?

A. Mutation in the gene for the inwardly rectifying potassium channel ROMK.
B. Mutation in the gene for 11β-hydroxysteroid dehydrogenase.
C. Mutation in the gene for the basolateral chloride channel CLC-Kb.
D. Mutation in the gene for the NaCl cotransporter.
E. A chimeric gene with portions of the 11β-hydroxylase gene and the aldosterone synthesis gene.

The correct answer is B. Aldosterone, the most important mineralocorticoid, increases sodium reabsorption and potassium secretion in the distal nephron. Excessive secretion of mineralocorticoids, or abnormal sensitivity to mineralocorticoid hormones, may result in hypokalemia, suppressed plasma renin activity, and hypertension. The syndrome of apparent mineralocorticoid excess (AME) is an inherited form of hypertension in which 11β-hydroxysteroid dehydrogenase (11-HSD) is defective. This enzyme converts cortisol to its inactive metabolite: cortisone. Because mineralocorticoid receptors themselves have similar affinities for cortisol and aldosterone, the deficiency allows these receptors to be occupied by cortisol, which normally circulates at much higher plasma levels than aldosterone. Licorice contains glycyrrhetinic acid and mimics the hereditary syndrome because it inhibits 11β-hydroxysteroid dehydrogenase.

Reference

White PC (2001) 11 beta-hydorxysteroid dehydrogenase and its role in the syndrome of apparent mineralocorticoid excess. Am J Med Sci 322:308–315

CASE 6

A 14-year old, previously healthy, female weighing 50 kg undergoes surgery for a ruptured infected appendix. During surgery, she is given 2 liters of lactated Ringer solution, and she is given 5% dextrose in 0.45% NaCl with 20 mEq KCl, at 250 ml/hour, postoperatively. Two days after surgery, she complains of a headache and vomiting. BP is 140/80 mmHg. She is alert and oriented, and the general physical and neurologic examinations are unremarkable. Laboratory studies show serum sodium 115 mEq/l, plasma osmolaity 241 mOsm/kg of H_20, and urine osmolality 850 mOsm/kg of H_20. The patient is not taking anything by mouth.

In addition to stopping the 5% dextrose in 0.45% NaCl infusion, which ONE of the following would be the most appropriate treatment?

A. 5% dextrose in 0.9% saline with 20 mEq KCl at 50 ml/hour.
B. 5% dextrose in 0.9% saline with 20 mEq KCl at 250 ml/hour.
C. 3% saline at 100 ml/hour plus intravenous furosemide until serum concentration is 132 mEq/l.
D. 3% saline at 50 ml/hour plus intravenous furosemide until the serum sodium is 120 mEq/l.
E. Change IV to heparin lock until the patient is able to resume a regular fluid-restricted diet.

The correct answer is C. The patient has developed hypotonic hyponatremia because of the nonosmotic release of vasopressin caused by the stress of surgery coupled with the intravenous administration of a large volume of hypotonic fluid. Her complaints of headache and vomiting are strongly suggestive of cerebral edema. Prompt, definitive treatment is needed to raise serum sodium concentration over the next few hours. Neither isotonic saline nor fluid restriction are satisfactory strategies for accomplishing this goal. Extracellular fluid volume expansion created by the postoperative and peri-operative fluid causes the patient to excrete large amounts of sodium in her urine. Vasopressin levels may remain elevated for several days after surgery, which will cause her urine to be concentrated. The sodium in each liter of isotonic saline she is given, therefore, may be excreted in less than one liter of urine. The infusate will thus be *desalinated*, causing positive water balance and worsening of the hyponatremia. Because of her volume-expanded state, the patient may excrete the equivalent of 0.9% saline in her urine even if intravenous fluids are discontinued. As a result, her sodium concentration may continue to fall spontaneously. Thus, intravenous hypertonic saline is needed to decrease the severity of the cerebral edema and eliminate the risk of herniation. Because the hyponatremia has evolved over 48 hours, there is some risk of osmotic demyelization if serum sodium concentration is increased too much (>18 mEq in 48 hours). Administration of 3% saline at 50 ml/hour plus IV furosemide will raise the serum sodium concentration by12 mEq/l in less than 24 hours. As post-operative vasopressin levels begin to fall spontaneously, the ensuing water diuresis may result in excessive correction. Because brain swelling of more than 5 to 10% is incompatible with life,

a 5% increase in serum sodium concentration (an increase of 6 mEq/l) is enough to bring the patient out of danger without risking iatrogenic injury from excessive correction. Addition of furosemide halts the risk of brain injury due to the excessive correction.

Reference

Lauriant SM, Berl T (1997) The hyponatremic patient: practical focus on therapy. J AM Soc Nephrol 8:1599–1607

CASE 7

An 18-year old male with neurogenic diabetes insipidus is admitted for an acute respiratory infection. The admission serum sodium concentration is 146 mEq/l. He is given desmopressin (DDAVP)® every 12 hours and hypotonic intravenous fluids. Three days later, his serum sodium concentration is found to be 100 mEq/l. He complains of nausea and difficulty concentrating, but he is otherwise asymptomatic.

In addition to discontinuing the hypotonic fluid, which ONE of the following would be the most appropriate management of his hyponatremia?

A. Give 5% dextrose in normal saline at 150 ml/hour, stop DDAVP® for 24 hours and then resume.
B. Give 3% saline at 150 ml/hour until serum sodium concentration is120 mEq/l, stop DDAVP® for 24 hour, and then resume.
C. Give 3% saline at 75 ml/hour until serum sodium concentration is 110 mEq/l, stop DDAVP for 24 hours, and then resume.
D. Continue DDAVP® and give 5% dextrose in normal saline at 150 ml/hour.
E. Continue DDAVP® and give 3% saline at 75 ml/hour until serum sodium concentration is 110 mEq/l.

The correct answer is E. DDAVP® administration may be complicated by acute or chronic hyponatremia. This patient has become severely hyponatremic over the course of three days. Despite the extremely low serum sodium concentration, he has rather mild symptoms, indicating that his brain has adapted to the disturbance. Post-therapeutic neurological complications are more likely with chronic hyponatremaia of this severity if the serum sodium concentration is increased by more than 12 mEq/l in a single day, or 24 mEq/l in two days. Discontinuation of DDAVP® will permit a water diuresis to emerge as soon as the drug is metabolically cleared. With maximally diluted urine—as would be expected in a patient with complete neurogenic diabetes insipidus—the serum sodium concentration will increase by 2 mEq/l per hour. Thus, discontinuing DDAVP® for 24 hours is a poor strategy because it risks excessive correction and may cause osmotic demyelization.

The patient should be treated in a similar manner as a patient with post-operative SIADH. Continuation of DDAVP® is analogous to SIADH. Administration of isotonic saline is contraindicated because it may be *desalinated*. Administration of enough 3% saline to increase the serum sodium concentration to 110 mEq/l will decrease the risk of seizures. Circulation of DDAVP® will prevent the serum sodium concentration from increasing too much. After the infusion of 3% saline at 75 ml/hour, the serum sodium concentration may be increased more gradually: options include giving oral salt and furosemide, administering a slow infusion at 15 ml/hr of 3% saline, or increasing the dose of DDAVP® to permit brief periods of diuresis.

References

Goldszmidt MA, Iliescu EA (2000) DDAVP to prevent rapid correction in hyponatremia. Clin Nephrol 53:226–229

Maghnie M, Genoveso E, Lundin S, et al. (1997) Iatrogenic extrapontine myelinolysis in central diabetes insipidus: are cyclosporine and 1-desamino-8-D-argenine vasopressin harmful in association? J Clin Endocrinol Metab 82:1749–1751

CASE 8

A 16-year old male presents to the emergency room with sudden onset of severe weakness of the lower and upper extremities. He has no history of prior episodes and denies weight loss, change in bowel habits, palpitations, heat intolerance, or excessive perspirations. He is not taking medications, including laxatives or diuretics, and denies drug or alcohol use. Family history is unremarkable. BP is 140/90 mmHg, heart rate 114 beats/min, respiratory rate 19/min, and temperature is 36.9 °C. There is a symmetric flaccid paralysis with areflexia in the lower and upper extremities. The remainder of the physical examination is unremarkable. Laboratory studies show sodium 140 mEq/l, potassium 1.6 mEq/l, chloride 102 mEq/l, bicarbonate 23 mEq/l, calcium 10.5 mg/dl, phosphate 1.5mg/dl, magnesium 1.4 mg/dl, glucose 133 mg/dl, BUN12 mg/dl, and creatinine 0.7 mg/dl. Urine potassium is 10 mEq/l, creatinine 142 mg/dl, and osmolality 510 mOsm/kg of H_20.

What is the BEST treatment for this patient?

A. KCl in 5% dextrose in water, 120 mEq over 6 hours.
B. KCL in normal saline, 120 mEq over 6 hours.
C. KPO4 in normal saline, 120 mEq over 6 hours.
D. Propranolol 100–200 mg orally.
E. Amiloride 10 mg orally.

The correct answer is D. Hypokalemic periodic paralysis may be familial with autosomal dominant inheritance, or it may be acquired in patients with

thyrotoxicosis. Thyroid hormone increases Na-K-ATPase activity on muscle cells and excess thyroid hormone may thus increase sensitivity to the hypokalemic action of epinephrine or insulin, mediated by Na-K ATPase. Treatment of paralytic episodes with potassium may be effective; however, this therapy may lead to post treatment hyperkalemia as potassium moves back out of the cells. Propranolol has been used to prevent acute episodes of thyrotoxic periodic paralysis and it may also be effective in acute attacks, without inducing rebound hyperkalemia.

Reference

Lin SH, Lin YF, Halperin ML (2001) Hypokalemic and paralysis QIM 194:133–139

CASE 9

A four-year old boy with severe nephritic syndrome is admitted because of progressive edema refractory to diuretics. Serum albumin is 1.0 g/dl.

Which ONE of the following accurately characterizes his diuretic resistance?

A. Diuretic response would more than double if sulfisoxazole were infused.
B. Diuretic response would be enhanced if albumin and furosemide were mixed together before infusion.
C. Secretion of furosemide into the tubular lumen is less than half that of normal subject.
D. All of the above.

The correct answer is B. Hypoalbuminemic nephrotic patients, particularly those with renal failure, are often resistant to diuretics. Because furosemide is protein-bound, it has been suggested that hypoalbuminemia impairs delivery of effective amounts of the diuretic to its site of action in the tubular lumen. In addition, the protein binding within the tubular lumen interferes with furosemide's effect on luminal transport. Displacement of furosemide from albumin with sulfisoxazole, however, does not enhance the natriuretic response to the diuretic, suggesting that diuretic resistance is likely caused by factors other than the altered pharmacokinetics of the diuretic. Therefore, administration of mixtures of albumin and loop diuretics has been recommended to enhance the diuretic response in hypoalbuminemic patients.

References

Brater DC (1999) Use of diuretics in cirrhosis and nephritic syndrome. Sem Nephrol 19:575–580
Brater DC, Gorski JC, Horlander JC Jr, et al. (2001) Effects of albumin/furosemide mixtures on responses to furosemide in cirrhosis patients with ascitis. Tran Am Clin Climatol Assoc 112:108–115

Chalasani N, Gorski JC, Horlander JC Sr et al. (2001) Effects of albumin/furosemide mixture on responses to furosemide in hypoalbuminic patients. J Am Soc Nephrol 12:1010–1016
Agrawal R, Gorski JC, Sundblad K, et al. (2000) Urinary protein binding does not affect response to furosemide in patients with nephritic syndrome. J Am Soc Nephrol 2000; 11:1100–1105

CASE 10

A seven-year old female with end-stage renal disease requiring hemodialysis presents with proximal muscle weakness. The serum potassium is 7.8 mEq/l, and an EKG shows peaked T-waves.

Which ONE of the following agents would lower her serum potassium concentration most quickly?

A. Calcium gluconate intravenously
B. Glucose and insulin intravenously
C. Propranolol intravenously
D. Kayexalate in sorbital orally
E. Sodium bicarbonate intravenously

The correct answer is B. Coadminstration therapy with glucose and insulin is effective in lowering the serum potassium concentration within minutes. Insulin acts on sodium-potassium ATPase to promote cellular uptake of potassium—an effect that is independent of glucose. Glucose is given concurrently with insulin to avoid hypoglycemia. Calcium gluconate is indicated in the treatment of hyperkalemic emergencies because its electrophysiological effect prevents cardiac arrest. Although the drug works extremely rapidly, it does not actually lower the serum potassium concentration. Propranolol is a beta-adrenergic blocking agent that has a mild hyperkalemic effect and is therefore contraindicated in this patient. Kayexalate must first reach the rectum to be effective in lowering the serum potassium level; when the drug is given orally, it does not work rapidly. Serum bicarbonate is theoretically beneficial because it favors the uptake of potassium by cells. Studies in patients with ESRD, however, have shown that potassium falls minimally within the first two hours.

References

Greenberg A (1998) Hyperkalemia: treatment options. Sem Nephrol18:46–57
Allon M (1995) Hyperkalemia in end-stage renal disease: mechanism and management J Am Soc Nephrol 6:1134–1142

CASE 11

A five-year old girl with primary polydipsia drinks large volumes of water (6–8 liters/day).

Which one of the following interferes with her ability to excrete maximally dilute urine?

A. *Aquaporin-2(AQP-2)* gene mutation
B. Thiazide diuretics
C. *V2* receptor gene mutation
D. Amiloride
E. Lithium

The correct answer is B. *AQP-2* gene mutation, *V2* gene mutation, and lithium are causes of nephrogenic diabetes insipidus. These disorders impair the ability to concentrate the urine without affecting the ability to excrete maximally dilute urine. Amiloride blocks sodium channels in the distal nephron, impairing sodium reabsorption and potassium secretion; it has little effect on the ability to dilute the urine. Although thiazide diuretics do not interfere with the ability to concentrate the urine, they impair renal dilution in several ways: 1) block sodium reabsorption in the cortical diluting site, 2) reduce delivery of solute to the diluting sites because of ECF volume contraction, decreased GFR, and enhanced proximal reabsorption, and 3) directly stimulate vasopressin release. Administration of thiazide diuretics to patients with primary polydipsia who rely on the excretion of maximally dilute urine to maintain water balance can cause acute hyponatremia and even death.

Reference

Spital A (1999) Diuretic-induced hyponatremia. Am J Nephrol 19: 447–452

CASE 12

A 17-year old nondiabetic boy (70 kg) develops progressive lethargy over several days and is admitted semicomatose with a serum sodium concentration of 180 mEq/l. A resident proposes an infusion of 5% dextrose in water at 500 ml/hour to rapidly return the serum sodium concentration to a safer level of 160 mEq/l.

Which ONE of the following complications is likely to complicate this therapeutic strategy?

A. Cerebral hemorrhage
B. Osmotic demyelization syndrome
C. Pulmonary edema

D. Hyperglycemia
E. Hyponatremia

The correct answer is D. One liter of D5W contains 50 g of glucose—approximately three times the total glucose content of body fluids when blood sugar is normal. Because several liters of D5W are required to repair a water deficit, severe hyperglycemia is a potential complication if the rate of glucose exceeds the rate of metabolism (10 to 20 g/hour). Infusion of D5W at 500 ml/hour provides 25 g glucose per hour and will predictably cause hyperglycemia, even if insulin is provided. Rapid rehydration in hypernatremic adult patients carries a risk of cerebral edema but this has been reported primarily in infants. Cerebral hemorrhage and osmotic demyelization is a complication of acute hypernatremia, but not a complication of chronic hypernatremia correction. D5W is free water that distributes throughout body fluids, causing little plasma volume expansion for each liter infused; therefore, it is unlikely to cause pulmonary edema. Although hyperglycemia lowers the serum sodium concentration by attracting water to the extracellular fluid, the effect is not large enough to dilute a serum sodium concentration to 160 mEq/l into the hyponatremic range unless the blood glucose were absurdly high.

Reference

Rosemarin DK, Wardlaw GM, Mirtallo J (1996) Hyperglycemia associated with high, continuous infusion rates of total parenteral nutrition dextrose. Nutrition in clinical practice 11:151–156

CASE 13

A five-year old boy with hypertension is found to have hyperkalemia, normal anion gap metabolic acidosis, and low plasma renin and aldosterone levels.

Which ONE of the following would be consistent with these findings?

A. Licorice ingestion
B. Gordon's Syndrome
C. Hemangiopericytoma
D. Gitleman syndrome
E. Renal artery stenosis

The correct answer is B. Familial hperkalemic hypertension, also called: pseudo-hypoaldosteronism Type II and Gordon's syndrome, is characterized by an autosomal dominant transmission of high BP and hyperkalemia without renal failure. Associated findings include a mild hyperchloremic acidosis, suppressed plasma renin activity, short stature, a stiff spine, and deformities of hands and feet. Affected patients respond well to thiazide, suggesting a primary defect in potassium secretion

in the distal tubule. Licorice also causes hypertension with low plasma renin and aldosterone levels. With licorice ingestion, however, these findings are associated with hypokalemia. Hemangiopericytoma and renal artery stenosis also cause hypertension, but plasma renin levels are high in these disorders and the serum potassium concentration is low. Gitleman syndrome causes normotensive and renal potassium wasting.

References

Scheinman SJ, Guay-Woodford LM, Thakker RV, et al.. (1999) Genetic disorders of renal electrolyte transport. N Engl J Med 340:1177–1187

Kalburova F, Robeva R, Belovezhdov N (1992) Gordon's syndrome hypertension and hyperkalemia associated with normal glomerular filtration rate. Nephron 60:124

CASE 14

A six-year old girl complains of profound weakness and polyuria. She is taking no medications and has no gastrointestinal complaints. Pertinent clinical findings include BP 90/50 mmHg with orthostatic dizziness. Laboratory studies show sodium 138 mEq/l, potassium 2.3 mEq/l, chloride 100 mEq/l, bicarbonate 33 mEq/l, BUN 20 mg/dl, and creatinine 0.5 mg/dl. A 24-hour urine contained: sodium 99 mEq/l potassium 63 mEq/l, chloride 5mEq/l, and calcium 285 mg. Plasma renin activity and aldosterone level are elevated.

These findings are most suggestive of which ONE of the following?

A. Gitleman syndrome
B. Licorice ingestion
C. Liddle syndrome
D. Adrenal adenoma
E. Bartter syndrome

The correct answer is E. This patient is an example of classic Bartter syndrome, characterized by early onset of metabolic alkalosis, renal potassium wasting, polyuria, and polydipsia without hypertension. Symptoms may include vomiting, constipation, salt craving, and a tendency to volume depletion. Growth retardation follows if treatment is not initiated. Unlike patients with Gitelman syndrome, their calcium excretion is elevated. Adrenal adenoma, licorice ingestion, and Liddle syndrome are all causes of hypokalemic metabolic alkalosis, but these disorders are associated with hypertension.

Reference

Shaer AJ (2001) Inherited primary renal tubular hypokalemic alkalosis: a review of Gitelman and Bartter syndrome. Am J Med Sci 322:316–173

CASE 15

A 14-year old girl develops severe cardiomyopathy and pulmonary edema. Despite therapy with angiotensin-converting enzyme inhibitors, beta blockers, spironolactone, and diuretics, she develops progressively marked edema. Furosemide is increased from 20 mg to 60 mg twice daily. Her BP is 93/52 mmHg. Jugular venous pulses are noted at the earlobes. Her breath sounds are decreased at both bases, and crackles are heard in the lower third of both lung fields. S3 gallop and holosystolic murmur are heard at the apex. A tender liver is palpable four finger-breadths below the right costal margin. Marked edema of the lower extremities extends to the hips. She is awake and alert and the neurological examination is unremarkable. Laboratory data include a sodium 115 mEq/l, potassium 5.1 mEq/l, chloride 87 mEq/l, bicarbonate 28 mEq/l, BUN 73 mg/dl, creatinine 1.4 mg/dl, and glucose 125 mg/dl. Urine osmolality is 759 mOsm/kg of H_2O, and sodium is 8 mEq/l.

Which ONE of the following therapeutic approaches would be the most appropriate for her hyponatremia?

A. Substitute metolazone (10 mg twice daily) for furosemide.
B. Start demeclocycline 600 mg daily.
C. Discontinue all diuretics.
D. Her hyponatremia can be disregarded because she has pseudohyponatremia.
E. Increase furosemide to 160 mg twice daily.

The correct answer is E. Hyponatremia is a poor prognostic finding in congestive heart failure. It reflects vasopressin secretion, which is part of the neuroendocrine response to inadequate circulation. In the case presented here, the patient has become hyponatremic while on furosemide. However, because hyponatremia has evolved while the patient was becoming more edematous with an extremely low urine sodium concentration, the diuretic is unlikely to be the cause of the electrolyte disturbance. Furosemide interferes with urinary concentration and is therefore an uncommon cause of hyponatremia.

Metolazone is a thiazide-type diuretic. Because this agent permits the urine to be maximally concentrated, substitution of this agent for furosemide is likely to exacerbate the patient's tendency to hyponatremia. Demeclocycline may be effective as an aquaretic, because it interferes with vasopressin's action on the collecting duct. However, the demeclocylcine accumulates in liver disease, causing nephrotoxicity; it is therefore a poor choice in a patient with severe congestive heart failure and hepatic congestion. Discontinuation of all diuretics is unlikely to be helpful in correcting the hyponatremia, and will permit edema to progress. Psudohyponatremia is incorrect; although the calculated serum osmolality is only slightly low $(2 \times 118 + 84/2.8 + 120/18 = 273)$, the serum osmolality is increased by urea, which has no effect on plasma tonicity.

The patient is developing progressive edema on her current doses of furosemide and she has a low urine sodium concentration. Diuretics have a dose-response curve

characterized by no natriuresis until a threshold of drug excretion is attained. In congestive heart failure, decreased intestinal perfusion, reduced intestinal motility, and perhaps mucosal edema may substantially slow the rate of drug absorption and therefore the rate of drug delivery to the kidney. There may also be decreased diuretic secretion into the tubular lumen because of decreased renal perfusion. In this setting, apparent resistance to seemingly adequate doses of oral furosemide may be overcome by increasing the dose. Hyponatremia does not contraindicate this therapy. Indeed, urine excreted in response to furosemide will have a lower sodium concentration than plasma; thus an increased urine output increases free water excretion, correcting hyponatremia.

References

Cadnapaphornchai MA, Gurevich AK, Weinberger HD, et al. (2001) Pathophysiology of sodium and water retention in heart failure. Cardiology 96:122–131

Kramer BK, Schweda F, Riegger GA (1999) Diuretic treatment and diuretic resistance in heart failure. Am J Med106:90–96

CASE 16

A 19-year old female with chronic obstructive pulmonary disease and congestive heart failure presents with anasarca. Her arterial blood gases (ABG) before therapy are as follows: pH 7.21, $HCO3^-$ 31 mEq/l, PCO_2 62 mmHg, PO_2 73 mmHg on 2 liters of O_2 by nasal prongs. After losing 4.8 kg during treatment with a furosemide drip, repeat ABGs are obtained: pH 7.33, PCO_2 88 mmHg, $HCO3^-$ 29, PO_2 61 mmHg. Serum potassium is 3.0 mEq/l. She is treated with KCL, raising her serum potassium to 4.2 mEq/l, but her ABGs do not change.

Which ONE of the following therapies would be the best treatment for her worsening hypercapnia?

A. Acetazolamide
B. Intravenous normal saline
C. Intravenous 100 mM hydrochloric acid (HCl)
D. Oral ammonium chloride
E. Hemodialysis

The correct answer is A. Sodium chloride is effective in correcting alkalosis caused by diuretics or loss of stomach acid. It is contraindicated in edematous patients, however, as it will increase edema and may not always improve the alkalosis. In patients with heart failure, cor pulmonale or cirrhosis, or enhanced proximal tubular reabsorption of bicarbonate may reflect poor renal perfusion caused by these disorders, and may not necessarily improve with volume expansion. Intravenous HCL or oral ammonium chloride administration will more definitely improve the metabolic

alkalosis, but these agents, such as sodium chloride, will expand the ECF volume, worsening edema.

Metabolic alkalosis in edematous patients can be improved by the administration of the carbonic anhydrase inhibitor acetazolamide, which inhibits proximal sodium bicarbonate reabsorption, correcting both the alkalosis and the fluid overload. The increase in bicarbonate delivery to the potassium secretory site in the collecting tubule enhances potassium secretion. Therefore, hypokalemia should be corrected before acetazolamide is given. Correction of metabolic alkalosis may be particularly important in patients with chronic respiratory acidosis because the compensatory hypoventilation can exacerbate hypoxemia and retard weaning from the respirator. Hemodialysis will also be effective in controlling edema, hypokalemia, and metabolic alkalosis, but it is the least cost-effective approach.

Reference

Mazur JE, Devlin JW, Peters MJ, et al. (1999) Single versus multiple doses of azetazolamide for metabolic alkalosis in critically ill medical patients. A randomized, double-blind trial. Crit Care Med 27:1275–1261

CASE 17

A 12-year old female presents with jaundice and pruritis. She is afebrile and in no distress. BP is 130/75 mmHg, heart rate 80 beats/min, and no jugular distension. Lungs are clear, and heart has no gallops. Liver is tender and enlarged. There are no ascites or edema. Serum Na^+ is 125, K^+ 3.5, Cl^- 94, $HCO3^-$ 25 (all in mEq/l); BUN 12 mg/dl, creatinine 0.8 mg/dl, glucose 95 mg/dl, serum osmolality 286 mOsm/kg H_20, urine osmolality 444 mOsm/kg of H_20, urine sodium 65 mEq/l, total serum protein 5.4 g/dl. Blood ethanol level is negative.

Which ONE of the following tests would be most likely to reveal the cause of her hyponatremia?

A. Computed tomographic (CT) scan of the brain
B. Plasma cortisol level
C. Serum triglyceride level
D. Serum cholesterol level
E. Methanol and ethylene glycol levels

The correct answer is D. The patient has hyponatremia with a normal serum osmolality, suggesting a possible diagnosis of pseudohyponatremia. Elevated triglycerides can cause pseduhyponatremia, but it should also cause lactescent serum. Methanol and ethylene glycol increase serum osmolality, causing an osmolar gap, but do not cause hyponatremia. A CT scan of the head and measurements of plasma cortisol would be appropriate in the evaluation of the patient if the serum

osmolality were low (true hyponatremia). Patient has pseduohyponatremia that is associated with high levels of cholesterol. In severe cholestasis (e.g., biliary cirrhosis), lipoprotein x is formed when there is reflux of unesterified cholesterol and phospholipids into the circulation from the cholestatic biliary ducts. Unlike LDL, HDL, and VLDL, the particles of lipoprotein x cholesterol are not soluble in plasma water and thus increase the solid fraction (and decrease its water content), causing pseudohyponatremia. Levels of lipoprotein x can be as high as several thousand milligrams per deciliter of cholesterol.

References

Turchin A, Seifter JL, Seely EW (2003) Mind the Gap. N Engl J Med 349:1465–1469
Milionis HJ, Liamis GL, Elisaf MS (2002) The hyponatremic patient: a systematic approach to laboratory diagnosis. Can Med Assoc J 166:1056–1062
Weisberg LS (1989) Pseudohyponatremia: a reappraisal. Am J Med 86:315–318

CASE 18

A 14-year old girl presents with hyponatremia, primary amenorrhea, and anorexia. She takes no medications. Physical examination reveals that she is normotensive and has no physical findings to suggest congestive heart failure (CHF) or liver disease. Abdomen is soft and nontender without masses or organomegaly. Laboratory data reveal serum Na^+ 127, K^+ 4.1, Cl^- 93, $HCO3^-$ 25 (all in mEq/L), BUN 6 mg/dl, creatinine 0.6 mg/dl, glucose 103 mg/dl, urine osmolality 684 mOsm/kg, urine Na^+ 99 mEq/l, urine K^+ 65 mEq/l, and urine creatinine 105 mg/dl. Thyroid stimulating hormone, triglyceride, and serum protein levels were normal. The chest and head computed tomographic (CT) scan were normal.

Which ONE of the following tests would be most likely to reveal the cause of the patient's hyponatremia?

A. CT scan of the abdomen
B. Plasma osmolality
C. Plasma luteinizing hormone and follicle stimulating hormone
D. Plasma aldosterone

The correct answer is D. The patient has hyponatremia. Most of the causes of nonhypotonic hyponatremia (psudohyponatremia) are excluded by the setting and laboratory tests. She is neither volume-depleted nor edematous, and has concentrated urine with a high urine sodium concentration. These findings are consistent with a diagnosis of SIADH. A cause must be sought. The CT scan of the chest makes lung pathology very unlikely, so broncoscopy will have a very low yield. Similarly, a CT scan of the abdomen is unlikely to be helpful because diseases other than lungs and CNS rarely cause SIADH. Measurement of plasma osmolality is unlikely to be helpful. Because the data have already excluded nonhypotonic

hyponatremia, the diagnosis of hypopituitarism with secondary cortisol deficiency should be considered because it may present with clinical features of SIADH. The diagnosis of hypopituitarism can be difficult. Low levels of gonadotropines may be helpful in making the diagnosis because these hormone levels are usually elevated in primary amenorrhea with an intact hypothalamic-pituitary axis. In contrast to Addison's disease (which presents with clinical signs of hypovolemia and hyperkalemia), aldosterone levels are normal in hypopituitarism.

Reference

Wong LL, Verbalis JG (2002) Systemic diseases associated with disorders of water homeostasis. Endocrinol Metab Clin N Am 31:121–140

CASE 19

Twelve hours after initiating therapy, the patient in Case 18 becomes comatose. Her BP is 90/50 mmHg, serum sodium concentration 151 mEq/l, blood glucose 200 mg/dl, and serum potassium is 2.5 mEq/l.

Which ONE of the following is most likely to improve her mental status?

A. 2 liters of 5% dextrose in water
B. 200 ml of 3% saline
C. 80 mEq of KCl
D. 1 ampoule of 50% dextrose
E. 2 liters of 0.9% saline

The correct answer is B. The patient has developed clinical signs of increased intracranial pressure during the course of treatment for ketoacidosis. The plasma tonicity [2 (plasma sodium mEq/l) + (plasma glucose mg/dl:18) + BUN mg/dl: 2.8] has fallen from 260 mOsm/l to 310 mOsm/l. Administration of hypertonic saline has been reported to be effective in this setting.

Reference

Carlotti AP, Bohn D, Halperin ML (2003) Importance of timing of risk factors for cerebral edema during therapy for diabetic ketoacidosis. Arch Dis Child 88:170–173

CASE 20

Eplerenone has recently shown to be effective in reducing morbidity and mortality among patients with congestive heart failure (CHF) complicating myocardial infarction.

In which ONE of the following ways does eplerenone differ from spironolactone, a drug that has also been shown to improve outcomes in CHF?

A. It selectively blocks the mineralocorticoid receptor and not the glucocorticoid, progesterone, or androgen receptors.
B. It has been shown to be safe and effective in patients with serum creatinine levels greater than 2.5 mg/dl.
C. It is effective in reducing mortality in patients with CHF without concurrent use of an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker.
D. It does not cause hyperkalemia.
E. It only improves outcomes in patients with diabetes mellitus.

The correct answer is A. Eplerenone, like spironolactone, has been shown to reduce overall cardiovascular mortality among patients with CHF. Like spironolactone, eplerenone blocks the mineralocorticoid receptor, but does not block the glucocorticoid, progesterone, or androgen receptors. Hyperkalemia may develop during therapy with eplerenon.

Reference

Pitt B, Remme W, Zannad F, et al. (2003) Eplerenon, a selective aldosterone blocker in patient with left ventricular dysfunction after myocardial infarction. N Engl J Med 348:1309–1321

CASE 21

A six-year old boy with acute lymphocytic leukemia receives a bone marrow transplant, after which pneumonia, respiratory failure, coagulase negative bacteremia, and sustained polyuria develop. The following laboratory data were obtained on the seventh hospital day, when the urine output was 4.5 liters/24 hours: serum Na^+ 155 mEq/l, BUN 65 mg/dl, creatinine 1.6 mg/dl, glucose 138 mg/dl, plasma osmolality 340 mOsm/l, urine Na^+ 33 mEq/l, urine K^+ 40 mEq/l, and urine osmolality 389 mOsm/lkg water.

Which ONE of the following is the most likely explanation for the polyuria?

A. Neurogeic diabetes insipidus due to leukemic infiltration of the hypothalamus
B. Nephrogenic diabetes insipidus due to leukemic infiltration of the kidney
C. Nephrogenic diabetes insipidus due to graft-versus-host reaction
D. Osmotic diuresis due to protein catabolism
E. Osmotic diuresis due to intravenous saline infusion

The correct answer is D. The patient's urine osmolality is close to plasma osmolality and urine solute excretion (urine osmolality × urine volume) is 1750 mOsm/day,

about twice the usual solute excretion on a daily recommended diet. Urine sodium excretion (urine Na concentration × urine volume) is only 148 mEq/day and the blood glucose value is only mildly elevated. Thus, the excess in the urine is most likely urea, reflecting protein catabolism.

Reference

Halperin ML, Bohn D (2002) Clinical approach to diagnosis of salt and water balance. Emphasis on integrative physiology. Cri Care 18:249–272

CASE 22

A seven-year old girl with a history of diabetes insipidus maintained on desmopressin (DDAVP)® is admitted after several days of nausea and vomiting. She is normotensive, lethargic, and confused. Serum Na^+ is 104 mEq/l and her weight is 30 kg. An infusion of 3% saline at 40 ml/hr is started, and DDAVP® is withheld. Six hours later, the serum Na^+ concentration is 116 mEq/l.

Which ONE of the following is the most appropriate treatment at this point?

A. Continue 3% saline at 40 ml/hr
B. Decrease 3% saline to 25 ml/hr
C. Stop 3% saline and start 0.9% saline at 100 ml/hr
D. Stop intravenous fluids and give DDAVP®
E. Stop intravenous fluids

The correct answer is D. The patient became hyponatremic as an outpatient and has only moderate symptoms despite a profoundly low serum Na^+ concentration. These features suggest a diagnosis of chronic hyponatremia. The serum Na^+ concentration has increased by 12 mEq/l over the course of six hours. The rate of increase (2 mEq/l/hr) is twice as fast as would be expected from the infusion of 3% saline at 1 ml/kg/hr. Thus, a water diuresis must be contributing to the correction of hyponatremia. Once DDAVP® has been completely metabolized, maximally dilute urine would be expected, which would increase the serum osmolality concentration by over 2 mEq/l/hr, even if no sodium was administered. The serum Na^+ value has already increased by more than should be targeted for a patient with chronic hyponatremia. Thus, the correct response is to stop IV fluids and give DDAVP®. All other choices would cause an excessive increase in the serum Na^+ concentration, risking osmotic demyelization.

Reference

Lin SH, Hsu YJ, Chiu JS, et al. (2003) Osmotic demyelization syndrome: a potentially avoidable disaster. QJM 96:935–947

CASE 23

After a prolonged abdominal surgery, using large volumes of 1.5% glycine (200 mEq/l) as an irrigant, a 10-year old boy develops hypotension and blurred vision. In the recovery room, serum sodium is 105 mEq/l. He is treated with an infusion of 200 ml of 3% saline and 40 mg of furosemide intravenously. Four hours later, he becomes obtunded. Serum sodium is now 120 mEq/l.

Which ONE of the following best explains the reason for the decrease in serum sodium concentration immediately after surgery?

A. Translocation of fluid from cells to the extracellular fluid
B. A nonosmotic stimulus to vasopressin secretion
C. Pseudohyponatremia
D. Extracellular volume expansion
E. Osmotic diuresis

The correct answer is D. The patient has nonhypotonic hyponatremia complicating absorption of glycine irrigant. Unlike pseudohyponatremia due to hyperlipidemia or hyperproteinemia, the low serum Na^+ concentration is not an artifact of laboratory measurement. The 1.5% glycine solution is hypo-osmolar; thus it does not cause translocation of fluid from cells to the extracellular space. Hyponatremia is caused by retention of the absorbed irregant in the extracellular fluid, expanding fluid volume and diluting sodium concentration.

Which ONE of the following is the most likely cause of the central nervous system (CNS) disorder?

A. Cerebral edema
B. Central pontine myelinolysis
C. Cerebral hemorrhage
D. Glycine metabolites
E. Post-anoxic encephalopathy

The correct answer is D. Absorption of glycine irrigant may present with the delayed neurological symptoms that are associated with high levels of plasma ammonia—a metabolite of the amino acid. Cerebral pontine myelinolysis is primarily a complication of chronic hyponatremia, and appearance of its clinical manifestations is delayed by at least 24 hours. Cerebral hemorrhage is a possibility but there is no reason for it to occur. Delayed anoxic encephalopathy is a rare complication of severe, prolonged anoxia, which are clinical manifestations appearing a week or more after the insult. Severe cerebral edema can complicate the absorption of sorbitol or dextrose containing irrigants but is not a prominent feature of glycine absorption because this agent is metabolized to urea and other amino acids that persist in circulation, maintaining a plasma osmolality that is only moderately low.

References

Roesch RP, Stoelting RK, Lingeman JE, et al. (1983) Ammonia toxicity resulting from glycine absorption during a transureteral resection of the prostate. Anesthesiology 58:577–579
Sandfeldt L, Hahn RG (1999) Comparison of irrigating fluids containing glycine and mannitol in volunteers. Prostate 41:89–98

CASE 24

A 19-year old boy with Type 2 diabetes mellitus and end-stage renal disease, who is being maintained on hemodialysis, develops muscle weakness. Laboratory data includes serum Na^+ 128 mEq/l, K^+ 7.4 mEq/l, Cl^- 92 mEq/l, $HCO3^-$ 15 mEq/l, BUN 99 mg/dl, creatinine 9.0 mg/dl, and glucose 295 mg/dl. When an electrocardiogram shows peaked T-waves, he is given calcium gluconate.

In addition to this treatment, which ONE of the following would be the most consistently effective therapy for his hyperkalemia?

A. Subcutaneous insulin and a slow intravenous infusion of glucose
B. Intravenous β2-adrenergic agonist
C. Intravenous insulin
D. Intravenous sodium bicarbonate
   Oral sodium polystyrene sulfonate (Katexalate) and sorbitol

The correct answer is C. Insulin directly activates Na-K ATPase, augmenting cellular uptake of potassium. Super physiologic doses of insulin are needed for the maximal hypokalemic effect, and concurrent administration of glucose is only necessary to prevent hypoglycemia. Administration of approximately 20 units of insulin causes a 1 mEq/l decrease in serum K^+ in less than one hour. Intravenous insulin is preferable to subcutaneous insulin because the bolus infusion produces much higher plasma insulin levels. Beta-2 adrenergic agonists, like albuterol, also activate Na-K ATPase, but approximately 20% of patients are resistant to this therapy and it is not possible to predict who will not respond. Sodium $HCO3^-$ and the cation exchange resin, Kayexalate, take several hours to lower the serum K^+ level. Although Kayexalate is widely used to treat hyperkalemia, there are remarkably few studies demonstrating its effectiveness.

Reference

Kamel K, Wei C (2003) Controversial issues in the treatment of hyperkalemia. Nephrol Dial Transplant 18:2215–2218

CASE 25

A 12-year old girl with cirrhosis due to Wilson disease develops severe metabolic alkalosis two days after a liver transplant.

Which ONE of the following is most likely to be responsible for the acid-base disturbance?

A. Increased urea genesis by the transplanted liver
B. Increased urinary ammonium excretion
C. Activation of the mineralocorticoid receptor by cryoglobulins
D. Transfusion of blood products
E. Hypoalbuminemia

The correct answer is D. Metabolic alkalosis develops in about half of patients undergoing orthotopic liver transplantation, and increases in serum bicarbonate in excess of 14 mEq/l are common during the first 72 hours after surgery. Citrate containing blood products infused during surgery are recently shown to be the major explanation for this phenomenon. Citrate's alkalinizing effect is due to its three negative charges, which are available to consume hydrogen ions. For every mole of citrate metabolized, three moles of bicarbonate are generated.

Reference

Contreas G, Grace G, Reich J, et al. (2002) Predictors of alkalosis after liver transplantation. Am J Kid Dis 40:517–524

CASE 26

Which ONE of the following does not impair the ability to concentrate the urine?

A. Hypercalcemia
B. Hypokalemia
C. Lithium therapy
D. Thiazide diuretic
E. Furosemide

The correct answer is D. Hypokalemia, hypercalcemia, and furosemide interfere with the ability to concentrate the urine by affecting the generation of a medullary concentration gradient in the Loop of Henle. Lithium causes nephrogenic diabetes insipidus by reducing the number of aquaporin 2 water channels that are inserted in

the collecting duct epithelium in response to vasopressin. Thiazides act in the renal cortical diluting segment but do not affect transport in the ascending limb. Thus, thiazides impair the ability to dilute the urine but not the ability to concentrate the urine. This characteristic of thiazide explains why hyponatremia may complicate their use.

References

Brater DC (2000) Pharmacology of diuretics. Am J Med Sci 319:38–50
Greger R (2000) Physiology of renal sodium transport. Am J Med Sci 319:51–62

CASE 27

An 18-year old female (60 kg) presents to the emergency room (ER) with severe pain in her mouth. She had dental work done five days ago and has now developed a tooth abscess. She has been taking a variety of pain pills and has been unable to eat solid food for several days. Past medical history was significant for a postpartum hemorrhage complicated with hypotension two years ago. Laboratory data reveals current levels of: sodium 110 mEq/L, chloride 72 mEq/L, potassium 3.8 mEq/L, CO2 29 mEq/L, BUN 11 mg/dl, creatinine 0.8 mg/dl, calcium 9.0 mg/dl, phosphate 3.9 mg/dl, magnesium 1.9 mg/dl, and albumin 4.0 g/dl. Hematocrit is 42%, and white blood count (WBC) are 5200 cells/ul. Urinalysis shows trace protein, negative glucose, no blood, and no casts, red blood count (RBC), or WBC. Urine sodium is 10 mEq/l and urine osmolality is 410 mOsml/kg.

What orders would you like to write (select all that apply)?

A. Restrict free water to <1500 ml/day
B. Oral surgery consult
C. Intravenous 0.9% saline, 3 liters/24 hours
D. Administer ADH
E. Intravenous 3% saline, 3 liters/24 hours

The correct answers are A, B, and C. It appears that the hyponatremia is due to a combination of reduced intake and antidiuretic hormone (ADH) secretion in response to extra cellular fluid (ECF) volume contraction, pain, and medications. Treatment therefore include restoration of ECF volume with isotonic saline, restriction of free water intakes until the other issues are resolve, and drainage of the abscess.

Reference

Goldberg M (1981) Hyponatremia symposium on body fluid and electrolyte disorders. Med Clin North Am 65:251–269

CASE 28

You are asked to see a 16-year old Caucasian girl with acute post-operative hyponatremia. The patient had been in a good health until yesterday when she fell and sustained a compound wrist fracture. It was recommended that surgery be performed immediately. She was started on a low dose of unfractionated heparin, a urinary tract catheter was placed, and she received prophylactic antibiotics and was taken to the operating room (OR). She is taking oxcabazepine for an anxiety disorder. Upon examination, she appears restless and confused and is complaining of significant pain in her right wrist. Temp is 37 °C, pulse 115, respiratory rate 28. The chest is clear. There is no abdominal distention, tenderness, or guarding. There is no organomegaly. There is no edema. The neurological examination is within normal limits except for mild to moderate confusion. Patient's pre-op laboratory study shows serum sodium 117 mEq/l, potassium 3.8 mEq/l, chloride 79 mEq/l, $HCO3^-$ 27 mEq/l, BUN 11 mg/dl, and creatinine 0.5 mg/dl. Calcium is 9.3 mg/dl, phosphate is 3.9 mg/dl, magnesium is 1.8 mg/dl, and albumin is 4.0 g/dl. White blood count is 5200 cells/ul and hematocrit is 14.0 g/dl. Urinalysis shows trace protein, negative glucose, and no blood, RBC, or WBC. Urine sodium is 40 mEq/L, urine osmolality is 490 mOsm/kg, and plasma osmolality is 241 mOsm/kg.

The post-op laboratory values are hematocrit 40%, WBC 5,500 cells/ul, BUN 11 mg/dl, creatinine 0.6 mg/dl, sodium 138 mEq/l, potassium 3.6 mEq/l, chloride 104 mEq/l, CO2 27 mEq/l, calcium 9.8 mg/dl, phosphate 3.9 mg/dl, uric acid 3.2 mg/dl, and albumin 2.2 g/dl. Her intake since this AM (over 6 hrs)—including the period of surgery and the recovery room—was 3 L of D5W. There was little estimated blood loss and she has output 100 ml of urine.

What is the likely cause of this condition?

A. Adrenal insufficiency
B. Postoperative SIADH associated with pain
C. Cirrhosis
D. Bronchogenic carcinoma
E. Reset osmostat

The correct answer is B. Major abdominal or thoracic surgery is commonly associated with hypersecretion of ADH, a response that is probably mediated by pain afferents. The length and severity of this condition increase with increasing age.

The fellow assigned to the case was interested in the problem and was planning to present it at the next conference. Without your knowledge he had a plasma vasopressin level drawn. He now says to you that the vasopressin level was low, NOT high. He wants to know how that can be if the patient has hyponatremia and a concentrated urine.

Your answer is which of the following?

A. The laboratory made a mistake
B. The patient has hypothyroidism
C. The patient is taking oxcabazepine
D. The patient likely has pseudohyponatremia due to marked hyperlipidemia
E. The patient has Addison disease

The correct answer is C. Hyponatremia associated with oxcarbazepine is not due to SIDH and vasopressin levels are not elevated. Rather, the drug directly enhances absorption of water in the collecting duct possibly by enhancing responsiveness to circulating ADH.

References

Assadi F (1993) Hyponatremia. Pediatr Nephrol 8:503–505
Maesaka JK (1996) An expanded views of SIADH, hyponatremia and hypourecemia. Clin Nephrol 46:79–83
Sachedo RC, Wasserstein A, Messenbrink PJ, et al. (2002) Effects of oxcarbazepine on sodium concentration and water handling. Ann Neurol 51:613–620

CASE 29

You are asked to see a 15-year old male with a serum sodium concentration of 123 mEq/L. He was in a good state of health until four months ago when he developed a persistent cough. He subsequently experienced a 6 kg weight loss. Shortness of breath developed five days ago. He has a history of mild hypertension, for which he was being treated with atenolol 25 mg per day. He does not drink alcohol. He denies the use of any other medications or over-the-counter supplements. Upon examination, he appears cachectic in no apparent acute distress. BP (BP) was 110/72 without orthostatic; pulse 68; RR 18; temp 98.6; Wt 62 kg; Ht 159 cm. Heart has regular rhythm, no murmurs. Chest is dull to percussion with diminished breathing sounds at the right base. There is no edema. The remaining of the PE is normal. A chest x-ray showed a right pleural effusion and he was admitted for further evaluation. Laboratory study showed serum sodium 126 mEq/l, potassium 3.5 mEq/l, chloride 91 mEq/l, bicarbonate 24 mEq/l, BUN 6 mg/dl, creatinine 0.7 mg/dl, calcium 9.1 mg/dl, phosphate 3.2 mg/dl, magnesium 1.9 mg/dl, uric acid 3.5 mg/dl, and albumin 3.6 g/dl. Urine osmolality was 305 mOsm/kg and serum osmolality was 250 mOsm/kg.

What causes of hyponatremia that should be considered in this case?

A. Dilutional hyponatremia (hyperglycemia)
B. Pseudohyponatremia (hyperproteninemia or hyperlipidemia)

C. Syndrome of inappropriate ADH secretion
D. Adrenal insufficiency
E. Reset osmostat

The correct answer is C. The diagnosis of SIDH with a primary lung disease is extremely likely in this patient. Rest osmostat typically occurs in chronically ill, malnourished, or cachectic patients with tuberculosis, and this patient is certainly a candidate.

How would you make the distinction between SIADH and reset osmostat in this patient?

A. Water restriction
B. Administer vasopressin
C. Administer a water load
D. Expand the ECF volume with isotonic saline
E. Administer 0.9% saline

The correct answer is C. A patient with SIDH will not respond with dilution of the urine. A patient with reset osmostat will respond to a water load with a water diuresis (urine osmolality $\leq$ 80 mOsm/kg) when the serum sodium concentration falls below the *reset* level.

Reference

DeFronzo RA, Goldberg M, Agus ZS (1976) Normal diluting capacity in hyponatremic patients, reset osmostat or variant of the syndrome of inappropriate antidiuretic hormone secretion. Ann Intern Med 84:538–542

CASE 30

A 19-year old male presents to the ER after five days of not feeling well. One week ago he began to take his father's diuretic because he had developed some peripheral edema and abdominal swelling. He claims that he has not eaten in six days and his only intake was beer.

He had been diagnosed with chronic hyponatremia several months ago with serum sodium consistently in the range of 128-132 mEq/L. Urine osmolality was 445 mosmol/kg. Workup revealed normal renal and adrenal function. Chest x-ray was normal. He was on no medications. He was given a diagnosis of SIADH and was subsequently lost to follow-up.

BP was 100/70 mmHg. Lab studies were: sodium 106 mEq/l, potassium 3.4 mEq/l, chloride 78 mEq/l, bicarbonate 22 mEq/l, BUN 10 mg/dl, creatinine 1.0 mg/dl, urine sodium 10 mEq/l and urine osmolality 686 mOsmkg.

What was the likely sequence of events leading to severe hyponatremia in this patient?

A. Worsening SIADH
B. Chronic mild hyponatremia plus superimposed volume contraction and beer drinkers potomania (low solute intake)
C. Reset osmostat
D. Aldosterone deficiency
E. Hypothyroidism

The correct answer is B. He likely had a severe limitation on his ability to excrete free water due to a chronic problem with superimposed volume concentration from the diuretics and low solute intake associated with massive beer intake.

The patient was given 2 liters of normal saline over the next four hours, at which point he began to excrete clear urine with a SP of 1.002. He excreted 6 liters over the next 10 hours, at which point his serum sodium was 129 mEq/L. His fluid therapy was changed to 5%DW because of the fear that the correction of his hyponatrema might be too rapid. At that point it was noted that his urine osmolality was 453 mOsm/kg.

What was the likely sequence of events?

A. Reset osmostat complicated by volume contraction and low solute intake
B. SIADH complicated by volume contraction and low solute intake
C. Volume contraction and low solute intake
D. Pseudohyponatremia
E. Aldosterone deficiency

The correct answer is A. The patient had a reset osmostat accounting for his chronic hyponatremia. Superimposed volume contraction and potomania prevented his ability to excrete the water load. When he was repleted with saline, this corrected the volume contraction and provided solute to allow free water to be excreted. When his serum osmolality exceeded his "reset" point, he began responded by concentrating his urine.

References

Assadi F, Agrawal R, Jocher C, et al. (1986) Hyponatremia secondary to reset osmostat J Pediatr 108:262–264

Bannister P, Sheidan P, Penney MD (1984) Chronic reset osmoreceptor response, agenesis of the corpus calosum, and hypothalamic cyst. J Pediatr 104:97–99

Friedman E, Shadel M, Halkin H, et al. (1989) Thiazide-induced hyponatremia. Reproducibility by single dose rechallenge and an analysis of pathogenesis. Ann Intern Med 110:24–30

Goldberg M (1981) Hyponatremia symposium on body fluid and electrolyte disorders. Med Clin North Am 65:251–269

CASE 31

You are asked to see a two-year old boy with congestive heart failure. His medications include digoxin and furosemide. On examination, he is lethargic and in mild respiratory distress, with a BP of 100/54 mm Hg and an irregular pulse of 104. Rales are present one quarter of the way up his lung fields, and there is 2+ ankle edema. Lab studies reveals the following: sodium 125 mEq/l, potassium 3.3 mEq/l, chloride 95 mEq/l, bicarbonate 24 mEq/l, BUN 11 mg/dl, creatinine 0.8 mg/dl, fasting blood glucose 90 mg/dl, serum osmolaity 230 mOsm/kg, and urine osmolality 600 mOsm/kg.

Which of the following statements concerning his hyponatremia are true (select all that apply)?

A. A plasma sodium concentration below 125 mEq/l typically represents near end-stage cardiac disease.
B. Hyponatremia can be easily managed with water restriction.
C. The hyponatremia is due to a decrease in cardiac output (effective volume depletion), which initiates a baroreceptor response and neurohumoral stimulation.
D. He most likely has SIADH due to medications.
E. He has reset osmostat.

The correct answers are A and C. In state of congestive heart failure, a decrease in cardiac output (effective volume depletion) initiates a baroreceptor response which triggers the renal response via secretion of the three *hyponatremia* hormones (renin-angiotensin II system, antidiuretic hormone (ADH), and norepinephrine).

The severity of the defect in water excretion (due to the neurohumoral activation) and of the associated reduction in the plasma sodium concentration parallels the severity of the heart disease. Patient survival is significantly reduced (in comparison to normonatremic patients) once the plasma sodium concentration falls below 137 mEq/L. A plasma concentration below 125 mEq/l typically represents near end-stage cardiac disease.

References

Churg HM, Kluge R, Schrier R et al. (1987) Clinical assessment of extracellular fluid volume in hyponatremia. Am J Med 83:905–908

Goldberg M (1981) Hyponatremia symposium on body fluid and electrolyte disorders. Med Clin North Am 65:251–269

CASE 32

A 50-kg male has SIADH due to a tumor. The plasma sodium is in steady state and 120 mEq/L, and plasma potassium is 4.0 mEq/L. There are no symptoms attributable to hyponatremia. Assume that the ECF volume is normal and that the patient is consuming a usual diet.

How much water restriction would correct the hyponatremia?

A. 1.5 liters
B. 2.3 liters
C. 3.0 liters
D. 3.4 liters
E. 4.0 liters

The correct answer is D. Physiologically, in patients with SIADH, the total body sodium (TBNa) is normal, but the total body water (TBW) is increased proportionately to the fall in plasma sodium (PNa^+) concentration, due to overproduction of ADH. Because $TBNa^+$ is the product of TBW and PNa^+ concentration, the excess water gain in SIADH can be estimated using the following equation:

TBNa ($\mathrm{TBW} \times \mathrm{PNa}^+$) in normal subjects = TBNA ($\mathrm{TBW} \times \mathrm{PNa}^+$) in SIADH patient or
$(50\,\mathrm{kg} \times 0.6) \times 135\,\mathrm{mEq/L} = (\mathrm{TBW} \times 120\,\mathrm{mEq/L})$ or
TBW in SIADH patient $= 50\,\mathrm{kg} \times 0.6\,[30\,\mathrm{liters}] \times 135\,\mathrm{mEq/L} : 120\,\mathrm{mEq/L}$ or
TBW in SIADH patient = 33.750 liters

The excess water gain in patients with SIADH can now be calculated from the difference between the TBW in normal subjects and the SIADH patient:
Water gain = (33.750 liters) – (30.00 liters) or 3.375 liters.

Reference

Chung HM, Kluge R, Schrier R, et al. (1987) Clinical assessment of extracellular fluid volume in hyponatremia. AM J Med 83:905–908

CASE 33

An 18-year old male with a history of schizophrenia was admitted to the psychiatric service with homicidal and suicidal ideation. There was no previous history of medical or surgical diseases. Medications on admission included Mellaril (thioridazine hydrochloride) in an unknown dosage, and Prolixin (fluphenazine hydrochloride) at 10 mg/6 hours.

Upon admission, the patient was moderately obese and in no distress. BP was 110/84 mm Hg (supine) and 110/90 mm Hg (standing), pulse 96/min (supine) and 106/min (standing), temperature 37 °C, and respiratory rate 14/min. Skin, eyes, neck, chest, heart, and abdominal examinations were normal. There was no peripheral edema.

Admission laboratory examination showed a serum sodium 144 mEq/l, potassium 4.2 mEq/l, chloride 103 mEq/l, bicarbonate 30 mEq/l, blood urea nitrogen 11 mg/dl, creatinine 1.1 mg/dl, albumin 4 g/dl, and uric acid 5.8 mg/dl. Urinalysis

showed a specific gravity of 1.010, pH 5.5, with no cells present. Chest x-ray and electrocardiogram were normal.

After admission, Mellaril and Prolixin were discontinued, and Ludiomil (maprotiline hydrochloride) 75 mg at bedtime was instituted. One month later, mental status and physical examination were unchanged, but the blood sodium was 121 mEq/l, chloride 88 mEq/l, potassium 4.5 mEq/l, bicarbonate 28 mEq/l, blood urea nitrogen 6 mg/dl, creatinine 1 mg/dl, pH 7.4, PCO_2 39 mm Hg, and pO_2 90 mm Hg. Urinalysis revealed specific gravity of 1.000, pH 5.5, and no cells in the sediment. Urine sodium was 10 mEq/l, chloride 10 mEq/l, potassium 2.8 mEq/l, osmolality 44 mOsm/kg H_2O. Serum thyroid function test and cortisol levels were normal; and uric acid was 3 mg/dl.

What is the etiology of the hyponatremia in this patient?

A. Psudohyponatremia
B. Reset osmostat
C. SIADH
D. Psychogenic polydipsia
E. Glucocorticoid deficiency

The correct answer is D. This patient has psychogenic polydipsia, and the hyponatremia is due to excessive water drinking. The serum sodium rose to the normal range with water restriction.

Hyponatremia may be seen in patients with or without edema. Patients with edema may be divided into those with a decreased effective arterial blood volume, including congestive heart failure, hepatic cirrhosis, and nephrotic syndrome; or those with an increased effective arterial blood volume, including renal failure and glomerulonephritis with salt retention. Hyponatremia in the non-edematous patient with volume contraction and decreased effective arterial blood volume may be due to gastrointestinal losses, adrenal insufficiency, salt wasting, renal disease, and diuretics. The nonedematous hyponatremic patient who is not volume-contracted may have the syndrome of inappropriate antidiuretic hormone secretion (SIADH), psychogenic polydipsia, or hypothyroidism. Because this patient did not have edema or clinical evidence for volume contraction, the differential diagnosis would be SIADH primary polydipsia or myxedema. Thyroid function tests were normal. Antipsychotic drugs have been associated with SIADH, including Navane (thiothixene hydrochloride) and Elavil (amitriptyline hydrochloride), but Ludiomil has not been associated with this syndrome. Patients with SIADH have concentrated urine with urine osmolality usually greater than 200 mOsm/kg. The low urine osmolality in this patient is consistent with appropriate water excretion in the face of excessive water intake. The low urine sodium does not indicate volume contraction but dilution of the urine with large water excretion.

Hyponatremia secondary to compulsive water drinking in patients with normal renal function, and normal urinary dilution capacity is extremely rare. The patient must drink in excess of 10 liters (probably 20) of water per day. This diagnosis

can only be made in patients who are known to ingest huge quantities of water and who maximally dilute their urine. These patients do not have a defect in urinary diluting or concentrating capacity. Rather, they overwhelm the system with free water overtaking the kidneys' ability to excrete the water load.

This man admitted to drinking a glass of water every five minutes. His urine specific gravity was that of water (1.000), and his urine was as dilute as physiologically possible (44 mOsm/kg H_2O). The low serum uric acid level of 3 mg/dl was also consistent with his water-overloaded state.

If patients with primary polydipsia can restrict their water intake, the urine will become appropriately concentrated, and serum sodium should return to normal. This patient was instructed to restrict his water intake to eight glasses of water a day. He immediately complied. His serum sodium level rose to 135 mEq/l, and his urine osmolality rose to 240 mosm/kg H_2O within one week, confirming the diagnosis of psychogenic polydipsia.

Reference

Hairprasad MK, Eisinger RP, Nadler IM et al. (1980) Hyponatremia in psychogenic polydipsia. Arch Intern Med140: 1639–1342

CASE 34

A 17-year old male is admitted for abdominal pain, fever, and ascites. He is found to have spontaneous bacterial peritonitis, and his physical examination shows a BP of 110/60 mm Hg, pulse 89 beats/min, respiratory rate 22 beats/min, and temperature 38 °C. He was alert and oriented and was noted to be icteric with an enlarged liver, tense ascites, and 2+ periorbital edema.

Laboratory findings showed serum sodium 136 mEq/l, potassium 2.9 mEq/l, chloride 98 mEq/l, bicarbonate 20 mEq/l, blood urea nitrogen 6 mg/dl, creatinine 1 mg/dl, glucose 60 mg/dl, total bilirubin 9.5 mg/dl, and albumin 2.3 g/dl. Urinalysis revealed an osmolality of 300 mOsm/kg H_2O, sodium 5 mEq/l, and potassium 60 mEq/l. In the hospital, repeated measurements of urine osmolality (Uosm) were 300 mOsm/kg H_2O over the next three days while the patient was ingesting one liter of water daily.

Because this patient has an almost isotonic urine, what will his free water clearance (CH_20) be, assuming the patient is ingesting 600 mosm/day? Will he develop hyponatremia?

A. 0.17 liter/day
B. 1.7 liters/day
C. 17 liters/day
D. .017 liter/day
E. Not enough data to calculate the CH_20

The correct answer is A. The patient's free water clearance (CH_20) is calculated as follows:

$$CH_2O = V - Cosm$$
$$Cosm = Uosm \times V \div Posm$$
$$Posm = 2 \times \text{serum Na} + BUN \div 2.8 \div \text{glucose} \div 18$$
$$= (2 \times 136 + 6 \div 2.8\ 60 \div 18) \text{ or } 277 \text{ mosm/kg } H_2O$$
V = osmolar intake/Uosm = 600/300 or 2 liters/day
$$Cosm = 300 \times 2 \div 277 = 2.17 \text{ liters/day}$$
$$CH_2O = 2 - 2.17 \text{ liters/day}$$
$$CH_2O = -0.17 \text{ liter/day}$$

It would appear that, with the condition of the patient, he is unable to generate free water. Thus, on a liter of water intake, he should develop hyponatremia. But actually, he does not. The reason is as follows: It should be mentioned that the urine osmolality (Uosm) includes osmolality contributed by sodium, potassium, and urea. Water that is lost with urea is still *free* water because it is lost without electrolytes and will not contribute to hyponatremia.

It is necessary to think of electrolyte-free water clearance, such as CH_2O and electrolyte osmolar clearance (Cosm).

$$CH_2O = V - Cosm$$
$$Cosm = Uosm \times V \div Posm$$
$$Uosm = 2 \times (\text{U Na} + \text{U K}) \text{ (mOsm/kg)}$$
$$= 2 \times (5 + 60) \text{ mosm/kg}$$
$$= 130 \text{ mosm/kg } H_2O$$
$$Posm = 2 \times \text{P Na} = (2 \times 136) \text{ or } 272 \text{ mOsm/kg } H_2O$$
$$Cosm = 130 \times 2 \div 272 = 0.95 \text{ liter/day}$$
$$CH_2O = V - Cosm \text{ liters/day}$$
$$CH_2O = 2 - 0.95 \text{ liters/day}$$
$$CH_2O = 1.05 \text{ liters/day}$$

It is easy to see why this patient does not develop hyponatremia in spite of essentially isotonic urine.

Reference

Golberg M (1981) Hyponatremia. Med Clin North Am 65:251–269

CASE 35

A six-year old male with cystic fibrosis was admitted for mild chronic obstructive pulmonary disease. On physical examination, the patient has a BP of 120/80 mm Hg, pulse 80 beats/min, respirations 20/min, and temperature 37 °C. There was no

postural change in his BP or pulse. There was no evidence of edema or congestive heart failure. His pulmonary examination shows mild increase in anteroposterior diameter and a slight decrease in breath sounds with mild prolongation in expiratory phase. The patient has been taking indomethacin 25 mg four times per day for joint pain for three months. He is on no other medications.

The laboratory data showed the following: serum sodium 120 mEq/l, potassium 3.8 mEq/l, chloride 93 mEq/l, bicarbonate 24 mEq/l, BUN 5 mg/dl, creatinine 0.8 mg/dl, glucose 90 mg/dl, and uric acid 2.2 mg/dl. Plasma osmolality was 250 mOsm/kg H_2O. The arterial blood gases showed pO_2 82 mm Hg and pCO_2 41 mm Hg on room air. Urine chemistries show osmolality 420 mOsm/kg H_2O and sodium 30 mEq/l. A chest x-ray showed no mass lesions. His thyroid function tests and serum cortisol levels were normal, and serum cortisol responded appropriately to adrenocorticotropic hormone stimulation.

What is the cause of hyponatremia in this patient?

A. SIADH
B. Reset osmost
C. Hypothyroidism
D. COPD
E. Use of indomethacin

The correct answer is A. This patient fits into the euvolemic causes of hyponatremia because there is no clinical evidence of volume depletion or edema. This includes: 1) Syndrome of inappropriate secretion of anti-diuretic hormone (SIADH); 2) hypothyroidism; 3) pure glucocorticoid deficiency due to panhypopituitarism; and 4) some cases of diuretic-induced hyponatremia, which have concomitant hypokalemia and pain and stress.

The inappropriately high urine osmolality does not help in determining the etiology. It merely indicates the existence of a diluting defect that is responsible for the hyponatremia. Although indomethacin may lead to impairment in diluting ability, this defect is mild, and it does not lead to hyponatremia in the absence of other factors that also impair the renal excretion of water. Chronic obstructive pulmonary disease (COPD) may lead to impairment in water excretion, but this depends on the severity of the underlying pulmonary disorder. Patients with mild COPD and normal arterial blood gas measurements have no defect in renal water excretion. COPD patients with hypoxia and/or hypercapnia have a mild decrease in free water excretion by the kidney, but patients with severe COPD manifested by edema, hypoxemia, and hypercapnia have marked inability to excrete water—thus, neither the patient's history of indomethacin use, nor his mild COPD, can readily explain his hyponatremia. In view of the normal thyroid function and cortisol secretion, he may probably have SIADH. He meets the criteria for SIADH, hypotonic hyponatremia, inappropriately high urine osmolality, high urine sodium, absence of cardiac renal, adrenal, thyroid, and liver disease. In addition, he has a low serum concentration of uric acid, which is seen in SIADH. Because SIADH is almost always due to an

underlying etiology, a search for this should be done. Because most cases of SIADH are secondary to pulmonary and central nervous system disorders, a scan of the brain would also be useful to do. In this case, a CT scan disclosed an unexpected brain tumor.

References

Assadi F, John E (1985) Hypourecemia in neonates the syndrome of inappropriate ADH secretion. Pediatr Res 19:424–427

Beck LH (1979) Hypourecemia in the syndrome of inappropriate ADH secretion. N Engl J Med 301:528–530

Maaesaka JK (1996) An expanded views of SIADH, hyponatremia and hypouricemia. Clin Nephrol 46:79–83

CASE 36

A seven-year old boy, weighing 22 kg, and with chronic obstructive lung disease due to cystic fibrosis of the pancreas, is admitted to the hospital with a two-week history of progressive lethargy and obtundation. The physical examination is within normal limits except for the obtundation.

The following laboratory studies are obtained: plasma sodium 105 mEq/l, potassium 4 mEq/l, chloride 72 mEq/l, bicarbonate 21 mEq/l, plasma osmolality 222 mOsm/kg H_2O, urine sodium 78 mEq/l, and urine osmolality 604 mOsm/kg H_2O.

What is the most likely diagnosis? How would you raise the plasma sodium concentration?
If sodium chloride is to be given, what solution should be used and at what approximate hourly rate to get the patient out of danger?

A. Reset osmost
B. SIADH
C. Psudohyponatremia
D. Psychogenic polydipsia
E. Hypoaldosteronism

The correct answer is B. The most likely diagnosis is SIADH. Because the plasma sodium concentration is very low and the urine osmolality high, hypertonic saline and furosemide should be given. The aim should be to raise the plasma sodium concentration to about 120 mEq/l in the first 12 hours. The amount of sodium required can be estimated from:

$$\text{Sodium deficit} = 0.6 \times \text{lean body weight} \times (120 - 105).$$
$$\text{Sodium deficit} = 0.6 \times 22 \times 15$$
$$\text{Serum deficit} = 198\ \text{mEq}$$

Three percent saline contains 513 mEq/l of sodium; therefore, 385 ml over 12 hours (32 ml/h) should raise the plasma sodium concentration to nearly the desired level. Furosemide will enhance this effect by making the urine relatively iso-osmotic to plasma, thereby reducing free water generation by the kidney.

Reference

Rose DB, Post TW (2001) Clinical Physiology of Acid Base and Electrolyte Disorders, 5rd ed, Mc Graw-Hill, New York; pp699–710

CASE 37

An eight-year old girl, treated with hydrochlorothiazide for idiopathic hypercalciuria, is admitted with a four-day history of a viral-like illness, diarrhea, and increasing confusion.

Physical examination reveals a 25 kg female with decreased skin turgor and dehydration but normal BP. The plasma sodium concentration is found to be 168 mEq/l, potassium 4.2 mEq/l, urine sodium concentration 5 mEq/l, and urine osmolality 606 mOsm/kg H_2O.

What are the most important factors in the development of the hypernatremia (select all that apply)?

A. Salt intoxication
B. Decreased free water intake
C. Insensible water and gastric fluid losses
D. Osmotic diuresis
E. Diabetes insipidus

The correct answers are B and C. Two factors were of primary importance in the development of hypernatremia in this patient—insensible water loss, and decreased thirst (due to the depressed mental status) that prevented correction of the water deficit. Diarrhea and diuretics cause hypotonic fluid losses, and the urine osmolality of 606 mOsm/kg H_2O makes diabetes insipidus unlikely because water is not being lost in excess of solute. Because the patient is also sodium and potassium depleted, an infusion of 0.2% saline containing 20 mEq/ KCl per liter would be a reasonable replacement solution, with a goal of decreasing the serum sodium concentration by 5 mEq/l over the next 12 hours. Although there is evidence of ECF volume depletion, the patient's hemodynamic status is not compromised enough to warrant the initial use of 0.45% or 0/9% saline. The estimated volume of total water is 15 liters (25×0.6). It is estimated that the retention of 1 liter of 0.2% saline containing 20 mEq KCl will reduce the serum sodium concentration by 8.1 mEq/l ($[34+20)-168] : [15+\mathrm{I}] = -7.1$). Because the goal is to reduce the serum sodium concentration by 5 mEq/l over the next 12 hours, 0.70 liter (700 ml) of the solution

is required (5: 7.1). With 1 liter added to compensate for ongoing losses (insensible and gastric losses), a total of 1.7 liters will be administered for the next 12 hours, or 141 ml/h. After 12 hours, the patient's clinical status and laboratory values will guide adjustments in the administration of fluids. Using the following conventional formula to estimate the water deficit is not recommended

$$\text{Water deficit} = \text{total body water} \times ([1\text{–}140 : \text{serum sodium concentration}])$$

Although this formula provides an adequate estimate of the water deficit in patients with hypernatremia caused by pure water loss, it underestimates the deficit in patients with hypotonic fluid loss. Furthermore, the conventional formula is not useful when potassium in addition to sodium must be prescribed, because the serum sodium concentration is determined by the ratio of the exchangeable portions of the body's sodium and potassium content to the total volume of body water.

Reference

Adrogue HJ, Madias NE (2000) Hypernatremia N Engl J Med 342:1493–1499

CASE 38

A five-week old white male was admitted to the hospital because of diarrhea and dehydration. His mother was a 22-year old white female who had an uncomplicated pregnancy and delivery. His birth weight was 2.4 kg. He was discharged from the premature nursery at two weeks of age. When seen in the emergency room, he was severely dehydrated and tremulous. His weight was 2.1 kg, temperature 99 °F, pulse 140/min, and respiratory rate 45/min. Physical examination was otherwise unremarkable.

Laboratory data on admission included a hematocrit of 50%, BUN 28 mg/dl, creatinine 1.7 mg/dl, Na^+ 121 mEq/L, Cl^- 118 mEq/l, and HCO_3^- 14 mEq/l. Urinalysis revealed the following: pH 5.5, specific gravity 1.019, trace protein, and no cells. Urinary Na^+, Cl^-, and K^+ were 8, 43, and 11 mEq/l, respectively. Serum glucose concentration was 88 mg/dl, calcium 9.2 mg/dl, and phosphorus 5.1 mg/dl. Liver function studies including SGOT (29 KU/ml), SGPT (13 KU/ml), alkaline phosphatase (197 KU/ml), and bilirubin (0.4 mg/dl) were normal. Serum cortisol (7.3 mcg/dl), thyroxine (9.1 mcg/dl), and aldosterone (71 pg/ml) levels were also normal.

On admission, the diagnosis of sepsis was suspected. Blood, stool, and urine cultures were obtained, and antibiotics were given for 10 days despite negative cultures. After three days of conventional intravenous fluid therapy, the infant was markedly improved. He gained 320 g in weight. His blood pH was 7.38, Na^+ 126, K^+ 4.3, Cl^- 99, HCO_3^- 22 mEq/l, BUN 10 mg/dl, and creatinine 0.3 mg/dl. Hyponatremia was unresponsive to a sodium intake of 10 mEq/kg, or administration of fludrocortisone orally, with 0.05 mg/day. Serum electrolytes values, while receiving salt

supplements and fludrocortisone, were as follows: Na^+ 127, K^+ 4.3, Cl^- 98, and HCO_3^- 21. Urine Na^+ concentrations ranged between 128 and 178 mEq/l. Urine osmolality was 689 mOsm/kg during the initial presentation and fell to an average of 56 mOsm/kg after the ECFV contraction was corrected. Computed tomography and nuclear magnetic resonance of the brain showed no abnormality in the hypothalamic area.

What is the most likely cause for this patient's hyponatremia?

A. Reset osmostat
B. SIADH
C. Hypoaldosteronism
D. Primary polydipsia
E. Hypothyroidism

The correct answer is A. In a patient with euvolemic hyponatremia, the diagnosis of reset osmostat should be considered after exclusion of the diagnosis of inappropriate ADH secretion and other endocrine disorders. Differentiation between the patients with hyponatremia resulting from reset osmostat and those with alterations in total body sodium and water content is important, because management differs according to diagnosis. The hyponatremia in patients with reset osmostat is asymptomatic and requires no specific therapy.

Many clinical disorders may be associated with hyponatremia, including water intoxication, sodium depletion, inappropriate ADH secretion, and endocrine dysfunction. Depending on the state of hydration, the hyponatremia may be associated with decreased, increased, or near-normal amounts of total body sodium. Patients with hyponatremia who have neither edema nor dehydration may have either inappropriate secretion of ADH, hypothyroidism, or secondary adrenal insufficiency. Euvolemic hyponatremia can also be secondary to an abnormal setting of the hypothalamic osmoreceptors. In this type of hyponatremia, renal diluting capacity is normal, but the normal regulation of serum tonicity takes place at a lower osmolality threshold.

The criteria for the diagnosis of reset osmostat in a patient with chronic hyponatremia includes: 1) normovolemic hypotonic hyponatremia, 2) normal renal, adrenal, and thyroid function, 3) ability to concentrate the urine when serum tonicity is raised above the reset level or serum osmolality, 4) ability to excrete a standard water load, with excretion of more than 80% within 4 hours and maintenance of urine osmolality at or below 100 mosm/kg during sustained water diuresis, and 5) maintenance of normal sodium balance without correction of hyponatremia during salt loading.

The mechanism responsible for *resetting of the osmostat* is not understood. Pathophysiology appears to be related to a primary reduction in the osmolality of cell fluids or a widespread increase in cell membrane permeability, resulting in intracellular accumulation of osmotically inactive sodium in exchange for potassium. Intracellular reduction in solute concentration, whether associated with primary

intracellular inactivation or in exchange for potassium, could explain the sustained hyponatremia. Initially, the decreased cellular osmolality results in extracellular volume depletion and stimulation of ADH release. This would then cause water retention, dilutional hyponatremia and resetting of osmoregulatory mechanisms to a subnormal level. Therefore, ADH release fluctuates around a serum osmolality that is low for normal individuals but normal for the patient.

Reference

Assadi F, Agrawal R, Jocher C, et al. (1986) Hyponatremia secondary to reset osmostat. J Pediatr 108:262–264

CASE 39

A 16-year old female was referred for evaluation of hypokalemia. She has no significant past medical history, does not smoke or drink alcohol, and denies the use of any medications. Family history is negative, but she is not sure if her parents or siblings have been diagnosed with hypertension. She avoids bread, pasta, and desserts. She denies the use of vitamins or herbal preparations or licorice, but she does eat grapefruit. Her most recent clinic visit was three years ago, at which time there were no abnormal physical or laboratory findings. Recently, the patient began to note occasional fatigue and muscle weakness during exercise. She also experienced occasional abdominal pain for which she saw her physician.

Physical examination was generally normal without edema but with mild lower extremity muscle weakness. BMI was 25.1 kg/sq m, BP 152/92 mmHg with little postural change, pulse 84 beats/min, respiration 12/min, and temperature 37 °C.

Laboratory studies showed blood sodium 142 mEq/l, potassium 2.9 mEq/l, bicarbonate 29, chloride 106 mEq/l, BUN 12, and serum creatinine 0.8 mg/dl. Urinalysis had specific gravity 1.030, otherwise negative with unremarkable sediment.

What further studies would you like to obtain at this time?

A. Spot urine for potassium
B. 24-hr urine for potassium and creatinine
C. Serum aldosterone level
D. Serum cortisol level
E. Spot urine for anion gap

The correct answer is A. The first step is the evaluation of measured urinary potassium excretion. A value exceeding 25 mEq/24 h is evidence of inappropriate urinary potassium excretion in the face of hypokalemia and helps to rule out diarrhea or laxative abuse as the cause.

Similar information can at times be obtained with spot urine potassium concentration measurements, but this value is also dependent upon urine volume and may

not always be an accurate reflection of urinary excretion when fluid intake and urine volume are reduced.

A 24-hr urine collection contained 45 mEq potassium and 1400 mg of creatinine in a volume of 1300 ml.

Which of the following have we ruled out as a likely cause of the hypokalemia with this measurement?

A. Excess gastrointestinal losses
B. Excess urinary losses
C. Lower GI tract potassium loss
D. Surreptitious diuretic abuse
E. None of the above

The correct answer is B. The urinary potassium excretion is inappropriate for someone with hypokalemia. This indicates that the likely cause is not lower GI loss of potassium. Upper GI loss could still be a proximate cause because the predominant mechanism for hypokalemia in that situation is renal due to secondary hyperaldosteronism and bicarbonate in the tubular fluid acting as a nonreabsorbable anion. The actual potassium loss from gastric losses is not very much because potassium concentration in gastric fluid is only 5–10 mEq/l.

Which of the following conditions remain under diagnostic consideration (select all that apply)?

A. Bartter's syndrome
B. Gitelman's syndrome
C. Diuretic abuse
D. Primary hyperaldosteronism
E. Secondary hyperaldosteronism
F. Apparent mineralocorticoid excess
G. Liddle's syndrome

The correct answer is D, E, F, and G. The presence of hypertension and mild metabolic alkalosis indicates that all causes of primary and secondary hyperaldosteronism, as well as Liddle's syndrome and the various forms of apparent mineralocorticoid excess, have to be considered. BP would not be typically elevated with Bartter's or Gitelman's syndrome, but the abuse of diuretics in hypertensive patients should still be considered.

Which of the following studies would you like to order at this time (select all that apply)?

A. Serum cortisol concentration
B. Diuretic screen concentration

C. Plasma aldosterone concentration
D. Plasma aldosterone and renin activity
E. Plasma magnesium concentration

The correct answers are C and D. Because we are considering the causes of hypokalemia associated with metabolic alkalosis and hypertension, measurements of plasma aldosterone concentration and plasma renin activity are necessary to differentiate the various conditions.

Hypomagnesemia is not a cause of hypertension, nor is diuretic abuse. Diuretic abuse in a hypertensive patient might be a possibility, but it would be of value to first document an elevated level of both renin and aldosterone. A plasma cortisol measurement may have value later but should not be the initial test in trying to make this differentiation.

Now, serum aldosterone level is 2.2 ng/dl (normal upright 4–31) and plasma renin activity <0.1 ng/ml/hr (normal upright 0.5–4).

Which of the following conditions remain under diagnostic consideration?

A. Primary hyperaldosteronism
B. Liddle's syndrome
C. Renovascular hypertension
D. Diuretic abuse
E. Syndrome of apparent mineralocorticoid excess
F. Cushing's syndrome
G. DOCA secreting tumor
H. Renin secreting tumor

The correct answer is E. The data are clearly consistent with suppressed levels of aldosterone and renin. The differential diagnosis, therefore, now consists of conditions associated with nonaldosterone-mediated mineralocorticoid excess.

Diuretic abuse, primary, and secondary hyperaldosteronisim are no longer considerations because all would have elevated levels of aldosterone. Diuretic abuse and secondary hyperaldosteronism, renovascular hypertension and rennin-secreting tumors would also be associated with elevated plasma renin activity.

The defect in the syndrome of apparent mineralocorticoid excess is due to inactivating mutations in the 11β-hydroxysteroid dehydrogenase Type 2 gene (11β-HSD-2). This enzyme is mainly expressed in the kidney and converts the biologically active cortisol into the receptor inactive form of cortisone. The effect is physiologically important, because cortisol binds as avidly as aldosterone to the mineralocorticoid receptor. Although cortisol has a much higher plasma concentration than aldosterone, it does not have a physiologically relevant mineralocorticoid activity, because it is converted locally to cortisone. In apparent mineralocorticoid excess, however, the reduced activity of 11β-HSD-2 allows normal levels of cortisol to induce a marked mineralocorticoid activity. Therapy most commonly includes

spironolactone. The diagnosis of apparent mineralocorticoid excess is made by an increased ratio of urinary free cortisol to urinary free cortisone.

At this point, it might be valuable to review the patient's history. Which of the following aspects of patient's history might have significance to her laboratory data?

A. Social history
B. Dietary history
C. Family history
D. Current medications
E. History of present illness

The correct answer is B. Two aspects of the dietary history are very important. She denies ingesting licorice, but apparently ingests large amounts of grapefruit. Acquired apparent mineralocorticoid excess is seen with ingestion of licorice and grapefruit. Dietary flavinoids present in licorice and in grapefruit inhibit the enzyme 11 beta-hydroxysteoid dehydrogenase allowing cortisol to occupy the mineralocorticoid receptor.

A decision was made to treat the patient. She was begun on spironolactone, 400 mg/day. She returns 10 days later. Her BP was 160/90 mmHg and her serum sodium was 140 mEq/l, potassium 3.1 mEq/l, chloride 107 mEq/l, and bicarbonate 30 mEq/l. She was then switched to amiloride, and returned two weeks later. At this point, BP was 127/78 mmHg.

What is the likely diagnosis?

A. Grapefruit-induced hypokalemia
B. Congenital syndrome of apparent mineralocorticoid excess
C. Liddle's syndrome
D. Gitelman's syndrome
E. Bartter's syndrome

The correct answer is C. The differential response to amiloride is indicative of Liddle's syndrome. The causes of apparent mineralocorticoid excess (genetic defect in 11 beta-hydroxysteroid dehydrogenase or acquired abnormality in 11 beta-hydroxysteroid dehydrogenase due to licorice or grapefruit) is enhanced mineralocorticoid activity by virtue of occupation of the mineralocorticoid receptor by glucocorticoids. Thus, the symptoms should respond to receptor occupation by spironolactone.

In contrast, Liddle's syndrome is due to enhanced activity of the sodium channel which is unaffected by spironolactone but is blocked by amiloride.

How would you confirm the diagnosis (select all that apply)?

A. Genetic testing
B. Measurement of the ratio of cortisol to cortisone in a 24-hr urine
C. Measurement of urinary 17 (OH) steroid
D. Measurement of plasma aldosterone level
E. Measurement of plasma renin level

The correct answers are A and B. Genetic testing can confirm the defect in Liddle's syndrome. At that point, family members should be evaluated so that any of them with hypertension can receive appropriate treatment. Diagnosis of apparent mineralocorticoid excess syndrome is usually done by demonstration of an excess of free urinary cortisol over free urinary cortisone in a 24-hour urine collection, although genetic testing can identify the congenital defect.

References

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Botero-Velez M, Curtis JJ, Warnock DG (1994) A brief report: Liddle's syndrome revisited-A disorder of sodium reabsorption in the distal tubule. N Engl J Med 33:178–181

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Morineau G, Sulmont V, Salomon B, et al. (2006) Apparent mineralocorticoid excess: Report of six new cases and extensive personal experience. J Am Soc Neprol 17:3176–3184

Palmer BF, Alpern RJ (1977) Metabolic alkalosis. J Am Soc Nephrol 8:1462–1469

CASE 40

A 12-year old girl with hypertension who has had nausea and vomiting for two days is brought to the hospital by her mother. According to the mother, the patient has experienced some intellectual impairment during the same period. Her medications include hydrochlorothiazide, 25 mg twice daily, and diazepam for chronic anxiety. Except for lethargy and prominent muscular twitching, physical examination fails to show any focal neurological deficits. The BP is 160/90 mmHg in both the supine and upright positions. Laboratory studies show sodium 109 mEq/l, potassium 2.8 mEq/l, chloride 63 mEq/l, and bicarbonate 33 mEq/l.

Of the following, which constitutes the most reasonable therapeutic intervention in managing this patient's hyponatremia?

A. Infusion of 2 liters 0.9% saline over 4 hours
B. Discontinuation of hydrochlorothiazide and administration of furosemide
C. Water restriction (300 ml over the next 24 hours)

D. Discontinuation of hydrochlorothiazide plus the administration of potassium chloride and 3% sodium chloride at a rate calculated to raise serum sodium by approximately 12 mEq/l in the next 24 hours
E. Administration of Compazine® (to stop nausea and vomiting) and potassium chloride

The correct answer is D. The slow rate of correction of the serum sodium (0.5 mEq/hr) is not associated with CNS myelinolysis. The potassium replacement will also cause the serum sodium to rise as water moves into cells with the intracellular osmolyte.

Reference

Rose BD (1989) Clinical physiology of acid-base and electrolyte disorders. 3d (ed). New York: McGraw-Hill, pp 589–603

CASE 41

A 15-year old female has a brain tumor. She has been stuporous. The patient is taking medications, and nutritional support has been provided by hyperalimentation. The nurse notes that the patient's urine volume has increased to 3 liters/day; whereas her BP is 110/60 mmHg and sweating and skin turgor are decreased. The serum sodium is 150 mEq/l, potassium 3.2 mEq/l, bicarbonate 25 mEq/l, chloride 92 mEq/l, glucose 350 mg/dl, BUN 50 mg/dl, and creatinine 1.5 mg/dl. Urine osmaolaity is 350 mOsm/kg. Urine sodium is 60 mEq/l.

The most likely cause of the hypernatremia is:

A. Central diabetes insipidus
B. Nephrogenic diabetes insipidus
C. Osmotic diuresis
D. Diarrhea due to enteral hyperalimentation
E. Addition of hypertonic sodium to the hyperalimentation solution

The correct answer is C. Osmotic diuresis is the most likely cause of hypernatremia in this patient because of elevated blood glucose and hyperalimentation leading to increasing urea production.

Reference

Richet GC (1994) Osmotic diuresis before Homer W. Smith: a winding path to renal physiology 45:1241–1252

CASE 42

An 18-year old male developed polyuria following resection of recurrent craniopharyngioma. His brain tumor was first detected when he was 10 years old. Surgical resection at that time was followed by the development of panhypopituitarism and diabetes insipidus requiring chronic hormonal replacement therapy. At 14 years of age, a recurrent tumor was treated with radiation and a ventriculo-peritoneal shunt was placed. Tumor growth led to another surgical resection six days ago. The procedure went smoothly and his recovery was uncomplicated until yesterday when he developed polyuria followed by headache and increasing lethargy. He has just had a generalized tonic-clonic seizure. His medications include synthyroid (levothyroxine sodium), carafate, hydrocortisone, and desmopressin acetate.

Examination revealed an obese, adolescent male who was afebrile, tachycardia (pulse 102/min) and relatively hypotensive (BP 104/56 mmHg). His chest was clear and cardiac exam was normal. He appeared to have adequate peripheral perfusion. Urinalysis showed specific gravity 1.012, pH 6, negative dipstick, and unremarkable microscopy. Serum sodium was 123 mEq/l, potassium 3.4 mEq/l, chloride 92 mEq/l, bicarbonate 25 mEq/l, BUN 17 mg/dl, creatinine 0.6 mg/dl, glucose 118 mg/dl, uric acid 5.2 mg/dl, and osmolality 259 mOsm/kg. Urine sodium was 224 mEq/l, potassium 22 mEq/l, chloride 261 mEq/l, creatinine 15 mg/dl, and osmolality 509 mOsm/kg. Fractional sodium excretion was 21%. His urine output over the last three days averaged 290 ml/h, exceeding his fluid intake.

Which ONE of the following is the MOST likely cause of hyponatremia in this patient?

A. Syndrome of inappropriate ADH
B. Diabetes insipidus
C. Hypoaldosteronism
D. Cerebral salt wasting syndrome
E. Interstitial nephritis

The correct answer is D. This patient abruptly developed polyuria, hypovolemia, and symptomatic hyponatremia five days after intracranial surgery. The differential diagnosis of his polyuria can be narrowed by examining the urine osmolality. An osmolality less than 100 mOsm/kg indicated deficiency of, or resistance to, ADH while hyperosmolar urine indicates a solute diuresis. This patient's urine osmolality exceeded 500 mOsm/kg, demonstrating that desmopressin was effective enough to produce a high rate of free water absorption (high urine flow rate on post-operative days) that undoubtedly contributed to his hyponatremia. Diabetes insipidus did not appear to be a major factor in this patient's decompensations.

The etiology of a solute diuresis can be determined by measuring urine electrolyte concentrations. The sum of this patient's urine sodium and chloride levels approximated his urine osmolality. Therefore, he was experiencing a *saline diuresis* that, in the presence of hypovolemia and hyponatremia, reflected inappropriate renal

salt wasting. Causes of sodium wasting include underlying renal disease, medications, hypoaldosteronism, and cerebral salt wasting. This patient medical history provided no evidence for a salt-losing interstitial nephritis or obstructive uropathy. He had not received any drugs known to affect sodium excretion. Mineralocorticoid secretion is generally normal in patients with hypopituitarism and this patient's low serum potassium level was not consistent with hypoaldosteronism.

The development of excessive natriuresis and hyponatremia shortly following brain surgery is consistent with the syndrome of cerebral salt wasting. This disorder can be differentiated from the syndrome of inappropriate ADH secretion by the presence of markedly negative water and sodium balance, higher rates of urine flow and sodium excretion, as well as a normal serum uric acid level. Treatment consists of vigorous saline replacement and, possibly, pharmacological doses of mineralocorticoids.

Reference

Ganong CA, Kappy MS (1993) Cerebral salt wasting in children: the need for recognition and treatment. Am J Dis Child 147:167–169

CASE 43

A 16-year old girl presents to the emergency room after ingesting a large amount of aspirin in a suicide attempt. The following laboratory tests find: sodium 138 mEq/l, potassium 3.2 mEq/l, chloride 102 mEq/l, bicarbonate 18 mEq/l, arterial pH 7.48, and pCO2 21 mmHg. Urine electrolytes include: sodium 38 mEq/l, chloride <10 mEq/l, and potassium 45 mEq/l.

Which ONE of the following statements is MOST correct regarding this patient?

A. The cause of the hypokalemia is a shift of K^+ into cells.
B. The serum uric acid levels are likely to be low normal level.
C. The high urine Na^+ relative to the urine Cl^- is due to proximal tubular dysfunction.
D. Lactic acid levels are likely to be normal.
E. Similar findings would likely be present in a 5-year old child who ingested a similar amount of aspirin.

The correct answer is B. With high dose aspirin therapy, or in the setting of an aspirin overdose, the renal excretion of uric acid is increased and hypouricemia may be present. In this setting, hepatic glucuronidation of salicylic acid is saturated and large quantities of free salicylate are filtered into the tubule. Free salicylate interferes in the reabsorption of uric acid by the proximal tubule accounting for the uricosuric effect. Aspirin overdose is associated with a variety of acid-base and electrolytes

disturbances. Salicylates have a direct stimulatory effect on the respiratory center such that respiratory alkalosis is a prominent feature in the overdose setting. An anion gap metabolic alkalosis is also present due primarily to increased production and accumulation of ketoacids and lactic acid. Salicylic acid accumulation accounts for only a minor component of the increase in anion gap. Lactic acid production (choice D) is increased due to the uncoupling effect of aspirin on oxidative phosphorylation in the mitochondria. Adult patients with aspirin overdose usually present with a mixture of respiratory alkalosis and anion gap metabolic acidosis. A pure metabolic acidosis is unusual in adults. By contrast, children with aspirin overdose (choice E) may present with anion gap acidosis alone very soon after ingestion. Hypokalemia (choice A) is the result of increased renal potassium excretion. Increased distal delivery of sodium (due to the sodium salicylate excretion—choice C), in combination with increased circulating aldosterone (secondary to volume depletion), accounts for the renal potassium wasting.

Reference

Temple A (1978) Pathophysiology of aspirin overdose toxicity, with implications for management. Pediatrics 62:873–876

CASE 44

A 12-year old girl comes to the emergency department because of paresthesias, perioral numbness, and generalized weakness. She denies use of any medications. Her BP is 120/88 mmHg, and a physical examination is only remarkable for multiple dental caries. Earlier in the day, she had ingested a large piece of cake at a birthday party. Laboratory studies found: sodium 130 mEq/l, potassium 2.9 mEq/l, chloride 90 mEq/l, and bicarbonate 28 mEq/l. Urine electrolytes included: sodium 28 mEq/l, potassium 38 mEq/l, chloride <10 mEq/l, pH 6.2, and aurinary calcium:creatinine ratio of 0.2 mg/mg.

Which ONE of the following is the MOST likely diagnosis?

A. Bartter syndrome
B. Surreptitious vomiting
C. Gitelman syndrome
D. Hypokalemic periodic paralysis
E. Licorice ingestion

The correct answer is B. The patient presents with hypokalemic metabolic alkalosis with a normal BP. The urinary electrolytes are most consistent with vomiting. The increased urinary K^+ in the setting of hypokalemia suggests renal K^+ wasting. The increase in urinary Na^+ relative to the urine Cl^- is due to the nonreabsorbable anion effect of bicarbonate. Urine Cl^- is low in vomiting due to avid renal retention

of NaCl due to underlying volume depletion. Bartter's syndrome (choice A) mimics the effect of a loop diuretic and is associated with increased urinary K^+ excretion complicated by increased urinary Na^+ and Cl^- concentration. Bartter's syndrome is also associated with hypercalciuria and would be associated with a urine Ca/creatinine ratio greater than 0.22 mg/mg. Gitelman syndrome (choice C) mimics the use of a thiazide diuretic and like Bartter's syndrome would be associated with increases in urinary Na^+, K^+, and Cl. However, urinary Ca^{++} excretion is low in this disorder (urine ca^{++}/creatinine ration less than 0.1 mg/mg). Licorice ingestion (choice E) presents with hypokalemic alkalosis in association with increased BP. The active component in licorice is glycyrrhetinic acid. This substance inhibits the enzyme 11-β-hydroxysteroid dehydrogenase Type II, allowing cortisol to act as the major endogenous mineralocorticoid. Urinary electrolytes show increased urinary Na^+, K^+, and Cl^- concentration. Hypokalemic periodic paralysis (choice D) is due to a shift of K^+ into cells in the setting of normal total body K^+ content. During the acute attack, urinary K^+ should be low and not increased.

References

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Ooi TC, Poznanski WJ, Ooi DS (1983) The value of urinary chloride measurement in distinguishing surreptitious vomiting from Bartter's syndrome. Clin Biochem 16:263–265

Schepkens H, Hoeben H, Vanholder R, et al. (2001) Mimicry of surreptitious diuretic ingestion and the ability to make a genetic diagnosis. Clin Nephrol 55:233–237

CASE 45

A 19-year old man is evaluated because of increasing dyspnea. He is HIV positive. Two months ago, he was found to have a CD4 count of 210 cell/*u*l and an HIV RNA level of 14,000 copies/ml. Highly active antiretroviral therapy (HAART) was started at that time. The chest radiograph shows bilateral infiltrates. His BP is 120.76 mmHg. Laboratory studies on admission find sodium 131 mEq/l, potassium 4.8 mEq/l, chloride 95 mEq/l, bicarbonate 22 mEq/l, BUN 20 mg/dl, and serum creatinine 1.3 mg/dl. Further evaluation leads to a diagnosis of pneumocystis carini pneumonia and therapy with pentamidine is begun, due to severe allergy to sulfa-containing drugs. His HAART is continued. Repeat laboratory studies one week later show sodium 132 mEq/l, potassium 6.2 mEq/l, chloride 93 mEq/l, bicarbonate 24 mEq/l, BUN 21 mg/dl, and creatinine 1.4 mg/dl. The urinalysis is normal.

Which ONE of the following choices is the MOST likely cause of the increased serum K^+ concentration in this patient?

A. Rhabdomyolysis due to HAART-induced muscle toxicity
B. Shift of K^+ out of cells due to HAART-induced lactic acidosis

C. Blockade of distal renal tubule K excretion due to pentamidine
D. Development of proximal RTA as a result of HAART therapy
E. Addison's disease due to adrenal HIV infection

The correct answer is C. Pentamidine in the tubular lumen of the collecting duct competes for Na movement on the epithelial Na channel. The decrease in Na reabsorption decreases luminal electronegativity, thus decreasing the driving force for potassium secretion. While rhabdomyolysis (choice A) can be a cause of hyperkalemia, there is no other evidence of this disorder. In particular, the serum creatinine is unchanged and there is no mention of dipstick positive blood in the absence of red blood cells to indicate the excretion of myoglobin in the urine. Lactic acidosis (choice B) can be associated with hyperkalemia due to leakage of K^+ out of cells as a result of cell death or ischemic. The absence of an increased anion gap excludes this disorder. HAART (choice D) can be associated with the development of proximal renal tubular acidosis (RTA). However, proximal RTA gives rise to hypokalemia. Adrenal insufficiency (choice E) can occur in HIV-infected patients due to a variety of causes, often infectious in origin, such as cytomegalovirus-induced adrenalitis. The short time course in this case is inconsistent with this diagnosis. In addition, hyperkalemia due to adrenal insufficiency would be accompanied by other findings such as a normal gap metabolic acidosis, hyponatremia, and evidence of renal salt wasting.

References

Palmer BF (2004) Managing hyperkalemia caused by inhibition of the renin-angiotensin-aldosterone system. N Engl J Med 351:585–592

Quimby D, Brito MO (2005) Fanconi syndrome associated with use of tenovir in HIV-infected patients: a case report and review of the literature. AIDS Read 15:357–364

CASE 46

A seven-year old girl with ESRD due to FSGS is taken to the operating room for incision and drainage of a perirectal abscess. She takes 50 mg metoprolol twice daily. Vital signs are: temperature 37 ° C, pulse 94 beats/min, respirations 18 breaths/min, and BP 140/84 mmHg. Laboratory studies show sodium 138 mEq/l, potassium 5.1 mEq/l, chloride 103 mEq/l, bicarbonate 21 mEq/l, BUN 65 mg/dl, and creatinine 21 mEq/l. She was last dialyzed one day before admission. In the operating room, BP drops to 90/60 mmHg. A neosynephrine (phenylephrine) drip made up in a D5W-containing solution is started and continued throughout the procedure with stabilization of BP. In the recovery room, profound weakness is noted, preventing extubation. Renal electrolyte measurements show a serum potassium concentration of 6.6 mEq/l.

Which ONE of the following is the MOST likely explanation for the development of hyperkalemia during the operative procedure?

A. β–adrenergic stimulation leading to K^+ efflux from the intracellular compartment
B. α-Adrenergic stimulation leading to K^+ efflux from the intracellular compartment
C. Metoprolol-induced suppression of renin leading to hypoaldosteronism
D. Insulin resistance leading to impaired insulin-mediated K^+ uptake into the intracellular compartment
E. Rhabdomyolysis as a complication of malignant hyperthermia

The correct answer is B. Phenylephrine is an alpha adrenergic receptor agonist used to support BP. Alpha adrenergic stimulation leads to K^+ efflux from the intracellular to extracellular fluid space. It is likely that the risk for hyperkalemia was further increased due to K^+ release from injured tissue during the abscess drainage procedure in a patient with no renal function. Beta adrenergic stimulation (choice A) causes hypokalemia by shifting K^+ into the intracellular fluid space. Beta receptor blockade (choice C) can suppress renin and potentially cause hypoaldosteronism, but impairment of renal K^+ secretion through this mechanism would not be an issue in a dialysis patient. Insulin resistance (choice D) is often present as a complication of uremia but would not explain the acute development of hyperkalemia in this patient. Malignant hyperthermia (choice E) can cause hyperkalemia as a result of rhabdomyolysis, but the absence of fever makes this diagnosis unlikely.

References

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Moratinos J, Reverte M (1993) Effects of catecholamines on plasma potassium: the role of alpha- and beta-adrenoreceptors. Fundam Clin Pharmacol 7:143–153

CASE 47

A 12-year old boy who was in good health suddenly feels weak and is unable to walk. He's lost 5 kg in three months despite having a good appetite. He also complains of a sore throat but has no other symptoms. There is no family history of similar findings and the patient has never experienced these symptoms before. On admission, his physical examination reveals a thin male with BP 135/70 mmHg, pulse 120 beats/min, and moist skin. His neck has no lymphadenopathy, the thyroid is palpable and tender, his deep tendon reflexes are absent, and no sensory changes are demonstrable. Laboratory studies show sodium 140 mEq/l, potassium 2.0 mEq/l, chloride 100 mEq/l, bicarbonate 24 mEq/l, BUN 10 mg/dl, and creatinine 1.0 mg/dl.

Which ONE of the following set of URINE electrolytes (in mEq/l) would be MOST consistent with this patient's most likely underlying disorder?

A. Na^+ 102; K^+ 10; Cl^- 98
B. Na^+ 60; K^+ 40, Cl^- <10
C. Na^+ <10; K^+ 15; Cl^- 80
D. Na^+ 72; K^+ 48; Cl^- 136
E. Na^+ <10; K^+ 50; Cl^- <10

The correct answer is A. The patient has features consistent with acquired hypokalemic periodic paralysis occurring in association with hyperthyroidism. Hyperthyroidism is suggested by weight loss and tachycardia. The renal response to the sudden shift of K^+ into cells is to maximally lower urinary K^+ concentration. Because there is no disturbance in extracellular fluid volume, the urinary Na^+ and Cl^- are not low and reflect dietary NaCl intake. The values in choice B reflect renal K^+ wasting due to the effect of non-reabsorbable anion (low urine Cl^-). The urinary K^+ is appropriately low in choice C; however, the low Na^+ and increased urine Cl^- is suggestive of chronic diarrhea.

Urine Cl^- is increased in chronic diarrhea due to increased urinary excretion of NH4Cl. Choice D shows evidence of renal K^+ wasting and is typical of ongoing loop or thiazide diuretic use. The urine K^+ in choice E also suggests renal K^+ wasting. In addition, the low urinary Na^+ and Cl^- are typical of a patient with volume contraction.

References

Battle DC, Hizon M, Cohen E, et al. (1988) The use of the urinary anion gap in the diagnosis of hyperchloremic metabolic acidosis. N Engl J Med 318:594–599

Groeneveld J, Sijpkens Y, Lin S, et al. (2005) Approach to the patient with severe hypokalemia: the potassium quiz. Q J Med 98:305–316

CASE 48

An eight-year old boy is referred to you because of the recent discovery of hypertension, hypokalemia, and metabolic alkalosis. His siblings had similar findings. His BP is 150/90 mmHg. Laboratory studies fine sodium 140 mEq/l, potassium 2.8 mEq/l, chloride 90 mEq/l, bicarbonate 32 mEq/l, and arterial ph 7.48. Urine electrolytes are: sodium 50 mEq/l, potassium 80 mEq/l, and choloride 140 mEq/l. Plasma renin activity is 0.5 U, aldosterone is 4 ng/dl, and cortisol is normal. Amiloride, but not spironolactone, improves his hypertension and electrolyte abnormalities.

Which ONE of the following choices offers the MOST likely diagnosis in this patient?

A. Renal artery stenosis due to fibromuscular dysplasia
B. Liddle syndrome
C. Ingestion of licorice
D. Cushing's syndrome
E. Surrepitious use of loop diuretics

The correct answer is B. The patient presents with hypokalemic metabolic alkalosis in the setting of hypertension. Other members of family have similar findings. The clinical features of patients with Liddle's syndrome are consistent with constitutive activation of the epithelial Na^+ channel in the collecting duct. Renin and aldosterone levels are suppressed. Amiloride or triamterene but not spironolactone, are effective therapies since the defect is at the level of the Na channel. Renal artery stenosis (choice A) would be associated with increased renin and aldosterone levels and would be sensitive to either amiloride or spironolactone. Renin and aldosterone levels are low in patients who ingest licorice (choice C) however both spironolactone and amiloride should be effective in such patients. Similarly, both spironolactone and amiloride should be effective therapy in patients with Cushing's disease (choice D). Surreptitious use of loop diuretics (choice E) would lead to increased renin and aldosterone levels and BP should not be increased.

References

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Palermo M, Quinkler M, Stewart PM (2004) Apparent mineralocorticoid excess syndrome: an overview. Endocrinol Metabol 48:687–696

Palmer BF, Alpern RJ (1998) Liddle's syndrome. Am J Med 104:301–309

CASE 49

A 15-year old boy with a 10-year history of insulin-dependent diabetes mellitus is referred to you for evaluation of hyperkalemia. He complains of light-headedness. His father died in a motor vehicle accident four years ago but was said to have had problems with increased potassium when he was younger. Physical examination reveals BP 100/70 mmHg supine and 85/65 mmHg standing. Laboratory studies show sodium 130 mEq/l, potassium 6.2 mEq/l, chloride 104 mEq/l, bicarbonate 16 mEq/l, creatinine 0.9 mg/dl, and BUN 23 mg/dl. Plasma renin activity and aldosterone level are both increased. Urine electrolytes are sodium 100 mEq/l, potassium 10 mEq/l, chloride 90 mEq/l, and pH 5.0.

Which ONE of the following statements about this patient is MOST correct?

A. Frequent pulmonary infections would likely be present.
B. The need for treatment to prevent hyperkalemia and salt-wasting is likely to decrease over time.
C. The patient is likely to have a Type IV renal tubular acidosis due to Type 1 diabetes.
D. The sweat choloride in this patient is likely to be increased.

The correct answer is B. This patient presents with evidence of renal salt wasting, hyperkalemic normal gap metabolic acidosis, and increased circulating renin and aldosterone levels. The patient's father had similar problems with potassium that later resolved, suggesting a familial disorder. These findings best fit with autosomal dominant form of pseudohypoaldosteronism Type 1. This form of the disease is due to an inactivating mutation in the mineralocorticoid receptor, giving rise to manifestations limited to the kidney. For reasons that are not entirely clear, the clinical manifestations tend to resolve over time. External manifestations such as skin rash and frequent pulmonary infections (choice A) is a feature of the autosomal recessive form of pseudohypoaldosteronism Type I, in which the defect is at the level of the epithelial Na^+ channel. Skin lesions in the autosomal recessive form of the disease have been attributed to increased sweat Na concentration making choice D false. The development of Type IV renal tubular acidosis (choice C) due to long standing diabetes is typically associated with hypertension and low circulating renin and aldosterone levels. Pseudohyperkalemia (choice E) is not accompanied by metabolic acidosis and is not a consideration given the clinical course of this patient.

References

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Martin JM, Calduch L, Monteagudo C, et al. (2005) Clinico-pathological analysis of the cutaneous lesions of a patient with Type I pseudohypoaldosteronism. J Eur Acad Dermatol Venereol 19:377–379

CASE 50

A five-year old boy presents to the emergency room with shortness of breath and fever for three days. His oral intake has decreased during this period of time. Physical examination reveals: temperature 38 °C; respirations 24 breaths/min, BP 110/70 mmHg supine and 90/60 mmHg standing; and pulse 76 beats/min. The remainder of the examination is significant only for rales in the right upper lobe. Laboratory studies finds sodium 140 mEq/; potassium 4.3 mEq/l; choloride 102 mEq/l; bicarbonate 22 mEq/l; BUN 28 mg/dl; and creatinine 1.2 mg/dl. Chest x-ray shows a right upper lobe infiltrate. He is treated with intravenous

ticarcillin/clavulanate. Two days later, his repeat laboratory studies show sodium 138 mEq/l, potassium 2.6 mEq/l, chloride 90 mEq/l, and bicarbonate 34 mEq/l. Urine electrolytes are sodium 35 mEq/l, potassium 40 mEq/l, choloride <10 mEq/l, and urinary pH 5.5.

Which ONE of the following choices is the MOST likely cause for the development of the fluid-electrolyte disorder in this patient?

A. Vomiting
B. Administration of loop diuretics
C. Posthypercapnic metabolic alkalosis
D. Effects of a non-reabsorbable anion

The correct answer is D. The administration of ticracillin to a volume-depleted patient can cause hypokalemic metabolic alkalosis due to the nonreabsorbable anion effects of ticracillin. Despite the presence of volume contraction, urinary Na^+ is increased because ticracillin is excreted as Na^+ salt. The increases in distal Na^+ delivery combined with increased circulating aldosterone (due to volume contraction) stimulates renal K^+ secretion in part due to increased luminal electronegativity. Distal H^+ ion secretion is also stimulated by more lumen negative charge, which results in the increase in H^+ ion secretion. Vomiting (choice A) is associated with increased renal K^+ secretion due to bicarbonate acting as a non-reabsorbalbe ion. However with active vomiting the urine pH will be alkaline as a result of the urinary excretion of sodium bicarbonate. Post hypercapnic metabolic alkalosis (choice C) is seen in patients with chronic respiratory acidosis in whom the elevated pCO2 has been rapidly corrected. Ongoing administration of a loop diuretic (choice E) is associated with hypokalemic alkalosis but is associated with increased urinary concentration of Na^+, K^+, and Cl^-. Remote use of a loop diuretic is also a consideration, however urine Na^+ and Cl^- would both be decreased as a result of diuretic-induced volume contraction.

References

Nanji AA, Lindsay J (1982) Ticracillin associated hypokalemia. Clin Biochem 15:118–119
Palmer BF, Alpern RJ (1997) Metabolic alkalosis. J Am Soc Nephrol 8:1462–1469

CASE 51

A 15-year old boy was admitted to the hospital with hematemesis. An upper gastrointestinal endoscopy showed a bleeding duodenal ulcer. The procedure was complicated by the development of an aspiration pneumonia and respiratory failure. A continuous infusion of intravenous lorazepam was required to control agitation and minimize peak respiratory pressures. Admission laboratory studies showed: sodium 142 mEq/l, potassium 4.3 mEq/l, chloride 105 mEq/l, bicarbonate 22 mEq/l, creatinine 1.4 mg/dl, BUN 25 mg/dl, hematocrit 36%, arterial pH 7.35, pCO2

45 mmHg, pO2 75 mmHg (room air). He was taken to the hospital operating room and his bleeding duodenal ulcer was repaired. The patient remained hemodynamically stable throughout the hospitalization but continued to require intravenous lorazepam for sedation. Repeat laboratory studies showed sodium 138 mEq/l, potassium 4.8 mEq/l, chloride 100 mEq/l, bicarbonate 10 mEq/l, creatinine 1.8 mg/dl, BUN 38 mg/dl, glucose 120 mg/dl, and serum osmolality 330 mOsm/kg (osmolar gap – 37 mOsm/l).

Which ONE of the following is the MOST likely primary cause of the patient's acid-base disturbance?

A. Propylene glycol toxicity
B. Diabetic ketoacidosis
C. Lactic acidosis
D. Absorption of blood protein from GI tract
E. Worsening renal failure

The correct answer is A. The development of the anion gap metabolic acidosis in association with an increased osmolar gap is best explained by propylene glycol toxicity. Propylene glycol is used as a diluent to enhance the solubility of various drugs, including lorazepam. With high doses infused for prolonged periods of time, propylene glycol can accumulate in the plasma and give rise to an osmolar gap. Lactic acid is a byproduct of metabolism, thus explaining the development of lactic acidosis. There are case reports that suggest prolonged exposure can also cause acute renal failure. The serum glucose concentration of 120 mg/dl excludes the diagnosis of diabetic ketoacidosis (choice B). Lactic acidosis (choice C) is likely present, but only as part of toxicity of propylene glycol toxicity. Lactic acidosis is not characteristically accompanied by an osmolar gap. Absorption of blood proteins from the gastrointestinal tract (choice D) is not a cause of lactic acidosis and an osmolar gap. The worsening of renal failure (choice E) is not of sufficient magnitude to explain the development of an anion gap acidosis.

References

Arroliga AC, Shehab N, McCarthy K, et al. (2004) Relationship of continuous infusion lorazepam to serum propylene glycol concentration in critically ill adults. Cri Care Med 32:1709–1714

Yaucher N, Fish J, Smith H, et al. (2003) Propylene glycol-associated renal toxicity from lorazepam. Pharmacol 23:1094–1099

CASE 52

A 12-year old boy presents with generalized weakness, diarrhea, vomiting, and a recent onset of confusion. His BP is 100/60 mmHg, but the physical examination is otherwise unremarkable. Laboratory studies show serum sodium 105 mEq/l, potassium 3.3 mEq/l, chloride 80 mEq/l, bicarbonate 18 mEq/l, BUN 16 mg/dl,

creatinine 0.5 mg/dl, glucose 127 mg/dl, serum osmolality 217 mOsm/kg, urine osmolality 210 mOsm/kg, and urine sodium 22 mEq/l. A CT scan of the head shows a large sellar mass. Thyroid hormone and cortisol levels are low. He is given steroid replacement and isotonic saline.

Which ONE of the following statements regarding this case is MOST correct?

A. The low serum bicarbonate concentration is inconsistent with hyponatremia caused by hypopituitarism.
B. After 1 liter of isotonic saline, his serum sodium level is likely to increase by only 1 mEq/l.
C. The low serum potassium concentration is inconsistent with hyponatremia caused by hypopituitarism.
D. As the patient has findings consistent with the syndrome of inappropriate antiduretic hormone secretion (SIADH), the serum sodium concentration is likely to decrease if isotonic saline is continued due to *desalination* of the infused saline.
E. Cortisol replacement may result in myelinolysis.

The correct answer is E. The patient presents with typical features of hypocortisolism due to hypopituitarism. In contrast to hypocortisolism due to primary adrenal disease, hypopituitarism does not cause mineralocorticoid deficiency, and thus does not result in hyperkalemia. Patients with the disorder characteristically exhibit a slightly low serum bicarbonate concentration. If isotonic saline were given to the patient prior to cortisol replacement, the serum sodium concentration could fall as in patients with SIADH due to other causes. After cortisol, however, the ability to dilute the urine is restored, and the serum sodium concentration is likely to correct rapidly, risking myelinolysis.

References

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Lasheen I, Doi SA, aL-shoumer KA (2005) Glucocorticoid replacement in panhypopituitarism complicated by myelinolysis. Med Princ Pract 14:115–117

Olchovsky D, Ezra D, Vered I, et al. (2005) Symptomatic hyponatremia as a presenting sign of hypothalamic-pituitary disease: a syndrome of inappropriate secretion of antiduretic hormone (SIADH)-like glucocorticoid responsive condition. J Endocrinol Invest 28:151–156

CASE 53

Which ONE of the following sets of findings would MOST likely be found in a child with a gain-of-function mutation in the vasopressin receptor?

A. Polyuria and polydipsia with undetectable plasma vasopressin levels
B. Polyuria and polydipsia with high plasma vasopressin levels

C. Hyponatremia with undetectable plasma vasopressin levels
D. Hyponatremia with high plasma vasopressin levels
E. Adipsic hypernatremia

The correct answer is C. Gain of function mutations in the V2 receptor were recently identified in two infants with clinical and laboratory evaluations typical of SIADH, but whose plasma arginine vasopressin (AVP) levels were undetectable. DNA sequencing of each patient's V2R gene identified missense mutations in both, with resultant changes in codon 137 from argentine to cystein or leucine. These novel mutations cause constitutive activation of the receptor, causing a nephrogenic syndrome of inappropriate antiduresis. Water retention caused by the abnormal vasopressin receptor leads to hyponatremia, which suppresses endogenous release of vasopressin. In answer A, polyuria and polydipsia with undetectable vasopressin levels are found in patients with neurogenic or dipsogenic diabetes insipidus. In answer B, polyuria and polydipsia with high levels of vasopressin are found in patients with nephrogenic diabetes (e.g., due to an inactivating mutation of the vasopressin receptor). In answer D, hyponatremia with high levels of vasopressin is found in patients with SIADH, heart failure or cirrhosis, or volume depletion. In answer E, adipsic hyponatremia is found in patients with hypothalamic abnormalities affecting both thirst and vasopressin secretion.

Reference

Feldman BJ, Rosenthal SM, Vargas GA, et al. (2005) Nephrogenic syndrome of inappropriate antidiuresis. N Engl J Med 352:1884–1890

CASE 54

A 19-year old male marathon runner has collapsed at the finish line. He is confused and hyperventilating. His BP is 90/56 mmHg, and bi-basilar crackles are heard at his lung bases. He develops a major motor seizure and during resuscitation it is noted that he has pink, frothy sputum. A wristband indicates that he is diabetic. A portable testing device shows that his blood glucose is 60 mg/dl. The serum sodium concentration is 100 mEq/l. He weighs 72 kg and his estimated volume of total body water is 36 liters (0.5×72).

Which ONE of the following is the BEST fluid prescription at this point?

A. Give 1 liter of 0.9% saline as rapidly as possible
B. Give 40 mg furosemide IV bolus
C. Start a 3% saline infusion at 30 ml/hr
D. Give 100 ml of 50% glucose IV bolus
E. Give 100 ml 3% saline IV over 10 minutes

The correct answer is E. Acute hyponatremia is a serious complication among poorly trained marathon runners who drink too much water during a race. Deaths due to cerebral edema have been reported, and affected runners may present with neurogenic pulmonary edema. Hyponatremic runners gain weight during the race due to ingested water. Thus, administration of isotonic saline, as in answer A, is inappropriate. It is not adequate for the hyponatremic emergency and it may exacerbate pulmonary edema. Administration of furosemide (answer B) or glucose (answer D) does address the patient's life-threatening acute hyponatremia. Administration of hypertonic saline at 30 ml/hr is appropriate therapy for a patient with moderate symptoms from chronic hyponatremia. Retention of 1 liter of 3% saline is estimated to increase the serum sodium by 10.9 mEq/l $(513 - 108) : (36 + 1) = 10.9)$. The initial goal is to increase the serum sodium level by 3 mEq/liter over the next three hours; thus, 0.27 liters of hypertonic saline (3:10.9) or 90 ml per hour (270 ml: 3 hrs) is required. Because the risk of osmotic demyelination is vanishingly low in a patient with hyperacute hyponatremia, because the serum sodium concentration may fall further because of delayed absorption of ingested water, and because there is risk of death from cerebral edema, administration of a larger bolus of hypertonic saline (answer E) is the best choice. This therapy is consistent with the recommendation of a consensus conference on the treatment of acute hyponatremia in runners.

References

Ayus JC, Varon J, Areff AI (2000) Hyponatremia, cerebral edema, and noncardiogenic pulmonary edema in marathon runners. Ann Intern Med 132:711–714

Hew-Butler T, Almond CS, Ayus JC, et al. (2005) Consensus statement of the 1st international exercise-associated hyponatremia consensus development conference, Cape Town, South Africa. Clin J Sport Med 15:208–213

CASE 55

A four-year old girl develops polyuria after resection of a large pituitary tumor. Urine osmolality is 100 mOsm/kg, and plasma sodium concentration is 148 mEq/l.

Which ONE of the following is the BEST fluid prescription for this patient?

A. She has diabetes insipidus that will require permanent use of desmopressin,
B. She has *upward resetting* of her osmoreceptor and needs no therapy.
C. Her polyuria reflects impending brain stem herniation and she should be treated with hypertonic Mannitol.
D. She may have diabetes insipidus and should be fluid-deprived for four hours before retesting her plasma sodium and urine osmolality before and after desmopressin.

E. She has diabetes insipidus, which is likely to be transient. She should be given desmopressin immediately and this should be discontinued one to two weeks after surgery.

The correct answer is E. The patient has hypernatremia and dilutes urine. These features are diagnostic of diabetes insipidus (nephrogenic vs. neurogenic), therefore fluid restriction prior to the administration of DDAVP® (choice D) is not indicated. Transient diabetes insipidus is common in the immediate post-operative period following pituitary surgery, making choices B and C unlikely. Although permanent diabetes insipidus may occur (choice A), diabetes insipidus may resolve with time. Therefore, a therapeutic schedule in which a scheduled DDAVP® dose is withheld, periodically allowing brief polyuric episodes has been advocated.

Reference

Smith D, Finucane F, Phillips J, et al. (2004) Abnormal regulation of thirst and vasopressin secretion following surgery for craniopharyngioma. Clin Endocrinol 61:273–279

CASE 56

A five-year old boy with end-stage liver disease presents with bacterial peritonitis. He is treated with ceftriaxone and intravenous (IV) hyperoncotic albumin, and his symptoms improve. Over the next three days his serum creatinine increases by 0.5 mg/dl daily. Urine osmolality is 310 mOsm/kg, and urine sodium concentration is <10 mEq/l. He is given an IV infusion of normal saline with 5% albumin, but the serum creatinine continues to increase.

Which ONE of the following is the BEST fluid prescription for this patient?

A. Desmopressin
B. Dopamine
C. Midodrine octreotide, and albumin
D. High-volume paracentesis and albumin
E. Emergency transjugular intrahepatic portosystemic shunts

The correct answer is C. A combination of midodrine and octreotide and albumin was recently shown to increase glomerular filtration rate, renal plasma flow, and fractional excretion of sodium in two-thirds of the patients with hepatorenal syndrome. The rational for this combination is to combine the alpha-adrenergic agonist effect of midodrine and the vasodilatation-inhibitory effect of octreotide to reduce vascular capacitance and to allow albumin to refill the intravascular volume. Although this was an uncontrolled study, the results are impressive because, without treatment, the median survival of patients with Type 1 hepatorenal syndrome is less than two weeks. Transjugular intrahepatic portosystemic shunts (TIPS) (choice C)

are effective in responders to this therapy but should not be primary therapy. Infusion of vasopressin VI-receptor agonist produces constriction of vascular smooth muscle. Terlipressin, in combination with albumin, is effective in approximately two-thirds of patients. Although this vasopressin analog has been available for many years and is widely used in Europe, it is not available in the United States. Choice A (DDAVP®) is a V2-receptor agonist (increases water reabsorption in the renal tubular cells), and therefore is an incorrect answer. Dopamine (choice B) is ineffective in this syndrome and high volume paracentesis (choice D) may cause it.

References

Cardenas A (2005) Hepatorenal syndrome: a dreaded complication of end-stage liver disease. Am J Gastroentrol 100:460–457

Wong F, Pantea L, Sniderman K (2004) Midodrine, octreotide, albumin, and TIPS in selected patients with cirrhosis and Type I hepatorenal syndrome. Hepatology 40:55–64

CASE 57

A six-year old female presents with a several-week history of polydipsia and polyuria. She has lost 4 kg of weight over this period of time. Nausea and vomiting started two days ago. An evaluation in the emergency room revealed the following laboratory findings: blood sodium 128 mEq/l, potassium 4 mEq/l, chloride 90 mEq/l, bicarbonate 8 mEq/l, glucose 980 mg/dl, urine sodium 90 mEq/l, potassium 54 mEq/l, and chloride 75 mEq/l. Serum and urinary ketones are strongly positive.

Which ONE of the following statements about this patient's potassium stores is MOST correct?

A. They are normal.
B. They are increased due to volume contraction and oliguria.
C. They are increased due to an osmotic diuresis, but not reduced enough to cause hypokalemia.
D. They are reduced due to osmotic diuresis, but serum potassium levels remain normal because potassium shifts out of cells in response to the metabolic acidosis.
E. They are reduced due to an osmotic diuresis, but serum potassium levels remain normal because potassium shifts out of cells in response to insulin deficiency and increased osmolality.

The correct answer is E. The patient presents with a diagnosis of diabetic ketoacidosis. Such patients are total body potassium-depleted, despite typically having increased plasma potassium concentrations upon admission. Thus, choices A and B are incorrect. The normal plasma potassium in this patient suggests a severe

decrease in total body potassium content. Total body potassium depletion in diabetic ketoacidosis is due to renal potassium wasting, resulting from increased distal sodium delivery coupled to increased circulating aldosterone. Distal sodium delivery is increased due to osmotic diuretic effect of the glucose and excretion of sodium-ketoacid salt. Volume depletion mediates the increase in aldosterone. Despite the total potassium depletion, serum potassium concentration is often increased, or in this case normal, due to insulin deficiency (choice C is incorrect). In addition, increased extracellular glucose concentration leads to water movement from intracellular space to the extracellular space, resulting in concentration of intracellular potassium. The increased intracellular to extracellular potassium gradient favors the outward movement of potassium. Potassium shifts are not due to metabolic acidosis because diabetic ketoacidosis is an organic acidosis. Only mineral acidosis causes potassium shifts out of cell (choice D is incorrect).

References

Milionis HJ, Dimos G, Elisef MS (2003) Severe hypokalemic in association with diabetic ketoacidosis in a patient presenting with severe generalized muscle weakness. Nephrol Dial Transplant 18:198–200

Perez G, Oster J, Vaamonde C (1981) Serum potassium concentration in academic states. Nephron 27:233–243

CASE 58

A 19-year old boy with chronic hepatitis C viral infection develops progressive ascites, peripheral edema, and confusion. Physical examination reveals sclera icterus, as well as tense ascites and ankle edema. Serum sodium is 128 mEq/l and blood ammonia concentration is elevated.

Which ONE of the following statements regarding the patient's hyponatremia is MOST correct?

A. It is strongly associated with an underlying hepatocelluar carcinoma.
B. It has no independent prognostic significance.
C. It is likely to cause low brain glutamine levels.
D. It is likely to cause low brain myoinositol levels.
E. Cerebral edema is likely to be demonstrable on magnetic resonance imaging.

The correct answer is D. Hyponatremia is a common complication of hepatic cirrhosis, caused primarily by vasopressin secreted in response to the systemic vasodilatation that occurs in patients who form ascites. Thus, answer A is incorrect. Answer B is incorrect because hyponatremia has been shown to be an important prognostic indicator in cirrhosis. Because ammonia can only be eliminated from

the brain through the conversion of glutamate to glutamine by the enzyme glutamine synthesizes, intracellular glutamine accumulates in brain cells in response to hyperammonemia. By somatically attracting water across the blood-brain barrier, brain accumulation of glutamine is thought to contribute to the cerebral edema that complicates severe, acute liver failure. Thus, answer C is incorrect. Hyponatremia causes an adaptive loss of organic osmolytes (myoinositol) from brain cells that militate against brain cell swelling. Depletion of myoinositol, the most abundant organic osmolyte in humans, occurs in response to both glutamine-induced and hyponatremia-induced brain cell swelling, and low levels of brain myoinositol without increased brain water has been demonstrated by magnetic resonance spectroscopy. Thus, answer D is correct. Cerebral edema complicates fulminate hepatic failure, but brain swelling has not been shown in patients with more modest disease as in this case. Thus, answer E is incorrect. The profoundly low myoinsositol levels in cirrhosis may explain the increased susceptibility of these patients to osmotic demyelination with overly aggressive correction of hyponatremia.

Reference

Restuccia T, Gomez-Anson B, Guevara M, et al. (2004) Effects of dilutional hyponatremia on brain organic osmolyte and water content in patients with cirrhosis. Hepatology 39: 1613–1622

CASE 59

A 15-year old female presents with a severe obtundation, dry mucous membranes, decreased skin turgor, fever, tachycardia, and a BP of 142/82 mmHg without orthostatic changes. The serum Na^+ concentration is 168 mEq/l, and the body weight is 57 kg. Hypernatremia is caused by hypodipsia and excessive insensible losses. The estimated total body water is 34 liters (0.6×57).

Which ONE of the following is the BEST initial fluid prescription for this patient?

A. Infusion of 0.9% saline at 150 ml/hr over the next 24 hours
B. Infusion of 0.45% saline at 150 ml/hr over the next 24 hours
C. Infusion of 5% dextrose at 150 ml/hr over the next 24 hours
D. Infusion of 0.2% saline at 150 ml/hr over the next 24 hours
E. Infusion of 0.2% saline containing 20 mEq KCL/liter at 150 ml/hr over the next 24 hours

The correct answer is C. Hypernatremia is caused by pure water depletion; therefore, an infusion of 5% dextrose is planned to estimate the effect of 1 liter of any infusate on serum sodium. The following formulas are recommended to manage hpernatremia:

$$\text{Change is serum } Na^+ = (\text{Infusate } Na^+ + \text{infusate } K^+) - (\text{Serum } Na^+) : \text{Total body water} + 1$$

The goal of treatment is to reduce the serum concentration by approximately 10 mEq/l over a period of 24 hours. It is estimated that the retention of 1 liter of 5% dextrose will reduce the serum Na^+ concentration by 4.8 mEq/l $[(0 - \text{`}68) : (34 + 1) = -4.8]$. Therefore, 2.1 liters of the solution (10: 4.8) is required. With 1.5 liters added to compensate for average obligatory water losses over the 24-hour period, a total of 3.6 liters will be administered for the next 24 hours, or 150 ml/hr. The serum glucose concentration will be monitored, with insulin therapy started at the first indication of hyperglycemia—a complication that would aggravate the hypertonocity. Close monitoring of the patient's clinical and laboratory values, initially at intervals of six to eight hours, will guide adjustment in fluids administration.

Reference

Adrogue HJ, Madias NE (2000) Hypernatremia. N Engl J Med 342:1493–1499

CASE 60

An 18-year old female with postoperative illus is undergoing nasogastric suction. She is obtunded and has diminished skin turgor and mild orthostatic hypotension. The serum sodium is 158 mEq/l, the potassium is 4.0 mEq/l, and the body weight is 63.0 kg. Hypernatremia is caused by hypotonic fluid loss is diagnosed.

Which ONE of the following is the BEST initial fluid prescription for this patient?

A. Administration of 0.2% saline at 250 ml/hr for the next 12 hours
B. Administration of 0.45% saline at 250 ml/hr for the next 12 hours
C. Administration of 0.9% saline at 250 ml/hr for the next 12 hours
D. Administration of 5% dextrose water at 250 ml/hr for the next 12 hours
E. Administration of 0.45% saline containing 20 mEq KCL/liter at 250 ml/hr for the next 12 hours

The correct answer is B. This patient's hypernatremia is caused by hypotonic sodium loss. Therefore, an infusion of 0.45% saline is planned, with the goal of decreasing her serum sodium concentration by 5 mEq per liter over the next 12 hours. The estimated total body water is 31.5 liters (0.5×63). It is estimated that the retention of 1 liter of 0.45% saline will reduce the serum concentration by 2.5 mEq/l $([77 - 158] : [31.5 + 1] + -2.5$. Because the goal is to reduce the serum sodium concentration by 5 mEq/l over the next 12 hours, 2 liters of the solution is required (5: 2.5). With 1 liter added to compensate for ongoing losses of gastric and other fluids, a total of 3 liters will be administered for the next 12 hours, or 250 ml/hr. After

12 hours, the patient's clinical status and laboratory values will guide adjustments in the administration of fluids. The use of conventional formula, such as

$$Na^+ \text{ requirement} = [\text{total body water X (desired serum } Na^+ \text{ level} - \text{current } Na^+ \text{ level})]$$

requires a complicated procedure to convert the amount of sodium required to raise the serum sodium concentration to an infusion rate for the selected solution.

Reference

Adrogue HJ, Madias NE (2000) Hypernatremia. N Engl J Med 342:1493–1499

CASE 61

A 17-year old male with advanced hepatic cirrhosis is receiving lactulose for the management of hepatic encephalopathy. Upon examination, confusion, ascites, and asterixis are present. His BP is 105/58 mmHg while the patient is in the supine position, and pulse is 110 beats/min. The sodium concentration is 160 mEq/l, the potassium 2.6 mEq/l, chloride 110 mEq/l, bicarbonate 19 meq/l, and the body weight is 64 kg.

Which ONE of the following is the BEST initial fluid prescription for this patient?

A. Administration of the 0.2% saline containing 20 mEq KCL/l at 220 ml/hr for the next 24 hours
B. Administration of the 0.45% saline containing 20 mEq KCL/l at 220 ml/hr for the next 24 hours
C. Administration of the 0.9% saline containing 20 mEq KCL/l at 220 ml/hr for the next 24 hours
D. Administration of the 5% dextrose containing 20 mEq KCL/l at 220 ml/hr for the next 24 hours
E. Administration of the 5% dextrose at 220 ml/hr for the next 24 hours

The correct answer is A. The hypernatremia in this patient reflects hypotonic sodium and potassium losses induced by lactulose. Thus, in addition to withdrawal of lactulose, 0.2 percent sodium chloride containing 20 mEq KCL/l will be administered. With the presence of ascites, the estimated volume of total body water is 38 liters (64×0.6). Because the serum sodium concentration is determined by the ratio of the *exchangeable* (osmotic ally active) portions of the body's sodium and potassium content to the total volume of body water, the addition of potassium to the solution requires its inclusion in the calculation of the change in the serum sodium concentration. Therefore, the retention of one liter of 0.2% saline

containing 20 mEq KCL/l will reduce the serum sodium concentration by 2.7 mEq/l ($[34 + 20) - 160] : [38 + 1] + -2.7$. To reduce the serum sodium concentration by 10 mEq/l over the next 24 hours, 3.7 liters of solution (10: 2.7) is required. With 1.5 liters added to compensate for ongoing obligatory fluid and electrolyte losses, a total of 5.2 liters will be administered over the next 24 hours, or about 220 ml/hour. The use of conventional formula:

$$\text{Water deficit} = \text{Total body water X } (1\text{–}[140 : \text{serum } Na^{+} \text{ concentration}])$$

is not recommended in this situation. Although this formula provides an adequate estimate of the water deficit in patients with hypernatremia caused by pure water loss, it underestimates the deficit in patients with hypotonic fluid loss. Furthermore, the conventional formula is not useful when sodium and potassium, in addition to water, must be prescribed.

References

Adrogue HJ, Madias NE (2000) Hypernatremia. 342:1493–1499
Adrogue HJ, Madias NE (1997) Aiding fluid prescription for dysnatremias. Intensive Care Med 23:309–316

CASE 62

A previously healthy 18-year old female has three grand mal seizures two days after an appendectomy. She receives 20 mg of diazepam and 250 mg of phenytoin intravenously and undergoes laryngeal intubation with mechanical ventilation. Three liters of 5% dextrose in water had been infused during the first day after surgery, and the patient subsequently drank an unknown but substantial amount of water. Clinically, she is euvolemic, and she weighs 56 kg. She is stuporus and responds to pain but not to commands. The serum sodium concentration is 112 mEq/l, the serum potassium concentration is 4.1 mEq/l, serum osmolality is 228 mOsm/kg of water, and urine osmolality is 510 mOsm/kg of water.

Which ONE of the following is the BEST initial fluid prescription for this patient?

A. Treatment should include the withholding of water, infusion of 3% saline at 60 ml/hr over the next three hours, and administration of 20 mg of furosemide.
B. Treatment should include the withholding of water, infusion of 0.9% saline at 60 ml/hr over the next three hours, and administration of 20 mg of furosemide.
C. Treatment should include the withholding of water, infusion of 0.45% saline at 60 ml/hr over the next three hours, and administration of 20 mg of furosemide.
D. Treatment should include the withholding of water, infusion of 0.2% saline at 60 ml/hr over the next three hours, and administration of 20 mg of furosemide.

E. Treatment should include the withholding of water, infusion of 5% dextrose in water at 60 ml/hr over the next three hours, and administration of 20 mg of furosemide.

The correct answer is A. Hypotonic hyponatremia in this patient is the result of water retention caused by the impaired excretion of water that is associated with the postoperative state. Planned treatment includes the withholding of water, the infusion of 3% saline, and the administration of 20 mg of furosemide. The estimated volume of total body water is 23 liters (0.5×46). The retention of one liter of 3% saline will increase the serum sodium concentration by 16.7 mEq/l $([513–112] : [23 + 1] = 16.7)$. Given the seriousness of the patient's symptoms, the initial goal is to raise the serum sodium concentration by 3 mEq/l over the next three hours; thus, 0.18 liter of hypertonic (3 : 16.7), or 60 ml/hr, is required. Frequent monitoring of the serum sodium concentration, initially every two to three hours, is necessary to make further adjustment in the amount of fluid administered.

Reference

Adrogue HJ, Madias NE (2000) Hyponatremia. 342:1581–1599

CASE 63

A 17-year old male with a mediastinal tumor presents with severe confusion and lethargy. Clinically, he is euvolemic, and he weighs 60 kg. The serum sodium concentration is 108 mEq/l, the serum potassium is 3.9 mEq/l, serum osmolality is 220 mOsm/kg of water, the serum creatinine is 0.5 mg/dl, and urine osmolality is 600 mOsm/kg of water. The physician makes a provisional diagnosis of the tumor-induced syndrome of SIADH on the basis of the presence of hypotonic hyponatremia and concentrated urine in a euvolemic patient, the absence of a history of diuretic use, and the absence of clinical evidence of hypothyroidism or hypoaldosteronism.

Which ONE of the following is the BEST initial fluid prescription for this patient?

A. Treatment should include the withholding of water, infusion of 3% saline at 38 ml/hr over the next 12 hours, and administration of 20 mg of furosemide.
B. Treatment should include the withholding of water, infusion of 0.9% saline at 38 ml/hr over the next 12 hours, and administration of 20 mg of furosemide.
C. Treatment should include the withholding of water, infusion of 0.45% saline at 38 ml/hr over the next 12 hours, and administration of 20 mg of furosemide.
D. Treatment should include the withholding of water, infusion of 0.2% saline at 38 ml/hr over the next 12 hours, and administration of 20 mg of furosemide.

E. Treatment should include the withholding of water, infusion of 5% dextrose in water at 38 ml/hr over the next 12 hours, and administration of 20 mg of furosemide.

The correct answer is A. This patient has symptomatic hypotonic hyponatremia due to the SIADH. The initial goal is to increase the serum sodium concentration by 5 mEq/l over the next 12 hours. The retention of one liter of 3% saline is estimated to increase the serum sodium concentration by 10.9 mEq/l ([513−108] : [36+1]+10.9. The initial goal is to increase the serum sodium concentration by 5 mEq/l over the next 12 hours. Therefore, 0.46 liter of 3% saline (5: 10.9), or 38 ml/hr, is required.

Reference

Adrogue HJ, Madias NE (2000) Hyponatremia. 342:1581–1589

CASE 64

An 18-year old female is brought to the hospital because of progressive drowsiness and syncope. She is being treated with a low-sodium diet and 25 mg of hydrochlorothiazide daily for essential hypertension. She has had diarrhea for the past three days. She is lethargic but has no focal neurological deficits. She weighs 60 kg. Her BP is 96/56 mmHg, and the pulse is 110 beats/min. The jugular veins are flat, and skin turgor is decreased. The serum sodium concentration is 106 mEq/l, the serum potassium concentration is 2.2 mEq/l, the serum bicarbonate concentration is 26 mEq/l, BUN is 46 mg/dl, the serum creatinine is 1.4 mg/dl, serum osmolality is 232 mOsm/kg of water, and urine osmolality is 650 mOsm/kg of water.

Which ONE of the following is the BEST initial fluid prescription for this patient?

A. Treatment should include the withholding of hydrochlorothiazide and infusion of 0.9%% saline at 500 ml/hr over the next eight hours.
B. Treatment should include the withholding of hydrochlorothiazide and water, and infusion of 0.9% saline containing 30 mEq KCL/l at 500 ml/hr over the next two hours.
C. Treatment should include the withholding of water and hydrochlorothiazide and infusion of 0.45% saline at 500 ml/hr over the next eight hours.
D. Treatment should include the withholding of hydrochlorothiazide and infusion of 0.2% saline at 500 ml/hr over the next six hours.
E. Treatment should include the withholding of water, infusion of 5% dextrose in water at 500 ml/hr over the next six hours.

The correct answer is B. Hypotonic hyponatremia associated in this patient is caused by thiazide therapy (sodium and potassium losses) and gastrointestinal losses

of sodium and potassium. It is projected that the retention of one liter of this solution will increase the serum sodium concentration by 2.8 mEq/l ($[154 + 30] - [160 : [27 + 1] = 2.8$. Considering the patient's hemodynamics status, it is reasonable to prescribe one liter of infusate per hour for the next two hours. At the end of this period, the BP is 128/72 mmHg, mental status is substantially improved, the serum sodium concentration is 112 mEq/l, and the serum potassium is 3.0 mEq/l. At this point, the patient's ECF volume nears stimulation and the nonosmotic stimulation to ADH release will cease, thereby fostering rapid excretion of dilute urine and correction of the hypernatremia at an overly rapid pace. Therefore, the prescription is switched to 0.45% saline containing 30 mEq KCL/l infused at 100 ml/hr. Despite the estimate that retention of one liter of this infusate will have no measurable effect on the serum sodium concentration ($[77 + 30] - 112 : [27 + 1] = -0.2$), the anticipated production of urine will lower sodium and potassium concentrations and those of the infusate will promote correction of the hyponatremia. Twelve hours later, the patient's condition continues to improve. The serum sodium concentration is 114 mEq/l and potassium is 3.2 mEq/l. To slow down further correction over the next 12 hours, an infusion of 5% dextrose in water containing 30 mEq KCL/l is started at a rate matching urinary output. Subsequently, long-term management of hyponatremia should be pursued.

Reference

Adrogue HJ, Madias NE (2000) Hyponatremia. 342:1581–1589

Chapter 2
Acid-base Disturbances

CASE 1

A 12-year old female is brought to the ER because of increasing weakness. She has been having low grade fever and severe diarrhea for four days. Laboratory studies reveal sodium 140 mEq/l, potassium 2.4 mEq/l, chloride 115 mEq/l, bicarbonate 15 mEq/l, BUN 21 mg/dl, creatinine 1.5 mg/dl, glucose 88 mg/dl, calcium 10.0 mg/dl, phosphate 3.5 mg/dl, magnesium 1.8 mg/dl, and plasma osmolality 284 mOsm/kg.

What do you estimate her arterial pH to be?

A. 7.20–7.24
B. 7.25–7.29
C. 7.30–7.34
D. 7.40–7.44
E. 7.45–7.49

The correct answer is C. The acid-base diagnosis is uncomplicated hyperchloremic acidosis due to severe diarrhea. This would allow you to estimate her pCO2 from Winter's formula, which applies only when simple (uncomplicated) metabolic acidosis is present:

$$\mathbf{\Delta pCO_2 = 1.2 \times \Delta HCO3^-}$$

or 12 mmHg. Thus, the predicted pCO_2 compensation would be 28 mmHg—the difference between normal pCO_2 and the expected fall in pCO_2 [normal pCO_2 (40)] – [ΔpCO_2 (12)]. The H^+ can then be calculated with the modified Henderson-Hassalbach equation:

$$\mathbf{H^+ = 24 \times pCO_2 : HCO3^-}$$

The value obtained is 45 nEq/l, which is equivalent to a pH of 7.35 (every 0.1 fall in pH is equivalent to a 10 nEq/l rise in plasma H^+ concentration).

F. Assadi, *Clinical Decisions in Pediatric Nephrology.*

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Δ10 nEq/l increment in H^+ = Δ 0.10 fall in PH
pH vs. **H^+ (nEq/l)**

7.40 = 40
7.30 = 50
7.20 = 60
7.10 = 70

The point of this exercise is to remind you that the principal indication for a blood gas is the inability to estimate pH when there are multiple acid-base abnormalities present, or when you cannot be sure that there is only one abnormality present.

References

Bushinsky DA, Coe FL, Katzenberg C, et al. (1982) Arterial pCO2 in chronic metabolic acidosis. Kidney Int 22:311–314
Narins RG, Emmett M (1980) Simple and mixed acid base disorders: A practical approach. Medicine 59:161–187
Sabatini S, Arruda JAL, Kurtzman NA (1978) Disorders of acid-base balance Med Clin North Am 62:1223–1255

CASE 2

An 18-year old girl is brought to the ER in a coma. There is no other history available. Physical examination revealed a thin, nonicteric Caucasian female in a coma. The patient is comatose without focal neurological sing. Temp is 98.6 F, BP is 136/88 mmHg, pulse is 98, respiratory rate is 24/min, weight is 60 kg, and length is 170 cm. The heart is regular without murmurs. The chest is clear without rales or rhonchi. The heart rate is regular, and there are no extra sounds or murmurs. The abdomen is soft. Mild hepatosplenomegaly is present without jaundice or ascites. No other masses are palpable. Bowel sounds are present. Mild kyphosis is noted. Extremities are free of rashes or edema. Laboratory studies reveal sodium 140 mEq/l, potassium 5.5 mEq/l, chloride 106 mEq/l, bicarbonate 6.0 mEq/l, BUN 30 mg/dl, creatinine 0.8 mg/dl, glucose 95 mg/dl, calcium 9.0 mg/dl, phosphate 2.9 mg/dl, magnesium 1.7 mg/dl, plasma osmolality 340 mosmo/kg, and serum ketones 1+.

Would you like to draw a blood gas?

A. Yes, I believe one is indicated.
B. No, I do not believe it is necessary.

The correct answer is A. A blood gas is indicated in this case. This is because you cannot be sure that there is only one acid-base disturbance present when there is no history available and you cannot predict the pH.

An arterial blood gas was obtained which revealed pH 7.20, pCO2 16 mmHg, $HCO3^-$ 15 mEq/l, and pCO2 110 mmHg.

What is the acid-base diagnosis?

A. Uncomplicated anion gap metabolic acidosis
B. Metabolic acidosis plus metabolic alkalosis
C. Metabolic acidosis plus respiratory acidosis
D. Metabolic acidosis plus respiratory alkalosis

The correct answer is A. The blood gas data are compatible with metabolic acidosis and appropriate respiratory compensation as determined by Winter's formula. Laboratory studies on venous blood reveal an increased anion gap (AG) and a reduced bicarbonate compatible with AG metabolic acidosis. The fall in the bicarbonate concentration (−18) is close to the change in the AG (+17), suggesting that another acid-base process is not present. The blood gas data are compatible with metabolic acidosis and appropriated respiratory compensation as determined by Winter's formula discussed earlier.

What is the likely cause of the anion gap metabolic acidosis in this patient?

A. Toxic ingestion (methanol, ethylene glycol)
B. Starvation ketoacidosis
C. Lactic acidosis
D. Alcoholic ketoacidosis

The correct answer is D. The potential causes of large AG metabolic acidosis include: starvation ketoacidosis, alcoholic ketoacidosis, methanol intoxication, ethylene glycol intoxication, lactic acidosis, inborn error of metabolism, and renal failure. Blood ketones are only trace positive and the serum creatinine is normal. However, the measured serum osmolality is considerably higher than the calculated osmolality (340 vs. 296 mOsm/kg). The presence of an osmol gap is consistent with toxic ingestion with a substance such as alcohol, methanol, or ethylene glycol, which produces acidosis by interfering with metabolism and in part by producing lactic acidosis.

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CASE 3

A nine-year old boy with nephritic syndrome presents to the ER with severe vomiting and the recent onset of chest pain. Vomiting began 48 hours ago and has continued until the present time without improvement. Fifteen minutes before arriving in the ER, the patient developed the sudden onset of left-sided pleuric chest pain, shortness of breath, and hemoptysis. Physical exam revealed a tachypneic male in acute distress with a respiratory rate of 30/min and complaining of chest pain. The remainder of the examination was normal. Lab data revealed sodium 140 mEq/l, potassium 3.0 mEq/l, chloride 92 mEq/l, bicarbonate 36 mEq/l, BUN 30 mg/dl, creatinine 1.3 mg/dl, calcium 10.0 mg/dl, phosphate 3.5 mg/dl, blood ketones negative, glucose 90 mg/dl, and plasma osmolaity 280 mOsm/kg. The chest x-ray showed marked pleural effusion on the left pleural chest with the left lower lobe infiltrate consistent with pulmonary embolism.

Would you like to draw a blood gas?

A. Yes, I believe one is indicated.
B. No, I do not believe it is necessary.

The correct answer is A. This is because the history suggests that more than one acid-base disturbance may be present and you cannot, therefore, predict the arterial pH.

The blood gas revealed a pH of 7.69, pCO2 of 30 mmHg, a $HCO3^-$ 35 mEq/l, and a pO2 of 75 mmHg.

What is (are) the acid-base diagnosis (es) (select all that apply)?

A. Metabolic alkalosis
B. Metabolic acidosis
C. Respiratory alkalosis
D. Respiratory acidosis

The correct answers are A and C. This is an example of metabolic alkalosis plus primary respiratory alkalosis. The combination of an elevated bicarbonate and alkaline pH are consistent with metabolic alkalosis. The combination of a low pCO2 and an alkaline pH are consistent with respiratory alkalosis.

The history of vomiting suggests the presence of metabolic alkalosis. The pulmonary embolism suggests that there may be superimposed acute respiratory alkalosis. Laboratory studies reveal an increased BUN-to-creatinine ratio consistent with volume contraction. The bicarbonate is increased and the AG is normal, consistent with metabolic alkalosis without metabolic acidosis. Blood gas values show a markedly increased pH with an increased $HCO3^-$ and a low pCO2, confirming the presence of both metabolic alkalosis and respiratory alkalosis.

References

Emmett M, Seldin DW (1985) Clinical Syndromes of Metabolic Acidosis and Metabolic Alkalosis in Seldin, Giebisch, The Kidney: Physiology and Pathophysiology, Raven Press, New York, Chapter 68 pp1567–1639

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CASE 4

A 14-year old female is seen for a routine physical examination. The history is basically non-revealing and she has no current complaints. She denies taking any medications now, but does admit to using diet pills in the past. She also relates that her potassium has been low on several occasions in the past.

Physical exam reveals a thin female in no distress. She is afebrile, BP is 110/80 mmHg, pulse 78 beat/min, respirations 12/min, weight 52 kg, and height 156 cm. Lungs are clear, the heart rate is regular, there are no extra sounds or murmurs. Abdomen is soft and there is no palpable mass. Bowel sounds are present. There is no edema. Neurologic examination is normal.

Laboratory studies reveal normal hemoglobin and white cell count. BUN 15 mg/dl, creatinine 1.1 mg/dl, sodium 136 mEq/l, potassium 3.0 mEq/l, chloride 95 mEq/l, $HCO3^-$ 32 mEq/l, calcium 10.0 mg/dl, phosphate 3.6 mg/dl, magnesium 1.7 mg/dl, and albumin 4.6 g/dl.

Would you like to draw a blood gas?

A. No, I do not believe that a blood gas is necessary in this case.
B. Yes, I would like to see the results of a blood gas before I make a diagnosis in this case.

The correct answer is A. A blood gas is not necessary in this case. There is sufficient information in the history and laboratory data to make a diagnosis of a single

acid-base disturbance. This allows prediction of the arterial pH from Winter's formula for that disturbance and a blood gas is not necessary.

What is the acid-base diagnosis and which studies would help with the differential diagnosis of this condition (select all that apply)?

A. Respiratory alkalosis
B. Metabolic acidosis
C. Metabolic alkalosis
D. Respiratory acidosis
E. Measurement of urinary aldosterone excretion
F. Urinary diuretic screen
G. Measurement of urinary chloride excretion

The correct answers are C, F, and G. This is a case of metabolic alkalosis. The history reveals that hypokalemia might be present. Diet pills are often diuretics that may cause a metabolic alkalosis. Laboratory data reveal increased bicarbonate, a normal AG, and hypokalemia associated with renal potassium wasting, suggesting the presence of metabolic alkalosis.

Renal potassium wasting and metabolic alkalosis in a normotensive individual are most commonly due to diuretics or upper GI losses (vomiting). Rarely, the etiology is one of the inherited salt-wasting nephropathies (Bartter's syndrome or Gitelman's syndrome). Urinary chloride excretion helps to distinguish between diuretics and vomiting as causes of metabolic alkalosis. Vomiting is associated with ECF volume depletion, chloride depletion, and a urinary chloride excretion less than 20 mEq/l. In contrast, urinary chloride excretion is usually greater than 40 mEq/l. Surreptitious diuretic abuse is the most likely diagnosis in this case, in light of the urine chloride concentration and the history of *diet pills* (often diuretics). This diagnosis can be confirmed with a urinary diuretic *screen*.

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Emmett M, Seldin DW (1985) Clinical Syndromes of Metabolic Acidosis and Metabolic Alkalosis in Seldin, Giebisch, The Kidney: Physiology and Pathophysiology, Raven Press, New York, Chapter 68 pp1567–1639

Narins RG, Emmett M (1980) Simple and mixed acid base disorders: A practical approach. Medicine 59:161–187

Seldin DW, Rector FC Jr (1972) Degeneration and maintenance of metabolic alkalosis. Kidney Int 1:306–321

CASE 5

You are called to see a four-year old boy found to be stuporous at home. According to his father who found him this morning, he has apparently been complaining of continuous tension-type headaches for the past several months. He is otherwise

asymptomatic in good health. On examination, he appears well-developed, yet stuporous. Temp is 37 C F, BP 141/88 mmHg, pulse 88 beats/min, respiratory rate 34/min, weight 59 kg, and height 160 cm. The heart rate is regular, and there are no extra sounds or murmurs. The chest is clear without rales or rhonchi. The abdomen is soft with no palpable masses. Bowel sounds are present. There is no edema. Several ecchymoses are apparent over his trunk and limbs. Laboratory data reveals serum sodium 140 mEq/l, chloride 108 mEq/l, potassium 3.8 mEq/l, $HCO3^-$ 13 mEq/, BUN 14 mg/dl, creatinine 1.2 mg/dl, glucose 96 mg/dl; blood ketones 2+; calcium 10.0 mg/dl, phosphate 3.5 mg/dl, magnesium 1.8 mg/dl, albumin 4.0 g/dl, and plasma osmolality 284 mOsm/kg.

A blood gas was obtained, and revealed the following: pH 7.4, pCO_2 20 mmHg, $HCO3^-$ 12 mEq/l, and pO2 105 mmHg.

What is the acid-base diagnosis (select all that apply)?

A. Metabolic acidosis
B. Metabolic alkalosis
C. Respiratory acidosis
D. Respiratory alkalosis

The correct answers are A and D. This is a mixed disturbance of metabolic acidosis and chronic respiratory alkalosis. There are no specific clues to an acid-base disturbance in the history. Headaches might suggest the use of salicylates or a CNS lesion, both of which might be associated with respiratory alkalosis.

The physical examination suggests that hyperventilation is present, which could indicate severe acidosis or primary alkalosis. Ecchymoses are consistent with the use of salicylates. Laboratory studies reveal a low $HCO3^-$ and an increased AG consistent with the presence of AG metabolic acidosis. The fall in the $HCO3^-$ concentration (−11) is greater than the increase in the AG (+7), however, suggesting the presence of another process that lowers the $HCO3^-$—either chronic respiratory alkalosis or hyperchloremic acidosis.

Blood gas values reveal a low $HCO3^-$, low pCO2, and a normal pH, which is indicative of a mixed disturbance with metabolic acidosis and primary respiratory alkalosis. The combination of AG metabolic acidosis and primary respiratory alkalosis occurs in several situations, including sepsis, salicylate intoxication, and lactic acidosis in a patient with hepatic failure. Salicylate intoxication is the likely diagnosis in this patient in view of the history of severe headaches, stupor, and the presence of ecchymoses.

Reference

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CASE 6

A ten-year old boy with a recent history of tuberculosis, diagnosed two months ago, returns for a follow-up examination. He has been complaining of shortness of breath upon exertion, as well as a chronic cough with sputum production in the morning. He was placed on furosemide several weeks ago. On examination, temperature is 37 °C, BP is 128/71 mmHg, pulse is 84 beat/min, respiratory rate is 22/min, weight is 63 kg, and height is 157 cm. The heart rate is regular, and there are no extra sounds or murmurs. Respiratory excursions are shallow and there is occasional wheezing. The abdomen is soft without palpable masses. Bowel sounds are present. There is 2+ edema on lower extremities. Lab data reveals hemoglobin 12.0 g/dl, WBC 6600 cells/ml, sodium 140 mEq/l, potassium 3.4 mEq/l, $HCO3^-$ 42 mEq/l, calcium 10.0 mg/dl, phosphate 3.5 mg/dl, magnesium 1.8 mg/dl, albumin 3.4 g/dl, blood ketones 0, glucose 94 mg/l, and plasma osmolality 284 mOsm/kg.

An arterial blood gas was obtained and revealed a pH of 7.53, pCO_2 20 mmHg, $HCO3^-$ 16 mEq/l, and pO_2 105 mmHg.

What is the acid-base diagnosis (select all that apply)?

A. Metabolic alkalosis
B. Respiratory acidosis
C. Respiratory alkalosis
D. Metabolic acidosis

The correct answers are A and B. The $HCO3^-$ is significantly increased while the pH is slightly above normal, consistent with metabolic alkalosis. The history suggests the presence of obstructive airway disease and the pCO_2 is markedly increased despite the fact that the pH is only minimally above normal. This is a mixed disturbance with chronic respiratory acidosis and metabolic alkalosis. The history and physical exam indicate that the patient has chronic bronchitis and COPD, which can produce chronic respiratory acidosis. He was placed on loop diuretics for apparent right-sided congestive heart failure. These may produce metabolic alkalosis. Laboratory data show an elevated $HCO3^-$ and a normal AG, which could represent either chronic respiratory acidosis or metabolic alkalosis or both. There is also mild hypokalemia consistent with the use of diuretics and metabolic alkalosis.

The pH is only minimally elevated above the normal range, with a markedly elevated pCO_2 and $HCO3^-$. These data are not compatible with either metabolic alkalosis alone or chronic respiratory acidosis with normal compensation alone. Therefore, both metabolic alkalosis and chronic respiratory acidosis are present.

Reference

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CASE 7

A 16-year-old female decided to attempt a starvation diet. To speed up initial weight loss, she also took furosemide. After one week, she had lost 5 kg but felt terrible and decided to see her physician. As she approached the office, she became acutely anxious and felt weak. Physical examination in the office revealed a BP of 90/60 mmHg and respiratory rate of 20/min. There was a positive Trousseau's sign. The remainder of the examination was normal. Laboratory data showed: hemoglobin 13.5 g dl, BUN 40 mg/dl, creatinine 1.5 mg/dl, sodium 140 mEq/l, chloride 98 mEq/l, potassium 3.0 mEq/l, $HCO3^-$ 18 mEq/l, calcium 10.0 mg/l, phosphate 3.5 mg/dl, magnesium 1.8 mg/dl, albumin 4.0 g/dl, blood ketones 0, glucose 99 mg/dl, and plasma osmolality 283 mOsm/kg. An arterial blood gas was obtained and revealed a pH of 7.53 mmHg, pCO2 of 20 mmHg, $HCO3^-$ of 16 mEq/l, and PO2 of 105 mmHg.

What is the acid-base diagnosis (select all that apply)?

A. Metabolic alkalosis
B. Respiratory alkalosis
C. Metabolic acidosis
D. Respiratory acidosis

The correct answers are A, B, and C. The history and physical examination suggest that three acid-base processes may be present: 1) starvation is associated with ketoacidosis, 2) loop diuretics with metabolic alkalosis, and 3) acute anxiety with hyperventilation and acute respiratory alkalosis.

Hypotension suggests volume contraction, which can maintain the metabolic alkalosis. Trousseau's sign is indicative of a reduction in ionized calcium concentration that can be caused by a sudden increase in pH due to respiratory alkalosis. The change in pH leads to increased binding of ionized calcium to protein—principally albumin. Laboratory studies reveal an increased BUN to creatinine ration consistent with volume contraction. The $HCO3^-$ is reduced and the AG is increased consistent with AG metabolic acidosis. The increase in the AG (+12), however, is significantly greater than the decrease in the $HCO3^-$ (−7), suggesting that metabolic alkalosis is also present. Blood gas studies show a significantly increased pH with a low pCO2, confirming the presence of respiratory alkalosis.

Thus, the data from the history and physical examination, laboratory studies, and blood gas studies together indicate the presence of a triple acid-base disturbance.

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Seldin DW, Rector FC Jr (1972) Degeneration and maintenance of metabolic alkalosis. Kidney Int 1:306–321

CASE 8

A 19-year old male is discovered unconscious in the park and is brought to the emergency department. Physical examination shows a BP of 120/50 mmHg, heart rate of 120 beats/min, temperature of 30 °C, slight scleral icterus and dullness, and bronchial breath sounds over the right lower lung fields. Laboratory studies show sodium 131 mEq/l, potassium 2.9 mEq/l, chloride 70 mEq/l, bicarbonate 21 mEq/l, BUN 34 mg/dl, creatinine 1.4 mg/dl, glucose 240 mg/dl, serum osmolality 320 mOsm/kg of H_20, serum ketones weakly positive, pH 7.53, pCO_2 25 mmHg, pO_2 60 mmHg, and serum albumin 3.8 g/dl.

Which ONE of the following choices best describes his acid-base disturbance?

A. Metabolic acidosis
B. Respiratory acidosis
C. Metabolic acidosis and respiratory alkalosis
D. Metabolic acidosis and metabolic alkalosis
E. Metabolic acidosis, metabolic alkalosis, and respiratory alkalosis

The correct answer is E. The patient has an alkaline blood pH indicating that he must have either metabolic or respiratory alkalosis. The low pCO_2 in the presence of alkalemia prompts the diagnosis of respiratory alkalosis. The patient also has a large anion gap (40 mEq/l), however, which indicates that he must also have a metabolic acidosis. The presence of serum ketones suggests that the metabolic acidosis may be caused in part by alcoholic ketoacidosis and the presence of an osmolar gap (calculated osmolality 287 vs. measured osmolality 320 mOsm/kg of H_20), and should prompt an evaluation for ethanol, methanol, or ethylene glycol intoxication. Circulating acetone in ketoacidotic patients will contribute to the osmolar gap despite the extremely large gap (28 mEq/l higher than normal). The serum bicarbonate is only 4 mEq/l lower than normal. The discrepancy between the change in the anion gap from baseline, and the change in the bicarbonate concentration from baseline, is suggestive of a third disturbance—metabolic alkalosis likely due to vomiting—which raised the serum bicarbonate concentration to a higher than normal level before it was reduced by the metabolic acidosis.

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CASE 9

A four-year old female with nephritic syndrome develops fever, chills, and abdominal pain. Physical examination reveals BP 85/50 mmHg, heart rate 100 beats/min, respirations 24/min, temperature 39 °C, eye exam shows sclera icterus, chest is clear, and heart is without murmur, gallop, or rub. The abdomen has right upper quadrant tenderness and guarding, and no edema in the extremities.

Laboratory values include hemoglobin 12.8 g/dl, WBC 18,000/mm^3, platelet 90,000/mm^3, serum Na^+ 135$^+$, K^+ 3.4, Cl^- 107, $HCO3^-$ 16 (all in mEq/l), and albumin 0.8 g/dl. Arterial blood gases are pH 7.44, pCO_2 24 mmHg, and pO_2 88 mmHg.

Which ONE of the following best describes the acid-base disturbance?

A. Respiratory acidosis
B. Normal anion gap metabolic acidosis
C. High anion gap metabolic acidosis
D. Normal anion gap acidosis and respiratory alkalosis
E. High anion gap metabolic acidosis and respiratory alkalosis

The correct answer is E. The anion gap is only $12[135 - (107 + 16)]$. The patient is severely hypoalbuminemic, however, causing the true anion gap to be underestimated. The albumin-corrected $\mathrm{AG} = \mathrm{AG} + 2.5(4.4 - \mathrm{albumin\ in\ g/dl}) = 12 + 2.5(4.4 - 0.8) = 22.5$. The albumin-corrected AG indicates that the patient has a high anion gap metabolic acidosis. The pCO_2 is too low ($\Delta \mathrm{pCO2} = 1.2\ \Delta \mathrm{HCO3^-} = 1.2(25 - 16) = 10.8$, thus the expected pCO2 should be $40 - 10.8 = 29.2\ \mathrm{mmHg}$), and the pH is too high to be accounted for by respiratory compensation for a simple metabolic acidosis. Therefore, the patient has a combined disturbance (choice E), most likely because of sepsis.

Reference

Gabow PA (1985) Disorders associated with an altered anion gap. Kidney Int 27:472–483

CASE 10

An 18-year old woman with hyperthyroidism is admitted with profound muscle weakness. An electrocardiogram shows high voltage and sinus tachycardia. Laboratory data shows serum Na^+ 134 mEq/l, K^+ 1.5 mEq/l, Cl^- 112 mEq/l, $HCO3^-$ 12 mEq/l, BUN 11 mg/dl, glucose 90 mg/dl, arterial blood pH 7.15, and pCO_2 32 mmHg. Urine Na^+ is 30 mEq/l, K^+ is 20 mEq/l, and Cl^- is 20 mEq/l.

Which ONE of the following is most consistent with these findings?

A. Proximal renal tubular acidosis (RTA)
B. Distal RTA
C. Hypokalemic periodic paralysis
D. Thyrotoxic periodic paralysis
E. Gitelman syndrome

The correct answer is B. The patient has severe hypokalemia associated with a normal anion gap metabolic acidosis. The urine pH is 6 and the anion gap is negative (urine $Cl^- <$ urine Na^+ + urine K^+)—findings that are consistent with a diagnosis of distal RTA. Distal RTA may present with hypokalemic paralysis, and the disorder can be associated with Graves's disease and other autoimmune diseases. Hypokalemic periodic paralysis may also complicate Graves's disease. This disorder typically affects Asian males—it is not associated with metabolic acidosis, and the urine K^+ concentration is low.

References

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CASE 11

A 15-year old girl with rheumatoid arthritis presents with dry eyes, dry mouth, and muscle weakness. Laboratory data show a normal anion gap metabolic acidosis and a serum K^+ level of 1.8 mEq/l. The urine pH is 6.0, and the anion gap is positive (Urine $Cl^- <$urine $Na^+ +$ urine K^+).

Which ONE of the following is most likely to be found?

A. Decreased urine citrate
B. Transtubular K^+ gradient >2 mEq/l
C. Fractional excretion of $HCO3^- > 5\%$
D. Urine $pCO_2 > 60$ Torr
E. Urine osmolal gap > 100 mOsm/l

The correct answer is A. The laboratory findings are consistent with renal tubular acidosis (RTA-1), or bicarbonate and potassium losses due to diarrhea. The patient presents with symptoms suggestive of Sjogren's syndrome, making RTA the more likely possibility. Renal acidification defects can be demonstrated in 50% of patients with Sogren's syndrome due to the absence of H^+-ATPase intercalated cells of the collecting duct. Urine citrate is low in distal RTA because citrate reabsorption is upgraded in the proximal tubule and serves to generate new bicarbonate. Patients with distal RTA waste K^+ in the urine so the transtubular K^+ gradient should not be low. A high fractional excretion of $HCO3^-$ is found in proximal RTA, a disorder that would not be expected to present with severe hypokalemia or a urine pH of 6. In distal RTA, the urine pCO2 is low after $HCO3^-$ loading, making answer D incorrect. A high urine osmolar gap would support diagnoses of toluene exposure, or high rates of ammonium excretion in response to diarrhea, but not a diagnosis of distal RTA.

Reference

Nicolette JA, Schwartz GJ (2004) Distal renal tubular acidosis. Curr Opin Pediatr 16: 194–198

CASE 12

A seven-month old infant is receiving hydrochlorothiazide 15 mg twice daily for bronchopulmonary dysplasia. Laboratory values taken after the start of this therapy are BUN 13 mg/dl, sodium 135 mEq/l, chloride 88 mEq/l, pH 7.53, uric acid 8.8 mg/dl, creatinine 0.7 mg/dl, potassium 3.1 mEq/l, $HCO3^-$ 33 mEq/l, and pCO_2 41 mm Hg.

What acid-base disorder has developed?

A. Uncomplicated metabolic alkalosis
B. Mixed metabolic alkalosis and respiratory alkalosis
C. Mixed metabolic alkalosis and respiratory acidosis
D. Mixed metabolic acidosis and metabolic alkalosis
E. Mixed metabolic acidosis, metabolic alkalosis, and respiratory alkalosis alkalosis

The correct answer is A. Elevated levels of serum bicarbonate and pH indicate the presence of metabolic alkalosis. Thiazide-induced loss of sodium chloride-containing urine results in mild ECF contraction and slight elevation of bicarbonate. Increased tubular secretion of acid and excretion of ammonium chloride results in the addition of new bicarbonate to the blood. The hypokalemia and volume contraction enables the tubule to increase its reabsorption of bicarbonate; thereby sustaining the elevated serum bicarbonate.

Respiratory compensation (Example: hypoventilation with resulting elevation of pCO_2) for metabolic alkalosis is much more erratic than respiratory compensation or metabolic acidosis. Although the reasons for this are not well understood, it may partially relate to developing hypoxia or hypokalemia and associated disorders that independently stimulate respiration. Any alkalosis will stimulate certain enzymes of glycolysis, resulting in lactate accumulation, but will rarely cause serum lactate to rise more than 3–4 mM/L.

References

Emmett M, Seldin DW. Clinical Syndromes of Metabolic Acidosis and Metabolic Alkalosis in Seldin, Giebisch, The Kidney: Physiology and Pathophysiology, Raven Press, New York 1985 Chapter 68 pp1567–1639

Metabolic Acid Base Disorders, Pathophysiology, Classification, and Treatment: In Arieff, De Fronzo, Fluid, Electrolyte, and Acid Base Disorders, Churchill, Livingston, New York, Chapter 7 pp269–384

Narins RG, Jones ER, Townsend R, Goodkin DA, Shay RJ (1985)

CASE 13

A six-year old black boy was referred to the Nephrology Service for evaluation of hyperkalemia. The patient has a history of sickle cell disease, which has necessitated multiple hospital admissions for crisis. Three years prior to referral, the patient suffered a left-sided cerebrovascular accident that resulted in high hemiplegia and mild excessive aphasia. The stroke was secondary to a left carotid artery thrombosis that occurred three days after triple arthrodesis of the left foot. The patient also has a past history of lead toxicity that was diagnosed at age three and has left the patient with a residual neurologic deficit consisting of both foot and wrist drop. The patient also had several episodes of gout prior to referral. When evaluated, his medications consisted of allopurinol and Dilantin®.

Physical examination revealed a normotensive black man in no distress. The only noteworthy findings were those related to his previous neurologic disorders. Laboratory examination showed plasma sodium of 137 mEq/l, potassium 6.5, chloride 110, and bicarbonate 17 mEq/l. Urinalysis showed pH was 7.0, specific gravity 1.006, with no blood or protein. Urine sodium was 66 mEq/l, potassium 59 mEq/l, and chloride 75 mEq/l. The urine anion gap was positive (urine Na^+ + urine K^+ > urine Cl^-). Plasma creatinine was 1.3, BUN 28, and uric acid 6.7 mg/dl. Creatinine clearance was 78 cc/min. A 24-hour urinary excretion of lead was 33 $\mu g/l$. Arterial blood showed a pH of 7.32, pCO_2 of 37 mm Hg, and urine pH of 6.0. On a diet containing 4.0 g of sodium/day, plasma renin activity was 0.71 ng/ml/h. Plasma aldosterone at this time was 2.0 ng/dl. These parameters were re-measured after the patient was placed on a 1.0 g sodium diet for five days and showed a plasma renin activity of 1.29 and plasma aldosterone concentration of 10 ng/dl.

What is the most likely cause of this patient's hyperkalemia (select all that apply)?

A. Voltage-dependent distal renal tubular acidosis
B. Aldosterone-resistance distal renal tubular acidosis
C. Proximal renal tubular acidosis
D. Cystinosis
E. Lead intoxication

The correct answers are A and B. This patient has hyperkalemic distal RTA. Hyperkalemic distal RTA can be divided into three types—aldosterone deficiency, aldosterone resistance, and voltage-dependent RTA. Voltage-dependent RTA results from a decreased capacity to reabsorb sodium in the collecting duct. This, in turn, reduces the lumen-negative potential difference in the tubule, which then reduces proton and potassium secretion. This defect is known to occur in patients with various sickle cell syndromes. This patient has Hb SS disease and, therefore, might be expected to develop voltage-dependent RTA. The patient also has a history of lead toxicity. The interstitial nephritis of lead is associated with hyporeninemic hypoaldosteronism. The patient clearly had decreased renin and aldosterone levels. Thus, the available data do not completely exclude aldosterone resistance as the cause of this patient's disorders. Two types of aldosterone resistance have been described. One is associated with profound salt wastage. This disorder is seen in very early childhood. Another form of aldosterone resistance has been described in adults and is associated with enhanced permeability of the distal nephron to chloride and is associated with salt retention. The absence of hypertension in this patient argues against this diagnosis. To make the diagnosis of voltage-dependent RTA with finality, we would have to demonstrate that this patient did not respond to mineralocorticoid administration while on a high salt diet, but that he did respond normally regarding potassium excretion, to the administration of sodium with a poorly reabsorbable anion (Example: sulfate).

Reference

Batlle DC, Arruda JAL, Kurtzman NA (1981) Hyperkalemic distal renal tubular acidosis associated with obstructive uropathy. N Eng J Med 304:373–380

CASE 14

A 19-year old white man presented to the emergency room because of hematemesis and melena. The patient gave a vague history of peptic ulcer disease with recent ingestion of large quantities of beer. The patient was able to walk but was only oriented to person. BP was 130/80 mm Hg, pulse 92 beats/min, and respirations 32/min. A nasogastric aspiration yielded coffee-ground material that was strongly heme-positive. Initial blood examination showed sodium of 105, potassium of 3.2,

chloride of 71, and bicarbonate of 12 mEq/l. BUN was 81, creatinine 0.8, and glucose 140 mg/dl. Serum osmolality was 234 mOsm/kg H_2O. Urine osmolality was 373 mOsm/kg H_2O. Urine sodium 73, potassium 29, and chloride 2 mEq/l, and there was trace ketonuria. Arterial blood pH was 7.36, pCO_2 18, and pO_2 111 mm Hg.

What is the MOST likely cause of this patient's acid-base disturbance (select all that apply)?

A. Salycilate intoxication
B. Lactic acidosis
C. Ethylene glycol intoxication
D. Ethanol intoxication
E. Methanol intoxication

The correct answers are C, D, and E. Despite the history of vomiting and the virtual absence of chloride in the urine, there is little evidence that this patient had metabolic alkalosis. Bicarbonate concentration is very low. The hypochloremia can almost entirely be accounted for by the hemodilution (Example: The degree of hypochloremia parallels the degree of hyponatremia). The low blood pH in the presence of any increased anion gap suggests metabolic acidosis. With a bicarbonate concentration of 12 mEq/l, one would expect a blood pH considerably lower than the observed 7.36 if this a case of uncomplicated metabolic acidosis. The pCO_2 of 18 mm Hg suggests the possibility that there is an associated respiratory alkalosis. The most likely cause of increased anion gap in metabolic acidosis in this patient is alcoholic ketoacidosis. This diagnosis is supported by the finding of a blood alcohol level of 52 mg/dl and trace ketones in the urine. Other causes of metabolic acidosis to be excluded include methanol, salicylate, ethylene glycol, paraldehyde, renal failure, and lactic acidosis. The establishment of a correct diagnosis in a patient such as this is essential because methanol or ethylene glycol ingestion should be treated with alcohol, while obviously a patient with alcoholic ketoacidosis should not be given alcohol. An additional piece of information helpful in the establishment of this diagnosis is the pattern of urinary electrolytes. This patient had 93 mEq/l of cation in his urine, with only 2 mEq/l of chloride. His urine pH was 5. Thus, the cause of the urinary anion gap could not be attributed to a high urinary concentration of bicarbonate. Because there was no reason to think that large amounts of phosphate and sulfate were present in the urine, the anion gap could only be attributed to the presence of the salt of a weak organic acid such as ketoacids.

Another useful piece of laboratory information that should also point toward the diagnosis of alcoholic ketoacidosis is that the calculated osmolality was 227 while the measured was 234 mOsm/kg H_2O. Under ordinary circumstances, the calculated osmolality exceeds the measured osmolality. The observation of several of these patterns suggests the presence of an osmotically active substance other than sodium, potassium, glucose, and urea. The presence of 17 mOsm/kg H_2O of alcohol (78:4.6) identifies the cause of this reversal in calculated and measured osmolality.

Bicarbonate was not administered to this patient because his blood pH was close to normal. Even when the blood pH is markedly reduced, bicarbonate should be administered sparingly because the salts of ketoacid represent potential bicarbonate. That is to say, when the generation of an increased amount of ketoacids ceases, these organic salts will be metabolized by the liver into bicarbonate. If large amounts of bicarbonate are given at the same time bicarbonate is regenerated, acute alkalemia may result. The cause of this patient's respiratory alkalosis is not immediately apparent. It was likely the result of the central nervous system effect of hyponatremia. This is supported by the fact that the patient had a grand mal seizure attributed to hyponatremia shortly after arriving in the emergency room. The hyponatremia was, no doubt, the result of volume contraction secondary to vomiting and loss of sodium in the urine accompanying the excretion of beta-hydroxybuturate and acetoacetate. This impression is confirmed by the observation of hyponatremia rapidly corrected following the expansion of volume with isotonic saline.

References

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Gabow PA (1985) Disorders associated with an altered anion gap. Kidney International 27: 472–483
Gennari JF (1984) Serum osmolality. Uses and limitations. N Engl J Med 310:102–105
Smithline N and Gardner K (1976) Gaps – amniotic and osmolal. J.A.M.A 236:1594–1597

CASE 15

A five-year old girl complained of easy fatigability and weakness. Her history was otherwise unrevealing, and she vigorously denied vomiting or the use of any medications, including diuretics. Physical examination revealed a thin, anxious child with a normal BP. Her examination was, otherwise, unremarkable. Her serum sodium was 141 mEq/l, potassium 2.1 mEq/l, chloride 85 mEq/l, and bicarbonate 45 mEq/l. Her urine sodium was 60 mEq/l, urine potassium was 130 mEq/l, and her urine chloride was 190 mEq/l.

What are the most likely causes of her hypokalemic metabolic alkalosis?

A. Bartter's syndrome
B. Primary hyperaldosteronism
C. Liddle's syndrome
D. Cushing's syndrome
E. Licorice ingestion

The correct answer is A. The findings of hypokalemia, metabolic alkalosis, a high rate of urinary potassium excretion, and a normal BP suggests the diagnosis of

Bartter's syndrome. Other forms of mineralocorticoid excess (Example: primary aldosteronism, adrenal enzyme defects, Cushing's syndrome, or licorice ingestion) are excluded by the normal BP.

A urinary chloride below 15 mEq/l would have been virtually diagnostic of the early phase of self-induced vomiting. The high urine chloride is most consistent with either diuretic abuse or Bartter's syndrome. The urine should be screened for the presence of diuretics and the plasma renin and aldosterone levels determined.

Treatment of hypokalemic alkalosis due to self-induced vomiting or diuretic abuse consists of volume replacement with sodium chloride and potassium supplementation with potassium chloride. Treatment will be successful only if the patient's cooperation can be enlisted and the self-abuse terminated, with psychiatric assistance if necessary.

Bartter's syndrome is a rare familial defect of chloride reabsorption in the ascending limb of Henle—Loop of Henle—associated with salt and potassium wasting and secondary (hyperreninemic) hyperaldosteronism. The hypokalemia induced by both a defect in potassium reabsorption in the thick ascending limb, and an increased secretion of potassium in the cortical collecting tubule due to high rates of distal sodium delivery, is particularly resistant to treatment, even with heroic doses (500 mEq/day) of potassium chloride. The hypokalemia is probably responsible for the decreased response to angiotensin-2 and high levels of urinary prostaglandins, which are characteristics of this disease. Modest sodium restriction and use of potassium-sparing diuretics like amiloride may be helpful. Some patients with Bartter's syndrome also exhibit defective magnesium conservation requiring magnesium supplementation.

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Sabatini S, Arruda JAL, Kurtzman NA (1978) Disorders of acid-base balance. Med Clin North Am 62:1223–1255

CASE 16

A four-year old boy was brought to the emergency room obtunded. On examination, the patient was lethargic and kept begging for water. His supine BP was 60/40 mm Hg and was not detectable in the upright position. His liver was firm, nontender, and enlarged. The physical examination was, otherwise, unremarkable. Chest x-ray showed a left lower lobe infiltrate. Central venous pressure was 3 cm H_2O. One liter of normal saline was rapidly infused, after which his BP was 80/60 mm Hg with a central venous pressure of 6 cm H_2O. At this point, his initial blood chemistries showed concentrations of serum chloride 46 mEq/l, bicarbonate 28 mEq/l, potassium 4.9 mEq/l, sodium 128 mEq/l, urea nitrogen 128 mg/dl, creatinine 8.5/dl,

and glucose 148 mg/dl. Blood pH was 7.41, pCO_2 44 mm Hg, and pO_2 60 mm Hg. The urinalysis was normal, and urine electrolytes were sodium 14 mEq/l, chloride 1 mEq/l, and potassium 60 mEq/l. Urine creatinine concentration was 203 mg/dl.

What is the most likely acid-base disorder in this patient?

A. Mixed metabolic acidosis and alkalosis
B. Uncomplicated metabolic acidosis
C. Uncomplicated metabolic alkalosis
D. Mixed metabolic acidosis and respiratory acidosis
E. Mixed metabolic alkalosis and respiratory acidosis

The correct answer is A. This is a case of mixed metabolic acidosis and alkalosis. The metabolic alkalosis is the result of severe and prolonged vomiting. Its presence is reflected by the urine chloride concentration of 1 mEq/l and a plasma chloride concentration of 46 mEq/l. The high anion gap metabolic acidosis is the result of a combination of factors. The patient was markedly volume-contracted. Volume contraction resulted in severe organ under-perfusion. This is, in part, reflected by the severe prerenal azotemia. The combination of tissue underperfusion and hypoxia—the result of chronic and acute pulmonary disease—doubtlessly resulted in the generation of excess lactic acid. It is also possible that this patient had ketonemia. The finding of no ketones in the urine does not exclude this possibility. In the presence of tissue hypoxia, the ratio of reduced-to-oxidized nicotinamide adenine dinucleotide (NAD) will increase, and ketones, should they be present, will be converted from acetoacetate to beta-hydroxybuturate. This latter salt does not react with the standard laboratory tests for ketones. Thus, the severe anion gap acidosis present in this patient was, most likely, the result of the accumulation of sulfate and phosphate, owing to severe renal under-perfusion, the generation of excess lactate, and possibly, to ketonemia as well. The loss of acid from the stomach negated the gain of acid from tissue hypoxia so that the blood pH was normal.

Following the infusion of large amounts of salt and water, the patient's BUN and creatinine fell within 72 hours to 20 and 0.9 mg/dl, respectively. During this period, his bicarbonate concentration increased to 35 mEq/l and his arterial pH rose to 7.51. This was, no doubt, the result of metabolism of the salts of weak organic acids into bicarbonate. This finding further suggests the presence of excess lactate and ketone bodies. In summary, this is a severe case of mixed metabolic acidosis and alkalosis due to vomiting and tissue hypoxia.

Reference

Emmett M, Seldin DW (1985) Clinical Syndromes of Metabolic Acidosis and Metabolic Alkalosis in Seldin, Giebisch (eds), The Kidney: Physiology and Pathophysiology, Raven Press, New York Chapter 68 pp1567–1639

CASE 17

A 19-year old primipara in her 28^{th} week of gestation was admitted through the emergency room with a two-week history of severe nausea and vomiting. Her past medical history included a right-sided uninephrectomy at 14 years of age for infection.

Physical examination revealed an acutely ill-appearing young, pregnant woman with decreased skin turgor, dry buccal mucosa, and a sweetish odor to her breath. She was breathing deeply 28 times/min. Her supine BP was 102/74 mm Hg, and her pulse was 96/min. Her standing BP was 80/50 mm Hg, pulse 116/min, and she complained of feeling faint.

Her serum sodium was 140 mEq/l, potassium 4.6 mEq/l, chloride 112 mEq/l, bicarbonate 8 mEq/l, urea nitrogen 10 mg/dl, creatinine 2.1 mg/dl, and glucose 62 mg/dl. Her arterial blood pH was 7.28, pCO_2 15.5 mm Hg, pO_2 110 mm Hg, and bicarbonate 7.1 mM/l. Her venous blood L-lactate was 0.6 mM/l (normal range 0.5–2.2 mM/l), and her serum was positive for ketone bodies in a 1:8 dilution.

How many acid-base disturbances can you spot in this patient?

A. Mixed metabolic acidosis and respiratory alkalosis
B. Mixed metabolic acidosis, respiratory alkalosis, and metabolic alkalosis
C. Mixed metabolic alkalosis and respiratory acidosis
D. Mixed metabolic acidosis and reparatory acidosis
E. Mixed metabolic acidosis, metabolic alkalosis, and respiratory acidosis

The correct answer is B. Her anion gap (AG) is 24.6 mEq/l, which is only slightly elevated, yet the patient clearly has a metabolic acidosis (low serum bicarbonate and arterial pH). Hyperchloremia has narrowed the AG nearly to normal, yet the serum sodium is normal; therefore, the hyperchloremia must be due to an acid-base disturbance from either a primary titration or loss of bicarbonate (normal AG metabolic acidosis), or a primary loss of CO_2 (chronic respiratory alkalosis with metabolic compensation). The patient is unlikely to be manifesting a combination of true metabolic acidosis (Example: both a normal AG acidosis and a high AG acidosis) because her bicarbonate is inappropriately low for the pH. If the low bicarbonate were due to titration of a noncarbonic acid (high AG acidosis) alone, there should be a nearly 1:1 correspondence of AG and bicarbonate. Yet, there has been a 13 mEq/l fall in bicarbonate with only an 8 mEq/l rise in the AG. This apparent discrepancy between AG and bicarbonate can only be explained by the effect of an additional acid-base disturbance that is lowering the bicarbonate and raising the chloride without lowering the pH, and that can only be chronic respiratory alkalosis. We have, therefore, identified two acid-base disturbances: 1) high AG metabolic acidosis and 2) chronic respiratory alkalosis.

It is clear that the unmeasured anions accounting for the high AG are ketoacidosis (acetoacetate and beta-hydroxybuturate) produced by lipolysis during energy

starvation. Ketonemia interferes with the laboratory determination of creatinine, leading to an apparent but false elevation of serum creatinine. Ketone bodies poorly reabsorbed by the renal tubule are rapidly excreted in the urine. Determination of urine electrolytes should show ample sodium and potassium being excreted with the ketones (unless severe volume depletion supervenes), whereas, the urine chloride will be low because of the presence of unmeasured ketones. All pregnant women have a mild chronic respiratory alkalosis caused by high levels of circulating progesterone, which stimulate the respiratory center. Vomiting is associated with loss of HCl from the stomach, which usually leads to a hypochloremic metabolic alkalosis. Volume depletion from the loss of chloride in the emesis and sodium in the urine (induced by filtration of bicarbonate), (Example: a loss of sodium chloride early in vomiting induces the production of aldosterone, which magnifies the loss of potassium from the distal nephron in exchange for the sodium being reabsorbed with bicarbonate). Although there is no evidence of it other than the history of vomiting, a third acid-base disturbance may also be present but is being masked by the other two—namely, a hypochloremic metabolic (volume) alkalosis with renal potassium wasting).

The starvation ketosis and the possible hidden hypokalemic metabolic alkalosis should readily be corrected by administration of salt, glucose, and potassium chloride. The respiratory alkalosis is physiologic and requires no treatment.

References

Emmett M, Seldin DW. Clinical Syndromes of Metabolic Acidosis and Metabolic Alkalosis in Seldin, Giebisch (1985) The Kidney: Physiology and Pathophysiology, Raven Press, New York Chapter 68 pp1567–1639

Sabatini S, Arruda JAL, Kurtzman NA (1978) Disorders of acid-base balance. Med Clin North Am 62:1223–1255

CASE 18

A six-year old white male is brought into the emergency room stuporous. Laboratory data show serum sodium 140 mEq/l, chloride 103 mEq/l, bicarbonate 10 mEq/l, potassium 3.9 mEq/l, urea nitrogen 10 mg/dl, and glucose 60 mg/dl. Serum ketones were trace positive. The blood pH was 7.50, and pCO_2 was 13 mm Hg. Prothrombin time was 18 min (normal 12 min). Blood salicylate was 85 mg/dl.

What is the most likely acid-base disturbance?

A. Uncomplicated metabolic acidosis
B. Uncomplicated respiratory alkalosis
C. Mixed metabolic acidosis and respiratory alkalosis
D. Mixed metabolic acidosis and alkalosis
E. Mixed metabolic acidosis, metabolic alkalosis, and respiratory alkalosis

The correct answer is C. A diagnosis of pure chronic respiratory alkalosis might be made in this patient with a blood pH of 7.5 because the level of plasma bicarbonate is appropriate for the level of pCO_2 ($HCO_3 = 0.5\ \Delta pCO_2$). There is an increased anion gap, however, that suggests the presence of metabolic acidosis as well.

The combination of respiratory alkalosis and high anion gap metabolic acidosis is seen in aspirin intoxication, in patients with sepsis, and in those with liver disease and lactic acidosis. This patient had ingested large quantities of analgesics, most likely containing salicylate, because she had elevated blood levels of salicylate.

Salicylates stimulate the respiratory center, and also cause uncoupling of oxidative phosphorylation and induce an increment in lactic acid and ketoacid production. Early studies suggested that respiratory alkalosis was common in adults, and metabolic acidosis was common in children. More recent studies have indicated that the combination of respiratory alkalosis and metabolic acidosis is actually seen in 50% of adults and children.

References

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Krapf R, Beeler I, Hertner D, et al. (1991) Chronic respiratory alkalosis: The effect of sustained hyperventilation on renal regulation of acid-base equilibrium. N Engl J Med 324:1394–1401

CASE 19

A 12-year old white male with a history of chronic lung disease was admitted to the hospital with a one-week history of increasing shortness of breath. He denied chest pain or hemoptysis. Physical examination revealed a well-developed male in respiratory distress. BP was 120/70 mm Hg supine and upright, pulse was 100/min, and temperature was 38 °C. There were diffuse rhonchi over both lungs. There were no murmurs or gallops and no peripheral edema. Laboratory data showed serum sodium 131 mEq/l, potassium 3.2 mEq/l, chloride 90 mEq/l, bicarbonate 38 mEq/l, serum creatinine 1.0 mg/dl, and urea nitrogen 15 mg/dl. The blood pH was 7.30 ($H^+ = 51$ nEq/l) and pCO_2 was 80 mm Hg.

What acid-base disturbance is present at this time?

A. Uncomplicated metabolic alkalosis
B. Mixed metabolic alkalosis and respiratory acidosis
C. Uncomplicated respiratory acidosis
D. Uncomplicated metabolic alkalosis
E. Mixed metabolic acidosis and alkalosis

The correct answer is C. The elevated blood pCO2 and bicarbonate and reduced blood pH are consistent with respiratory acidosis. Moreover, the level of plasma

bicarbonate concentration is within the range expected for an individual with pure chronic hypercapnia ($\Delta\ HCO3^{-} = 0.35\ \Delta\ pCO2$). The history of several days of respiratory distress is very helpful in documenting the chronicity of the acid-base disturbance.

The increase in plasma bicarbonate concentration noted in response to chronic elevations in pCO_2 occurs in two steps. Initially, a small rise in plasma bicarbonate of a few mEq/l occurs as a result of titration of nonbicarbonate buffers by carbonic acid arising from the CO_2. The largest increment in plasma bicarbonate is generated as the elevated pCO_2 stimulates both acid excretion (thereby adding a substantial quantity of bicarbonate to body fluids) and renal bicarbonate reabsorption, thus sustaining the elevated plasma bicarbonate concentration. Studies in animals exposed to graded degrees of hypercapnia indicated that three to five days were required for a steady state to emerge. At that time, it was found that the plasma bicarbonate concentration had risen by an average of 3.5 mEq/l, and the H^{+} concentration by 1.7 nEq/l for every 10 mm Hg rise in pCO_2. Studies in humans exposed to acute hypercapnia for several hours have confirmed the similarity of response in animals. Examination of acid-base parameters in patients with chronic hypercapnia as a result of chronic lung disease has generally demonstrated a qualitatively similar response.

After therapy, both blood pCO_2 and pH were decreased significantly, but blood bicarbonate remained elevated, suggesting the development of metabolic alkalosis. Some degree of metabolic alkalosis commonly complicates the course of chronic respiratory acidosis for the following reason: the rate of mobilization and excretion of carbon dioxide by the lung is much more rapid than the rate of mobilization and excretion of bicarbonate by the kidney. Therefore, metabolic alkalosis will be seen in all patients if ventilation is rapidly improved, as in this case. This type of metabolic alkalosis is transient, and acid-base parameters will return to normal as bicarbonate is excreted in the urine. During the adaptation to chronic hypercapnia, there are increased losses of chloride, sodium, and potassium in the urine. If sufficient dietary chloride is not given to the individual when pCO_2 has returned to normal, excretion of bicarbonate by the kidney will be curtailed just as it is in other forms of chloride-responsive metabolic alkalosis. The regimen of dietary sodium restriction contributed to the metabolic alkalosis in this patient.

Reference

Kappy M, Morrow G (1980) A diagnostic approach to metabolic acidosis in children. Pediatr 65:351–356

CASE 20

A 19-year old white male was found unconscious in the street and was brought into the emergency room. The patient was stuporous without focal neurological signs. BP was 120/80 mm Hg and pulse was 80/min. Examination of the head, eyes, ears,

nose, and throat was unremarkable. Chest was clear to auscultation and percussion. The remainder of the physical examination was unremarkable.

Laboratory data showed: serum sodium concentration 137 mEq/l, potassium 4.6 mEq/l, chloride 102 mEq/l, bicarbonate 15 mEq/l, urea nitrogen 43 mg/dl, creatinine 10 mg/dl, and glucose 200 mg/dl. Serum ketones were trace positive, and serum osmolality was 330 mosm-kg H_2O. Arterial pH was 7.32, and pCO_2 was 30 mm Hg. Urinalysis was negative with a pH of 5.

What acid-base disorder is present?

A. Uncomplicated metabolic acidosis
B. Uncomplicated respiratory alkalosis
C. Mixed metabolic acidosis and respiratory alkalosis
D. Mixed metabolic acidosis and alkalosis
E. Mixed respiratory acidosis and alkalosis

The correct answer is A. A low plasma bicarbonate concentration, and a low pH signify the presence of metabolic acidosis. The pCO_2 is depressed by 10 mm Hg, and the plasma bicarbonate concentration is depressed by 9 mEq/l. This level of respiratory compensation is appropriate for the steady-state level of bicarbonate. The fall in plasma bicarbonate concentration is matched by a commensurate rise in the unmeasured anion concentration, therefore this is a pure high AG-type of metabolic acidosis.

Sodium and its counterbalancing anions—bicarbonate and chloride and glucose and urea—account for the bulk of the osmolality active particles present in the circulation. Thus, the serum osmolality can rapidly be estimated by the following formula:

$$2(\mathrm{Na}^+) + \mathrm{BUN}\ (\mathrm{mg/dl})/2.8 + \mathrm{glucose}\ (\mathrm{mg/dl})/18$$

The value obtained with this calculation will not exceed the value measured using freezing point depression by more than 10 mOsm. A value greater than this indicates the presence of an additional osmotically active substance in the circulation. The difference between the measured and the estimated serum osmolality is often termed the *osmolar gap*. Methanol intoxication, ethylene glycol intoxication, and alcohol ketoacidosis are disorders associated with high anion gap metabolic acidosis and increased serum osmolality. Thus, the value of the latter is helpful in the diagnosis of such disorders. The serum osmolality in this patient was 330 mOsm/kg H_2O, giving an osmolar gap of 30 mOsm/kg H_2O. The patient had no oxalate crystals in the urine, as found in ethylene glycol intoxication, and there was no evidence of optic papillitis or funduscopic examination as might be anticipated in a patient with methanol intoxication.

Reference

Kappy M, Morrow G (1980) A diagnostic approach to metabolic acidosis in children. Pediatr 65:351–356

CASE 21

A 16-year old white male was admitted to the hospital with a weight loss of 5 kg and decreased appetite. There was no history of nausea or vomiting. The patient denied any history of hypertension, kidney disease, or diuretic ingestion.

Physical examination revealed a cachectic white male in no acute distress. BP was 160/110 mg Hg supine, and 160/105 mm Hg upright. Pulse was 80/min, temperature was 38.5 °C, and weight was 46 kg. Examination of the chest showed rales at the left base, and a chest x-ray revealed an infiltrate in this area of the lung.

Laboratory data show a serum sodium level of 142 mEq/l, potassium 3.3 mEq/l, chloride 91 mEq/l, bicarbonate 35 mEq/l, creatinine 0.9 mg/dl, and urea nitrogen 30 mg/dl. Blood pH was 7.55 (H^+ 26 nEq/l), pCO_2 was 38 mm Hg, and urinary pH was 6.

The patient was given an unrestricted salt intake, and two days later, repeat laboratory values revealed the following: serum sodium 139 mEq/l, potassium 2.8 mEq/l, chloride 86 mEq/l, and bicarbonate 33 mEq/l.

What acid-base disturbance is present?

A. Uncomplicated respiratory acidosis
B. Uncomplicated metabolic alkalosis
C. Mixed respiratory acidosis and metabolic alkalosis
D. Mixed metabolic alkalosis and acidosis
E. Mixed respiratory acidosis and alkalosis

The correct answer is B. The presence of an elevated serum bicarbonate concentration and blood pH signifies metabolic alkalosis. Classically, metabolic alkalosis is also associated with an elevated plasma pCO_2 ($\Delta pCO_2 = 0.4–0.7\Delta HCO_3^-$). This is the consequence of suppression of ventilation by the elevated pH. It requires 24–36 hours for the maximal suppression of ventilation to become manifest. At that time, it should be anticipated that pCO_2 would have risen by approximately 5 mm Hg for every 10 mEq/l rise in plasma bicarbonate concentration. In this patient, the pCO_2 did not increase appropriately, and the patient was hyperventilating secondary to his pneumonia, giving him a picture of metabolic alkalosis with superimposed respiratory alkalosis.

Measurement of urinary chloride is very helpful in the assessment of the cause of metabolic alkalosis. A low urinary chloride concentration (less than 10 mEq/l) is usually seen in patients with metabolic alkalosis due to vomiting, gastric drainage, post-chronic diuretic therapy, post-hypercapnia and chloride-losing diarrhea. In

such patients, the metabolic alkalosis responds well to sodium chloride administration. Metabolic alkalosis with high urinary chloride (more than 15 mEq/l) is encountered in patients with Bartter's syndrome, active chronic diuretic use with severe hypokalemia, states with excess mineralocorticoids, and licorice ingestion. In these patients, the metabolic alkalosis is not easily corrected with administration of sodium chloride. The urinary chloride in this patient was 40 mEq/l, and he failed to correct his metabolic alkalosis with the administration of sodium chloride. Subsequent evaluation revealed that the patient had primary aldosteronism.

Slight increase in the anion gap of 3–5 mEq/l is a common finding in pure metabolic alkalosis, although more pronounced in the saline-responsive form of metabolic alkalosis. Thus, metabolic alkalosis is one of the exceptions to rule out—an elevated unmeasured anion concentration signifies the presence of metabolic acidosis. The increased anion gap appears to be due, in part, to titration of the negative charges on circulating proteins as pH rises.

References

Emmett M, Seldin DW (1985) Clinical Syndromes of Metabolic Acidosis and Metabolic Alkalosis in Seldin, Giebisch (eds), The Kidney: Physiology and Pathophysiology, Raven Press, New York Chapter 68 pp1567–1639

Seldin DW, Rector FC Jr (1972) Degeneration and maintenance of metabolic alkalosis. Kidney Int 1:306–321

CASE 22

A seven-year old boy was admitted with severe vomiting, dehydration, and oliguria over the past two days. On examination, his BP was 76/36 mmHg, temperature wass 38 °C (orally), and he was 10% dehydrated. He was not pale or jaundiced, and he did not have clinical signs of an acidosis. The abdomen was soft, with a 3-cm hepatomegaly. The hands showed increased pigmentation in the hand creases and the skin creases over the joints of the fingers. Initial laboratory data showed: hemoglobin 9.3 g/dl, white cell count 6000/ml, serum sodium 132 mEq/l, potassium 5.7 mEq/l, chloride 105 mEq/l, bicarbonate 15 mEq/l, BUN 22 mg/dl, and creatinine 2,2 mg/dl. The C-reactive protein level was 10 mg/dl, amylase was 116 units/l, blood cultures were negative, and streptococcus viridans was cultured from a throat swab. His urine showed 1+ protein, no blood, a pH of 6, and no visible eosinophils. The fractional excretion of sodium was 3%. Urine culture was sterile. He was rehydrated and treated as if he had septicemia. The renal function tests rapidly returned to normal. Ultrasound examination of the kidneys was normal. The paternal grandmother had pernicious anemia, and paternal aunt had increased pigmentation of the face and in the hand creases and had missing eyelashes and eyebrows. He was discharged well.

Seven days later he was readmitted in shock, and his temperature rose to 39C°. The liver was now 6 cm. The gallbladder was tender and edematous upon

sonography; a diagnosis of acalculus cholecystitis was considered. On admission, venous blood showed: sodium 130 mEq/l, potassium 5.5 mEq/l, chloride 101 mEq/l, bicarbonate 17 mEq/l, BUN 15 mg/dl, and creatinine 1.1 mg/dl. Serum complements C3 and C4 levels, as well as ANA and dsDNA antibody titers, were normal. Urinary sodium was 135 mEq/l, potassium was 19 mEq/l, and chloride was 109 mEq/l. The fractional sodium excretion was 2.2%. A brain MRI was normal. He was resuscitated, treated, and further investigated.

What ONE of the following choices is the most likely diagnosis?

A. Acute tubular necrosis
B. Acute interstitial nephritis
C. Adrenoleukodystrophy
D. Pre-renal azotemia
E. Obstructive hydronephrosis

The correct answer is C. The urinary anion $[(\mathrm{Na}^{+}\ (135) + \mathrm{K}^{+}\ (19) - \mathrm{Cl}^{-}\ (109)]$ is positive, associated with metabolic acidosis, and hyperkalemi suggests a Type-4 renal tubular acidosis that can be associated with an Addison crisis, and this would also explain the increased fractional sodium excretion. In a male child presenting with Addison's disease, adrenoleukodystrophy needs to be excluded, because adrenal insufficiency may be the first manifestation. Methods to diagnosis include: MRI to demonstrate a typical bright parieto-occipital white matter and an increase in very long-chain fatty acids, which are consistent with the diagnosis of X-linked adrenoleukodystrophy.

Treatment consists of cortisol and fludrocortisone acetate for adrenal insufficiency, and the leucodystrophy is treated with dietary modification and/or a bone marrow transplant. The acute tubular necrosis could not be explained because fractional excretion of sodium was only marginally increased, and renal function returned to normal on rehydration. A fractional excretion of sodium of 3% is too high for pre-renal failure—barely high enough for acute tubular necrosis—but is what one would expect with a mineralocorticoid deficiency. A diagnosis of interstitial nephritis associated with urinary tract infection could not be substantiated because of negative urine culture. Obstructive hydronephrosis can be excluded in the presence of normal renal ultrasound.

References

Battle DC, Hizon M, Cohen E, et al. (1988) The use of the urinary anion gap in the diagnosis of hyperchloremic metabolic acidosis. N Engl J Med 318:594–599

Moser HW, Moser AD, Frayer H, et al. (1981) Adrenoleukodystrophy: increased plasma content of saturated very long chain fatty acids. Neurology 31:1241–1249

Rizzo WB, Leshner RT, Odore A, et al. (1989) Dietary erucic acid therapy for X-linked adrenoleukodystrophy. Neurology 39:1415–1422

Sadeghi-Nejad A, Senior B (1988) Adrenomyeloneuropathy presenting as Addison's disease in childhood. N Engl J Med 322:6–13

CASE 23

A 13-year old girl presents with proximal muscle weakness. Laboratory data include: blood pH 7.3, sodium 139 mEq/l, potassium 2.7 mEq/l, chloride 11 mEq/l, bicarbonate 17 mEq/l, creatinine 0.5 mg/dl, and osmolality 294 mOsm/kg. The urine pH is 6.6, sodium is 86 mEq/l, potassium is 32 mEq/l, chloride is 113 mEq/l, and osmolality is 450 mOsm/kg.

Based on the urine anion gap and the serum electrolytes, which ONE of the following statements is MOST likely to be correct?

A. The patient has Type 1 distal renal tubular acidosis.
B. Renal tubular acidosis has been ruled out.
C. A diagnosis of renal tubular acidosis in this patient requires an acid-loading test.
D. A diagnosis of renal tubular acidosis in this patient requires a measurement of the fractional excretion of bicarbonate.
E. A diagnosis of renal tubular acidosis requires a measurement of urine pCO_2.

The correct answer is A. The patient has a normal anion gap metabolic acidosis with hypokalemia. The following findings in this case support a diagnosis of renal tubular acidosis (RTA): a) there is renal potassium wasting with a urine potassium of 32 mEq/l despite hypokalemia, b) the urine pH is >5.5 despite of academia, c) the positive urine anion gap is inconsistent with a high urinary ammonium concentration as would occur in diarrhea. An acid loading test (answer C) is needed to diagnose incomplete RTA in patients with a normal serum bicarbonate concentration, but it is not needed in this patient, who is acidemic. Bicarbonate loading is used to distinguish between proximal and distal RTA, but is not needed to make the diagnosis of RTA and is contraindicated in this patient because of hypokalemia; therefore, answer D is incorrect. Urine pCO_2 (answer E) would help identify an occult acid secretary defect if the urine pH were low and it could help identify the mechanism for RTA, but is not needed to make a diagnosis in this patient who has classic features of distal RTA.

References

Batlle DC, Hizon M, Cohen E, et al. (1988) The use of urinary anion gap in the diagnosis of hyperchloremic metabolic acidosis. N Engl J Med 318:594–599
Nicolette JA, Schwartz GJ (2004) Distal renal tubular acidosis. Curr Opin Pediatr 16:194–198

Chapter 3
Disorders of Divalent Ion Metabolism

CASE 1

You are asked to evaluate a family with a high incidence of hypercalciuria and nephrolithiasis, and you find that two children born to a sibling with hypercalciuria and nephrolithiasis died in early childhood of renal failure and had "calcium in their kidneys." An extensive work-up reveals that the family members affected with hypercalciuria also demonstrated hypomagnesaemia and hypermagnesuria.

Which ONE of the following is the MOST likely basis for this disorder?

A. Isolated recessive hypomagnesaemia
B. Familial hypomagnesaemia secondary to mutations in paracellin gene
C. Familial defect in Ca/Mg-sensing receptor
D. Hypomagnesaemia with secondary hypercalciuria associated with a defect in transient receptor potential channel
E. Abnormal proximal tubular oxalate transporter

The correct answer is B. Paracellin-1—a tight-junction protein mediating paracellular transport—is mutated in the familial hypomagnesaemia, complicated by hypercalciuria and nephrolithiasis. Isolated recessive hypomagnesaemia is not associated with hypercalciuria, and defects in the calcium sensing receptor are not associated with nephrolithiasis in this fashion. Defects in the tubular reabsorption of phosphate are associated with hypocalcemia. An abnormality in oxalate transport would not produce hypercalciuria.

Reference

Konard M, Weber S (2003) Recent advances in molecular genetics of hereditary magnesium-losing disorders. J Am Soc Nephrol 14:249–260

F. Assadi, *Clinical Decisions in Pediatric Nephrology.*

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CASE 2

A five-year old boy is evaluated for hypercalcemia. The patient has been asymptomatic. The abnormality was detected on a routine screening laboratory panel. The patient has been followed for one year after undergoing a negative evaluation for an occult malignancy. His physical examination remains normal, and his laboratory studies reveal: serum calcium 12.5 mg/dl, phosphorous 2.9 mg/dl, PTH 40 pg/ml, and urine calcium 463 mg/24 hours.

Which ONE of the following choices would be best for this patient?

A. Continued observation
B. Parathyroidectomy
C. Begin a calcimimetic agent
D. Evaluate family members for genetic defect in the calcium sensing receptor
E. Begin therapy with calcitriol

The correct answer is B. This patient has primary hyperparathyroidism and fulfills the criteria for surgical removal of hyperparathyroidism because his 24-hour urinary calcium excretion is greater than 250 mg, and his serum calcium is greater than 1 mg/dl above normal.

Reference

Bilexikian JP, Potts JT, Jr, Fuleihan Gel H, et al. (2002) Summary statement from a workshop on asymptomatic primary hyperparathyroidism: a perspective for the 21st century. J Clin Endocrinol Metab 87:5353–5361

CASE 3

Which ONE of the following statements BEST describes the actions of a high-protein diet (2g/kg/day) versus a low-protein diet (0.7 g/kg/day) on calcium metabolism?

A. Intestinal absorption of dietary calcium is 40% higher on a high-protein diet than it is on a low-protein diet.
B. High-protein diet stimulates parathyroid hormone secretion.
C. Hypercalciuria induced by a high-protein diet is unrelated to gastrointestinal calcium absorption.
D. High-protein intake leads to a fall in bone mineral density.
E. Renal tubular defects of high protein intake on calcium reabsorption are excreted in the proximal tubule.

The correct answer is A. In the study cited, low dietary protein was associated with secondary hyperparathyroidism because it led to reduced dietary calcium

absorption. Recent data also suggest that high dietary protein intake is not associated with a reduction in bone mineral content—in fact, the opposite was found.

Reference

Kerstetter JE, O'Brian KO, Insogna KL (2003) Low protein intake: the impact on calcium and bone homeostasis in humans. J Nutr 133:855S–861

CASE 4

You are asked to see a seven-year old boy because of hypocalemia during a hospitalization for the evaluation of a recent seizure disorder, which occurred three days ago. Phenytonin has been given for his seizure. Past medical history is significant for chronic kidney disease of unknown etiology. He has been taking sevelamer hydrochloride for the control of mild hyperphosphatemia, and he has received no vitamin D products. Shortly after admission, he undergoes a magnetic resonance imaging scan of the brain with gadolinium contrast that shows signs of a small, healed, left-sided cerebral infarct. The patient feels well. His vital signs are: BP 110/70 mmHg, pulse 80 beats/min, respirations 15 breaths/min, temperature 37 °C. The remainder of physical examination is unremarkable and includes the absence of Chvostek and Trousseu signs. His laboratory data include the following: calcium 5.8 mg/dl, phosphate 4.1 mg/dl, albumin 3.8 g/dl, sodium 139 mEq/l, potassium 4.2 mEq/l, chloride 105 mEq/l, bicarbonate 22 mEq/l, BUN 33 mg/dl, and creatinine 1.3 mg/dl.

Which ONE of the following is the MOST likely cause of hypocalcemia in this patient?

A. Hypoparathyroidism
B. Gadolinium-induced pseudohypocalcemia
C. Hypomagnesemia
D. Vitamin D deficiency
E. Sevelamer administration

The correct answer is B. Macrocyclic gadolinium complexes used in MR scanning are known to interfere with the colorimetric determination of calcium by binding with the test reagents. Patients with renal insufficiency can have spuriously low serum calcium.

Reference

Prince MR, Erel HE, Lent RW, et al. (2003). Gadoldiamide administration causes spurious hypocalcemia. Radiology 227:639–646

CASE 5

A 16-year old adolescent male who has passed a kidney stone without complications is referred to you for follow-up. The patient's evaluation reveals idiopathic hypercalciuria that responds to thiazide therapy. On his initial CT scan, at least four other asymptomatic stones (<15 mm each) are seen. He inquires whether he should have lithotripsy to avoid another painful episode.

Which ONE of the following statements provides the BEST answer to this inquiry?

A. Lithotripsy in this setting will reduce the likelihood of future hospitalization compared with observation with medical therapy.
B. Lithotripsy usually reduces anxiety about future stone passage.
C. Lithotripsy will reduce the likelihood of his needing an invasive procedure for stone complications over the next two years.
D. Because lithotripsy produces irreversible changes in kidney function, it should not be used in this asymptomatic patient.
E. He should avoid lithotripsy unless he has another painful episode.

The correct answer is C. A policy of observation is associated with a greater risk of requiring more invasive procedures. Prophylactic extracorporeal shock wave lithotripsy for small asymptomatic renal calyceal stones does not appear to offer any advantage to patients in terms of stone-free rate, quality of life, renal function, symptoms, or hospital admission.

References

Keeley FX, Jr, Tiling K, Elves A, et al. (2001) Preliminary results of a randomized controlled trial of prophylactic shock wave lithotripsy for small asymptomatic renal calyceal stones. BJU Int 87:1–8

Brater DC (2000) Pharmacology of diuretics. Am J Med Sci 319:38–50

CASE 6

Which ONE of the following statements regarding the use of bisphosphonates in the treatment of the hypercalcemia of malignancy is correct?

A. A hypercalciuric effect of bisphosphonates contributes to lowering serum calcium.
B. Pamidronate is the most effective hypocalcemia-inducing bisphosphonate.
C. Biposphonates are as effective after recurrence of hypercalcemia as during the initial treatment.
D. Bisphosphonates block the hypocalciuric effect of parathyroid hormone-related protein (PTHrp).

E. When treating hypercalcemia with biphosphonates, the highest recommended dose should be used initially.

The correct answer is E. Bisphosphonates do not produce hypercalciuria. Zoledronic acid (bisphosphonate) is 100 times more potent that pamidronate. Bisphosphonates are most effective as an initial treatment for hypercalcemia. PTHrp-induce hypercalciuria is not influenced by bisphosphonates.

Reference

Berenson JR (2002) Treatment of hypercalcemia of malignancy with bisphosphonates. Semin Oncol 29: (6 Suppl 21) 8–12

CASE 7

A 15-year old female underwent a liver transplant two years ago for the treatment of Wilson disease-induced cirrhosis. She was found to have osteoporosis with a T-score 3.5 SD below the mean standard on a routine dual energy x-ray absorptiometry (DEXA) scan study. Over the last two years, she has been treated with a variety of immunosuppressive agents, including tacrolimus, cyclosporine, sirolimus, glucocorticoids, mycophenolate mofetile, and azathioprine.

In addition to steroid-induced bone loss, which ONE of the following mechanisms contributes to this finding?

A. Tacrolimus-induced hypercalciuria
B. Tacrolimus-induced activation of osteoclasts
C. Sirolimus-induced hypercalciuria
D. Azothioprine-induced hypercalciuria
E. Mycophenolate mofetile-induced activation of osteoclasts

The correct answer is A. Tacrolimus increases urinary calcium excretion primarily by reducing renal transport of proteins for calcium and magnesium in the distal nephron. It has no effect on osteoclasts. The other agents do not alter urinary calcium excretion nor do they have important direct effects on bone.

Reference

Nijenhuis T, Hoenderop JG, Bindels RJ (2004) Down regulation of Ca and Mg transport proteins in the kidney explains tacrolimus (FK506)-induced hypercalciuria and hypomagnesemia. J Am Soc Nephrol 15:549–557

CASE 8

You are called for a *curbside consult* about a three-year-old child who has developed growth failure, muscle weakness, and bone pain. Radiographic studies indicate the presence of rickets, including bowed legs, thick fuzzy growth plates, and widened knee joints. Laboratory data reveal serum sodium 140 mEq/l, potassium 3.9 mEq/l, chloride 104 mEq/l, bicarbonate 29 mEq/l, BUN 12 mg/dl, creatinine 0.4 mg/dl, calcium 8.1 mg/dl, phosphate 2.5 mg/dl, magnesium 1.9 mg/dl, albumin 3.9 g/dl, PTH 87 pg/ml, calcidiol 45 ng/ml, calcitriol 98 pg/ml, hemoglobin 14.0 g/dl, and white blood count 5600 cell/ul. Urinalysis was normal.

What is the correct diagnosis?

A. Pseudovitamin D-deficient rickets (1-alpha hydroxylase deficiency, vitamin D-dependent rickets Type 1)
B. Vitamin D deficiency
C. Hypoparathyroidism
D. Pseudohypoparathyroidis
E. Hereditary vitamin D-resistant rickets (HVDRR)

The correct answer is E. Hereditary resistance to vitamin D is an autosomal recessive disorder. It is associated with end-organ resistance to calcitriol usually caused by mutations in the gene encoding the vitamin D receptor; the defect in the receptor interferes with binding of the hormone-receptor complex to DNA, thereby preventing calcitriol action and leading to hypocalcemia and secondary hyperparathyroidism.

Reference

Malloy PT, Wesley Pike J, Feldman D (1999) The vitamin D receptor and the syndrome of hereditary 1, 25 dihydroxyvitamin D-resistant rickets. Endocrine Rev 20:156–188

CASE 9

You are called by the emergency department to see a 17-year old female complaining of cramps and tightening in her throat. Past medical history is significant for mild hypertension for which she is being treated with hydrochlorothiazide, 12.5 mg/day. She had a total thyroidectomy for a large toxic, multinodular goiter two years ago and is maintained on 1-thyroxine 100 $\mu g/day$. Bone densitometry was consistent with osteoporosis and she was started on alendronate 10 mg/day. Several days later, she began to note intermittent severe cramps in her hands and feet. Today, she noted some tightening in her throat and came to the emergency room. She denies the use of any other medications or over-the counter supplements. She avoids all dairy products.

Upon examination, her BP is 140/86 mmHg, pulse 86 beats/min, respirations 12/min, temperature 37 °C, weight 62.5 kg, and height 159 cm. The rest of the physical examination was normal. Laboratory studies revealed hemoglobin 13.0 g/l, white blood count 5100 cells/ul, sodium 138 mEq/l, potassium 4.1 mEq/l, chloride 100 mEq/l, $HCO3^-$ 27 mEq/l, BUN 6 mg/dl, creatinine 0.7 mg/dl, calcium 7.7 mg/dl, phosphate 6.3 mg/dl, magnesium 1.9 mg/dl, and albumin 4.2 g/dl. Urinalysis showed trace protein, negative for glucose, and blood. Her EKG showed prolonged QT intervals.

What would you do at this point (select all that apply) ?

A. Draw PTH level
B. Draw serum magnesium level
C. Draw calcitriol level
D. Draw calcidiol level
E. Give intravenous magnesium

The correct answers are A, B, and E. The combination of hypocalcemia and hypophosphatemia in the absence of renal failure certainly suggests the presence of hypoparathyroidism. Hypomagnesemia (usually due to diarrhea) can cause suppression of PTH secretion and/or resistance to PTH, and produce acute hypocalcemia. It is appropriate to consider this and draw a serum magnesium level. In the absence of renal insufficiency, magnesium infusion is safe and reasonable while waiting for the results to come back from the laboratory.

Her symptoms did not abate and her serum calcium was unchanged following administration of magnesium. She was given intravenous calcium and experienced relief of her acute symptoms. She was maintained on intravenous calcium for several days until her laboratory studies, which were obtained in the ER, returned as follows: PTH 15 ng/ml, serum magnesium 2.0 mg/dl.

What is the primary diagnosis?

A. Hypoparathroidism
B. Alendronate toxicity
C. Vitamin D deficiency
D. Hypomagnesemia
E. Pseudohypoparathyroidism

The correct answer is A. She has hypocalcemia and a PTH value that is inappropriately in the low-normal range consistent with hypoparathyroidism. Permanent hypothyroidism occurs in 2–10% of cases after thyroid surgery. She likely had subclinical hypoparathyroidism that was undiagnosed and that now has been masked by alendronate therapy.

References

Chase LR, Slatopolsky E (1974) Secretion and metabolic efficiency of parathyroid hormone in patients with severe hypomagnesemia. J Clin Endocrinol Metab 38:363–371
Agus ZS (1999) Hypomagnesemia. J Am Soc Nephrol 10:1616–1622

CASE 10

A five-year old boy was admitted with a 10-day history of abdominal fullness and pain. Physical exam revealed a lethargic but alert male. BP was 130/60 mmHg, pulse 116 beats/min, respirations 24/min. He was afebrile. There was a palpable left supraclavicular node and firm, nontender hepatosplenomegaly.

Laboratory data showed hemoglobin 9.7 g/dl, white blood count 11,600 cells/ul, BUN 36 mg/dl, creatinine 2.9 mg/dl, sodium 136 mEq/l, potassium 2.9 mEq/l, chloride 97 mEq/l, $HCO3^-$ 20 mEq/l, calcium 6.9 mg/dl, phosphate 7.0 mg/dl, uric acid 20 mg/dl, and albumin 3.7 g/dl. Urinalysis revealed pH 5.0, but no blood or protein.

Which diagnoses should receive most consideration in this case (select all that apply)?

A. Acute interstitial nephritis
B. Tumor lysis syndrome
C. Urinary tract obstruction
D. Rhabdomyolysis
E. Acute glomerulonephritis

The correct answers are B and D. Spontaneous tumor lysis syndrome is unusual but can occur. It typically presents with hypocalcemia, hypophosphatemia, metabolic acidosis, and acute renal failure with marked hyperurecemia. It is rare in solid tumors, and usually occurs in patients with leukemia/lymphoma. The diagnosis is certainly consistent with his physical examination.

Rhabdomyolysis also can present with these findings. The etiology is not always clear in the absence of trauma, exertion, or offending drugs. Most such cases are probably due to unrecognized enzyme deficiencies, ultra structural abnormalities of muscle, or viral infections. The diagnosis is less likely in this case because there is no evidence of myoglobin on urinalysis. Creatine kinase is cleared less rapidly than myoglobin and measurement may help to rule out rahbdomyolysis.

References

Knochel JP (1992) Hypophosphatemia and rhabdomyolysis. Am J Med 92:455–457
Cairo MS, Bishop M (2004) Tumor lysis syndrome: New therapeutic strategies and classification. British J Hematol 127:3–11

CASE 11

A seven-year old boy presents in the office, complaining of slowly progressing pain in his upper right chest. The pain began about two weeks ago and is described as being similar to a toothache. It is unrelated to exercise or position. It initially responded to nonsteroidal anti-inflammatory drugs (NSAIDs), but they are no longer effective.

Review of systems reveals that he has noted some urinary urgency and frequency over the last four months and has nocturia three times weekly. He has also noted episodes of tingling around his mouth and occasional cramps of his hands and legs in the last several weeks.

Upon examination, vital signs are normal, the chest is clear, and there is tenderness over the fourth rib in the midline. There are no murmurs, and the abdomen is soft and nontender. There is mild hepatosplenomegaly. There is no edema. The neurologic examination is within normal limits. Rectal examination reveals a stony hard indurated nodule in the left lobe of the prostate gland.

Initial laboratory studies reveal a hemoglobin of 11.0 g/dl, white blood count of 15600 cells/*u*l, predominantly leukocytes, BUN 20 mg/dl, creatinine 1.6 mg/dl, sodium 140 mEq/l, chloride 106 mEq/l, potassium 4.0 mEq/l, bicarbonate 25 mEq/l, calcium 6.9 mg/dl, phosphate 3.3 mg/dl, and albumin 3.7 g/dl. Urinalysis is normal.

Which of the following do you expect to find (select all that apply)?

A. Elevated PTH
B. Low PTH
C. Elevated alkaline phosphatase
D. Low alkaline phosphatase
E. High calcidiol
F. Low calcidiol
G. High calcitriol
H. Low calcitriol

The correct answers are A, C, and E. The most likely cause of the hypocalcemia is deposition of calcium in osteoblastic metastasis from acute leukemia. This condirion is characterized by elevated levels of PTH, alkaline phosphatase and calcitriol.

Reference

Tommaso CL, Tucci JR (1979) Metabolic studies in a case of hypocalcemia and osteoblablastic metastases. Arch Intern Med 139:238–241

CASE 12

A 12-year old male presents to the ER with acute abdominal pain. He noted the onset of steady right upper quadrant pain yesterday. The pain radiates in a band-like fashion to the back and is relieved somewhat by bending forward. He has also experienced nausea and vomiting for the last 10 hours. He has had multiple hospitalizations in the past with similar presentation. Review of symptoms reveals that he has been having loose, greasy, foul smelling stools that are difficult to flush for the last month. Current medications include dilantin and phenobarbital for a history of generalized seizures over the last several years. Upon examination, he appears restless and is in significant pain. Vital signs reveal a temp of 39 C, BP of 103/65 mmHg, a pulse of 110 beats/min, and a respiratory rate of 25/min with shallow respirations. The chest is clear. There is epigastric distention and tenderness with guarding. The liver and spleen are not palpable. There is no edema. The neurological examination is intact.

Which of the following may be contributing to the hypocalcemia (select all that apply)?

A. Hypophosphatemia
B. Hyperphosphatemia
C. Hypomagnesemia
D. Hypermagnesemia
E. Low calcidol
F. Extravascular deposition of calcium

The correct answers are C, E, and F. Vitamin D deficiency, hypomagnesemia, and precipitation of calcium soaps in the abdominal cavity all may play a role in patients with chronic pancreatitis.

Reference

Gardner EC Jr, Hersh T (1981) Primary hyperparathyroidism and gastrointestinal tract. South Med J 74:197–199

CASE 13

Which of the following may be contributing to the low levels of calcidiol in this patient (select all that apply)?

A. Renal failure
B. Malabsorption
C. Dietary deficiency of vitamin D
D. Dilantin®
E. Liver disease

The correct answers are B, C, D, and E. Liver disease (loss of 80–90% of functioning tissue) can be associated with reduced hydroxylation of vitamin D to calcidiol. Penobarbital and dilantin increase the activity of the p450 mitochondrial system, which can metabolize calcidiol into inactive metabolites. Dilantin® may also interfere with the absorption of vitamin D. Dietary vitamin D deficiency and/or malabsorption associated with chronic pancreatitis is typically a feature in alcoholic patients.

Reference

Wharton B, Bishop N (2003) Rickets. Lancet 362:1389–1400

CASE 14

A 19-year old, HIV-positive male noted the onset of blurring vision several weeks ago. Indirect ophthalmoscopy revealed white, fluffy retinal lesions, located close to retinal vessels and associated with hemorrhage. CMV retinitis was diagnosed and he was begun on intravenous therapy with foscarnet, 120 mg/kg IV, twice daily. This was to be continued for two weeks, to be followed by maintenance therapy with 90 mg/kg IV, once daily.

He complained of several episodes of numbness and tingling, particularly around his mouth, with the first several treatments. This morning he experienced a generalized seizure immediately following completion of his treatment.

Laboratory studies included a hemoglobin 10.0 g/dl, white blood count 4600 cells/ul, BUN 8 mg/dl, creatinine 1.0 mg/dl, sodium 140 mEq/l, potassium 4.0 mEq/l, chloride 108 mEq/l, $HCO3^-$, 25 mEq/l, calcium 9.9 mg/dl, phosphate 3.5 mg/dl, magnesium 1.9 mg/dl, and albumin 3.7 g/dl.

His clinicians are concerned and confused. His symptoms sound like hypocalcemia but his serum calcium concentration and serum albumin concentration are normal.

What would you recommend be done next (select all that apply)?

A. Measure a PTH level
B. Reduce the foscarnet dose and measure the serum ionized calcium at the end of the net infusion.
C. Measure a calcidol level.
D. Measure serum ionized magnesium level.
E. Order a head CT scan.
F. Check a blood gas during the infusion.

The correct answers are B, E, and F. Foscarnet (trisodium phosphonoformate) has been shown to chelate serum calcium. The plasma ionized calcium (but not total) typically falls by a mean value of 0.17 mmol/l with a 90 mg/kg dose, and by 0.29 mmol/l with a 120 mg/kg dose. These changes are clinically significant and can

be associated with paresthesias and seizures. Acute respiratory alkalosis associated with hyperventilation due to pain or anxiety can also reduce the ionized calcium concentration.

Reference

Jacobson MA, Gambertoglio JG, Aweeka FT, et al. (1991) Foscarnet-induced hypocalcemia and effects of foscarnet on calcium metabolism. J Clin Endocrinol Metab 72:1130–1135

CASE 15

The patient is a 14-year old female who presents with a seven-month history of aching in her bones affecting her arms and legs. More recently, she has noted the onset of muscle weakness such that her gait has become cautious and she uses her arms to rise from a sitting position. She has no significant past medical history and she does not smoke or drink alcohol. She denies the use of any medications. Her most recent office visit was six months ago, at which time there were no abnormal physical or laboratory findings.

Upon examination, she appears as a thin female in no acute distress. BP is 126/78 mmHg, pulse 76 beats/min, respirations 12/mim, temperature 37 °C, weight 55.0 kg, and height 160 cm. The rest of the physical exam is normal.

Laboratory studies showed normal hemoglobin, white cell count, and urinalysis. Serum sodium is 140 mEq/l, potassium 3.9 mEq/l, chloride 101 mEq/l, $HCO3^-$, 28 mEq/l, BUN 8 mg/dl, creatinine 1.0 mg/dl, calcium 9.8 mg/dl, phosphate 1.9 mg/dl, magnesium 1.7 mg/dl, and albumin 4.2 g/dl.

Which of the following symptoms can be associated with her electrolytes abnormalities?

A. Muscle weakness
B. Osteoporosis
C. Osteopenia
D. Osteomalacia
E. Hypertension
F. Hperparathyroidism

The correct answer is A. Muscle weakness and osteomalacia (often presenting as bone pain) are classic signs of marked hypophosphatemia. Hypophosphatemia-induced manifestations of muscle dysfunction include a proximal myopathy, affecting skeletal muscle, and dysphasia and ileus, affecting smooth muscle. Metabolic bone disease refers to conditions that produce a diffuse decrease in bone density (osteopenia) and/or strength because of an increase in bone resorption and/or a decrease in bone formation. These conditions include osteoporosis, osteomalacia, and hyperparathyroidism.

Which diagnostic tests should be done first in attempting to distinguish the diagnosis (select all that apply)?

A. 24-hr urine phosphate collection
B. 24-hr urine creatinine collection
C. 24-hr urine calcium collection
D. Serum calcidiol level
E. Serum calcitriol level

The correct answers are A and B. The first step in the diagnostic approach to hypophosphatemia is to establish whether or not there is GI loss or urinary loss as the causative factor. This is done by evaluating the appropriateness of urinary phosphate excretion. Thus the 24-hour urinary collection for phosphorus and creatinine is necessary to ensure the adequacy of the collection and to allow estimation of the fractional excretion of phosphate.

The 24-hour urine phosphate and creatinine excretion were 800 mg and 1250 mg, respectively. The fractional phosphate excretion was 43%.

What medical conditions should now be considered in the differential diagnosis (select all that apply)?

A. Primary hyperparathyroidism
B. Poor phosphate intake and diarrhea
C. Excess ingestion of phosphate binding antacids
D. Vitamin D deficiency
E. Fanconi syndrome
F. X-linked hypophosphatemic rickets
G. Oncogenic osteomalacia

The correct answers are E, F, and G. The fractional phosphate excretion indicated reduced phosphate transport. The causes include hyperparathyroidism and vitamin D deficiency (with secondary hypoparathyroidism).

The normal calcium concentration is not consistent with primary or secondary hyperparathyroidism. The causes of primary renal phosphate wasting include a generalized defect in proximal tubule transport (Fanconi syndrome), hereditary hypophosphatemic rickets, and oncogenic osteomalacia.

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CASE 16

Further evaluation revealed the following: normal blood levels of 25 (OH) vitamin D, PTH (3 pg/ml), uric acid (5 mg/dl), and 1, 25 (OH) 2 vitamin D level (10 pg/ml). Urine contained no glucose or amino acids with normal uric acid excretion.

What is the most likely diagnosis now?

A. Fanconi syndrome
B. Hereditary hypophosphatemic rickets
C. Oncogenic osteomalacia
D. Vitamin D deficiency

The correct answer is C. The condition appears to be acquired and the calcitriol level is very low, consistent with this diagnosis.

What is the presumed pathogenesis of this disorder?

A. Tumor secretion of cyclic AMP
B. Tumor production of the phosphatonin FG23
C. Tumor production of PTH
D. Tumor production of calcitonin
E. None of the above

The correct answer is B. There are several *phosphatonins* that have been identified. Overproduction of FG23 appears to be the most common in patients with these tumors. These substances lead to underexpression of the cotransporter that is responsible for phosphate reabsorption in the proximal tubule.

What should be done next (select all that apply)?

A. Treat with oral phosphate.
B. Treat with 1,25 (OH)2 vitamin D.
C. Total body magnetic resonance imaging (MRI).
D. Scintigraphy using octreotide labeled with indium-111.
E. Treat with 25 (OH) vitamin D.

The correct answers are A, B, C, and D. Patients with this syndrome require a combination of oral phosphate and calcitriol. This is because the use of phosphate

alone may lower ionized calcium and lead to secondary hyperparathyroidism. Therapy should continue until the tumor can be identified and removed. Removal of the tumor leads to prompt reversal of the biochemical abnormalities and healing of the bone disease.

Identification of the tumor can involve total body magnetic resonance imaging or scintigraphy using octreotide labeled with indium-111 (since the tumors typically express somastatin receptors).

The patient underwent scanning with indium-11 labeled octreotide. Intense nasopharyngeal uptake was demonstrated indicating an occult octreotide avid hemangiopericytoma. Surgery was recommended.

The patient asks what the likely prognosis is with successful removal of the tumor. What do you tell her?

A. The tumors are typically benign and do not recur; in all likelihood she will be cured.
B. Tumors often recur.

The correct answer is A. The tumors are typically benign and do not recur; in all likelihood she will be cured. The patient underwent surgery. Her weakness subsequently improved and her serum phosphate returned to normal. She has been well for five years.

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CASE 17

You are asked to see a 19-year-old female college student in the ER with hypercalcemia and renal failure. She noted the onset of mild polyuria and nocturia six to eight months ago. Headache, constipation, and malaise became apparent approximately six weeks ago. She began using a tanning salon four weeks ago. Yesterday, she visited her mother, who noted that she was "not herself" and seemed confused. She brought her to the ER for evaluation. Past medical history is significant for passing a single kidney stone two years ago. She has a one-year history of mild hypertension for which she was treated with hydrochlorothiazide 50 mg/day. She does not smoke or drink alcohol. She denies the use of any other medications or over-the-counter supplements. She denies any hormonal therapy and avoids all dairy products. On examination, she appears in no acute distress. BP is 140/92 mmHg, pulse is 86, RR is 12, temp is 39 °C, weight is 62.5 kg, and height is 159 cm. Heart rate is regular

with no murmurs, lungs are clear, abdomen is soft with no masses, and there is no pitting edema. Neurologic examination shows mild depression and some cognitive dysfunction. Laboratory studies show hematocrit 46%, WBC 12,500 cells/ml, BUN 61 mg/dl, creatinine 3.0 mg/dl, sodium 140 mEq/l, potassium 3.9 mEq/l, chloride 101 mEq/l, $HCO3^-$ 22 mEq/l, calcium 13.8 mg/dl, phosphate 3.9 mg/dl, magnesium 1.9 mg/dl, and albumin 4.2 g/dl. Urinalysis shows trace protein, glucose negative, no blood, 2–4 hyaline casts/hpf, and no RBC or WBC. Chest x-ray shows bilateral hilar adenopathy. A PPD test iss negative.

Which of the following treatment modalities would you like to order now (select all that apply)?

A. Calcitonin
B. Intravenous saline
C. Surgical consult
D. Mitramycin
E. Pamidronate/Zolendronate

The correct answers are A, B, and E. The initial treatment of symptomatic hypercalcemia should have three elements to provide some efficacy, both initially and several days later. Virtually all patients with significant hypercalcemia have some element of ECF volume contraction. For this reason, it is important to start therapy with several liters of intravenous saline. Calcitonin is effective in approximately 70% of patients. It's safe, relatively nontoxic, and acts to lower the serum calcium within several hours. For this reason, it should be the initial agent of choice to provide some benefit before the more potent bisphosphonates become maximally effective. It typically loses its effectiveness within 48 hours in most patients. For this reason, it is important to begin therapy with a bisphosphonate at this time, as well.

Bisphosphomates act by interfering with metabolic activity of osteoclasts; they are also cytotoxic to osteoclasts. Pamidronate, zelendronic acid, and etidronate are the currently available agents that are approved by the FDA for the treatment of malignancy-associated hypercalcemia. Zelendronate appears to be the most efficacious with maximum effect occurring in 48–72 hours.

Which of the following signs and symptoms are due to the effects of hypercalcemia per se (select all that apply)?

A. Polyuria
B. Muscle weakness
C. Band keratopathy
D. Shortening of the Q-T interval
E. Constipation
F. Shortness of breath
G. Cognitive dysfunction
H. Supraventricular tachycardia

The correct answers are A, C, D, E, and G. Chronic hypercalcemia leads to a defect in concentrating ability that may induce polyuria and polydipsia in up to 20 percent of patients. This is due to down regulation of aquaporin-2 water channels and activation of the normal calcium-sensing receptor in the Loop of Henle, which reduces sodium-chloride reabsorption in this segment and thereby impairment of the interstitial osmotic gradient.

Hypercalcemia directly shortens the myocardial action potential, which is reflected in a shortened QT interval. Band keratopathy, a reflection of subepithelial calcium phosphate deposits in the cornea, is a very rare finding in patients with hypercalcemia. It extends, as a horizontal band across the cornea in the area that is exposed between the eyelids. Calcium salts probably precipitate in that site because of the higher local pH induced by the evaporation of CO_2.

Constipation is the most common gastrointestinal complaint in patients with hypercalcemia. It is likely related to decreased smooth muscle tone. Personality changes and affective disorders have been described at serum calcium concentrations above 12 mg/dl—confusion, organic psychosis, hallucinations, somnolence, and coma are rare until the serum calcium concentration is above 16 mg/dl.

Which of the following factors may be contributing to the renal failure at the initial presentation (select all that apply)?

A. ECF volume contraction
B. Hypercalcemia induced renal vasoconstriction
C. Nephrocalcinosis
D. Granulomatous glomerulonephritis

The correct answers are A, B, C, and D. Mild hypercalcemia is only rarely associated with renal insufficiency. Higher elevations in the serum calcium concentration (serum calcium 12 to 15 mg/dl) can lead to a reversible fall in glomerular filtration rate that is mediated by direct renal vasoconstriction and natriuresis-induced volume contraction.

Long-standing hypercalcemia and hypercalciuria lead to the development of chronic hypercalcemic nephropathy, which may be irreversible and continue to progress despite cure of the underlying condition, such as hyperparathyroidism. Calcification, degeneration, and necrosis of the tubular cells lead to cell sloughing and eventual tubular atrophy and interstitial fibrosis and calcification (nephrocalcinosis). These changes are most prominent in the medulla but can also be seen in the cortex.

Interstitial calcium deposition can be detected radiographically. Nephrocalcinosis that can be detected by a plain film of the abdomen is advanced and reflects severe renal parenchymal involvement. Ultrasonography or computed tomography can detect earlier stages of the disease. An interstitial nephritis with granuloma formation is common in sarcoidosis, but the development of clinical disease manifested by renal insufficiency is unusual.

While the patient is receiving therapy, and you are monitoring the serum calcium, it is time to begin ordering diagnostic studies.

Which of the following would you order first (select all that apply)?

A. Parathyroid hormone level
B. Calcitriol level
C. Calcidiol level
D. PTHrp level
E. Abdominal CT
F. Abdominal flat plate
G. Bone marrow examination
H. Serum electrophoresis

The correct answers are A, B, and F. The diagnosis of primary hyperparathyroidism is always high on the first list in an patient presenting with hypercalcemia. Granulomatous disease is certainly a possibility given the hilar adenopathy and hypercalcemia of several years duration. Measurement of calcitriol is therefore a good idea. An abdominal flat plate to look for nephrocalcinosis is reasonable given the history of renal failure.

The PTH level was 2 pg/ml (normal is 10 to 65 pg/ml) and the 1,25(OH)2 D (calcitriol) was 72 ng/ml (normal range is 9–47 ng/ml). The abdominal flat plate shows bilateral nephrocalcinosis.

Which are the most likely diagnoses (select all that apply)?

A. Primary hyperparathyroidism
B. Malignancy
C. Granulomatous disease
D. Nephrocalcinosis
E. Milk-alkali syndrome
F. UV light toxicity from the tanning salon

The correct answers are C, D, and F. The elevated calcitriol and low PTH are consistent with granulomatous disease. There is hilar adenopathy on the chest x-ray, which makes the diagnosis of sarcoidosis very likely. It is very unlikely that exposure to a tanning salon alone would lead to elevated calcitriol production that is normally feedback-regulated. However, in a patient with a granulomatous disease where calcitriol production is not feedback-regulated, increased production of 25 (OH) D would aggravate the hypercalcemia.

Which of the following would be appropriate as part of the therapeutic regimen for this patient?

A. Low calcium diet
B. Low oxalate diet
C. Pamidronate
D. Low dose corticosteroid therapy
E. Avoidance of tanning salon
F. Furosemide administration

The correct answers are A, B, D, and E. Treatment of the hypercalcemia and hypercalciuria is aimed at reducing intestinal calcium absorption and calcitriol synthesis. This can be achieved by reducing calcium intake (no more than 400 mg/day), reducing oxalate intake, eliminating dietary vitamin D supplements, avoidance of sun exposure, and low-dose glucocorticoid therapy (10 to 30 mg/day of prednisone). The serum calcium concentration typically begins to fall in two days, but the full hypocalcemic response may take 7 to 10 days, depending upon the prednisone dose. Inhibition of calcitriol synthesis by the activated mononuclear cells is thought to play a major role in this response, although inhibition of intestinal absorption and of osteoclast activity also may contribute.

Concurrent restriction of dietary oxalate is required to prevent a marked increase in oxalate absorption and hyperoxaluria. The latter may increase the risk of kidney stone formation, even though urinary calcium excretion is reduced. Oxalate absorption is normally limited by the formation of insoluble calcium oxalate salts in the intestinal lumen. Dietary calcium restriction leads to more free oxalate than can then be absorbed if oxalate intake is unchanged.

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CASE 19

A 15-year old female returns for her annual checkup. When seen last year, physical examination and laboratory studies were within normal limits. Routine bone densitometry revealed low bone density (more than 2.5 standard deviations below normal) and she was placed on alendronate. She now returns for her annual check-up with no complaints. Laboratory studies show hematocrit 46%, BUN 14 mg/dl, serum creatinine 1.1 mg/dl, sodium 140 mEq/l, potassium 3.9 mEq/l, chloride 105 mg/dl, bicarbonate 26 mEq/l, calcium 11.3 mg/dl, phosphate 3.4 mg/dl, magnesium 1.9 mg/dl, and albumin 4.2 g/dl. Urinalysis shows trace protein, glucose negative, no blood, and no casts, RBC, or WBC. The PTH level was 57 pg/ml (normal range, 10 to 65 pg/ml).

What is the most likely diagnosis based upon the laboratory studies?

A. Familial hypocalciuric hypercalcemia
B. Primary hyperparathyroidism
C. Malignancy
D. Granulomatous disease
E. I am not sure, I would like to order a sestamibi scan for verification.

The correct answer is B. A PTH level in the high normal range is inappropriate in a patient with hypercalcemia, and indicates the presence of primary hyperparathyroidism. This occurs in 15–20% of patients with this condition.

What would you like to do now?

A. Order a sestamibi scan
B. Call the surgeon
C. Follow the patient and schedule follow-up in 6 months

The correct answer is B. Surgery is indicated in the following patients:

– Patients with a serum calcium level of 1.0 mg/dl or more above the upper limit of normal
– Patients with hypercalciuria (>400 mg/day) while eating their usual diet
– Patients with a creatinine clearance that is 30 percent or lower than that of age-matched normal subjects

– Patients with bone density at the hip, lumbar spine, or distal radius that is more than 2.5 standard deviations below peak bone mass (T score < -2.5)
– Patients who are less than 50 years old
– Patients in whom periodic follow-up will be difficult

The patient has a serum calcium level which is more than 1 mg/dl above normal and has a significant decrease in bone density. She is in good health otherwise and should be offered surgery as the first option.

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CASE 20

A 17-year old female was referred for evaluation of hypokalemia. She has no significant past medical history, and does not smoke or drink, and she denies the use of any medications. Her most recent clinic visit was one year ago, at which time there were no abnormal physical or laboratory findings. Recently, the patient began to note occasional fatigue and muscle weakness during exercise. She also experienced occasional abdominal pain for which she saw her regular physician. Laboratory studies in this office indicated hypokalemia and she was referred to you for evaluation. Repeat laboratory data show HCT 46%, BUN 16 mg/dl, serum creatinine 1.0 mg/dl, sodium 140 mEq/l, potassium 2.4 mEq/l, chloride 101 mEq/l, CO2 32 mEq/l, calcium 10.0 mg/dl, phosphate 3.9 mg/dl, magnesium 1.2 mg/dl, and albumin 4.6 g/dl.

Which of the following abnormalities are present in your initial assessment of the patient (select all that apply)?

A. Hypocalcemia
B. Hypokalemia
C. Hypomagnesemia
D. Metabolic acidosis
E. Metabolic alkalosis

The correct answers are C and E. Elevated serum bicarbonate concentration and decreased serum potassium concentration are consistent with hypokalemic metabolic alkalosis. The serum magnesium level is also reduced.

The diagnosis approach that you will take to this patient should be based upon your answer to the following question:

Which of the following statements is true?

A. Hypokalemia can alter the renal handling of magnesium and cause hypomagnesemia.
B. Hypomagenesemia can alter the renal handling of potassium and cause hypokalemia.
C. Both statements are true.
D. Neither statement is true.

The correct answer is B. Hypomagnesemis causes renal potassium wasting likely by opening potassium channels in the cortical thick ascending limb (CTAL). For this reason, the diagnosis of combined hypokalemia-hypomagnesemia is best approached by considering causes of hypomagnesemia.

If we proceed in a step-wise fashion to make the diagnosis, which study would be the best initial laboratory study for the diagnosis of the cause of the hypomagnesemia?

A. Diuretic screen
B. 24-hour urine for calcium, magnesium, and creatinine
C. Plasma renin and aldosterone
D. Arterial blood gas
E. 24-hour urine for sodium, potassium, and creatinine

The correct answer is B. Measurement of the urinary magnesium excretion will help to distinguish between GI loss of magnesium and renal magnesium wasting.

The urinary magnesium excretion was 120 mg/24 hrs and the urinary calcium excretion was 305 mg/d24 hrs.

Which diagnoses should now receive further consideration (select all that apply)?

A. Primary hyperaldosteronism
B. Bartter's syndrome
C. Laxative abuse
D. Primary renal magnesium wasting
E. Diuretic abuse
F. Gitelman's syndrome

The correct answers are B and E. Metabolic alkalosis, hypercalciuria, renal magnesium wasting, and hypomagnesemia all can occur in Bartter's syndrome. Diuretic (loop diuretics) abuse is also a good choice because it causes the same type of transport defect.

Which study would you like now to differentiate between Bartter's syndrome and diuretic abuse?

A. Diuretic screen
B. 24-hour for Ca^{++}, Mg^{++}, creatinine
C. 24-hour urine for Na^{+}, K^{+}, creatinine
D. Plasma rennin and aldosterone

The correct answer A. A diuretic screen is the only way to rule out diuretic abuse.

The diuretic screen was negative. However, the lab calls to tell you that the urinary calcium excretion in the 24-hour collection was misreported—the correct value is 30 mg/24 hrs, not 305.

What is the likely diagnosis now?

A. Bartter's syndrome
B. Gitelman's syndrome
C. Primary hyperaldosteronism
D. Primary renal magnesium wasting

The correct answer is B. Gitelman's syndrome is the only one of these conditions which is associated with hypocalciuria. Gitelman's syndrome is a variant of Bartter's syndrome, characterized by hypokalemia, hypomagnesemia, hypocalciuria, and hypovolemia.

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CASE 21

Which of the following genetic defects is an integral part of the pathogenesis of Gitelman's syndrome?

A. Na-K-2Cl co-transport defect
B. Chloride channel defect
C. Na-Cl co-transporter defect
D. Na-K-ATPase defect

The correct answer is C. A genetic defect in the thiazide-sensitive Na-Cl cotransporter has been identified in Gitelman's syndrome. The L623P mutation (which substitute praline for leucine) in the thiazide-sensitive Na-Cl cotransporter gene is suggested to impair the transporter activity, and to underline the Gitelman's syndrome. Gitelman's syndrome is inherited in an autosomal recessive fashion.

Reference

Takeuchi K, Kure S, Kato T, et al. (1996) Association of a mutation in thiazide-sensitive Na-Cl cotransporter with familial Gitelman's syndrome. J Clin Endocrinol Metab 12:4496–4499

CASE 22

Which of the following might have the most beneficial therapeutic effects in a patient with Gitelman's syndrome (select all that apply)?

A. Thiazide diuretics
B. K-sparing diuretics
C. Oral magnesium
D. Low salt diet
E. Loop diuretics

The correct answers are B and C. Magnesium supplements are typically necessary to increase the serum magnesium and the serum potassium concentrations. Amiloride can be very useful in this condition because it may help to enhance distal tubular reabsorption of magnesium, as well as inhibit potassium secretion.

As you continue to ponder, the pediatric resident shows you an ECG of another patient who has just delivered a full-term baby following an episode of eclampsia with hypertension and hyperreflexia. The ECG shows significant prolongation of the Q-T interval with a serum calcium of 5.2 mg/dl. You tell the resident what to do and now you understand the reason for the SICU patient's hypocalcemia.

What should be done next to define the likely cause of the hypocalcemia?

A. Draw blood for a PTH assay.
B. Give IV magnesium.
C. Draw blood for a calcitriol level.
D. Draw blood for a calcidiol level.
E. Draw blood for a plasma magnesium level.

The correct answer is E. Checking the plasma magnesium level to look for hypermagnesemia as the cause of hypocalcemia is essential in this situation. Hypermagnesemia at these levels can suppress PTH secretion and cause hypocalcemia.

You check the medications that the patient was receiving and realize that no one had discontinued the supplemental magnesium that she was receiving for Gitleman's syndrome. Hypermagnesemia and subsequent hypocalcemia may have ensued when she developed renal failure. Hemodialysis was instituted and hypermagnesemia resolved over two treatments and hemodialysis was discontinued. She was subsequently returned on magnesium supplements after her renal function returned to baseline values over five days.

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CASE 23

A five-year old boy presents with the complaint of severe muscle weakness and bone pain. Physical exam reveals 3+/4+ muscle strength in the proximal muscles of the upper and lower extremities. There is a soft, poorly defined soft tissue mass in the left thigh. Lab studies reveal normal electrolytes, calcium 9.6 mg/dl, phosphate 1.6 mg/dl, PTH 50 pg/ml, and 1.25 $(OH)_2$ Vitamin D 10 pg/ml (normal,15 to 35 pg/ml). Fractional excretion of phosphate is 18%.

Which of the following best explains the pathophysiology of this condition?

A. Increased levels of PTH-related protein
B. Increased levels of fibroblast growth factor
C. Increased levels of stanniocalcin
D. Increased PEX gene activity (x-linked hypophosphatemia)
E. Genetic defect in Na-Pi Type II transporter in the kidney

The correct answer is D. X-linked hypophosphatemia (X-LH) is a defect in a gene located on Xp22.1. The function of this gene is to degrade phosphatonin that is produced normally by osteoblasts and acts on bone to regulate bone metabolism and bone formation. This gene encodes a neutral endopeptidase enzyme defined as PEX. When the enzyme is absent, as in X-LH, the phosphotonin is present in higher levels in the circulation and acts on the kidney to reduce proximal tubular phosphate transport by reducing the number and activity of the Type II NA-PI transporter.

Oncogenic osteoblastoma, a rare syndrome in which patients develop hypophosphatemia with excess renal phosphate wasting and low 1,25 (OH)3 despite hypophosphatemia, osteomalacia, and muscle weakness. In oncogenic osteomalacia, it is proposed that the tumors, typically of vascular origin, produce excess amounts of phosphatonin in quantities that exceed the degradation capacity of the PEX endopeptodase, and the phosphtonin escapes into the circulation and eventually produces the same renal defects as seen in X-LH.

Reference

A gene (PEX) with homologies to endopeptidases is mutated in patients with x-linked hypophosphatemic rickets (The HYP Consortium. Nat Genet 1995; 11:130)

CASE 24

A nine-year old girl presents with a chief complaint of decreased mental acuity and increasing urinary frequency. She has been well her whole life and has no other complaints. She is taking no prescribed medications but does take occasional vitamin preparations. Physical exam is unremarkable except for some mild confusion. Laboratory studies reveal: calcium 15.0 mg/dl, creatinine 2.4 mg/dl, 1,25 $(OH)_2$ vitamin D 20 pg/ml (normal, 15 to 35 pg/ml), 25 (OH) vitamin D 400 ng/ml (normal, 12 to 72 pg/ml), PTH 40 pg/ml, and serum albumin 4.1 g/dl.

What is the likeliest cause of this condition?

A. Sarcoidosis
B. Exogenous vitamin D administration
C. Occult malignancy
D. Milk alkali syndrome

The correct answer is B. In a patient with hypercalcemia, azotemia, and anemia, one should consider Vitamin D toxicity and assess both 25-OH and 1,25 $(OH)_2$ vitamin D levels.

Reference

Selby PL, Davies M, Marks JS, et al. (1995) Vitamin D intoxication causes hypercalcemia by increased bone resorption which responds to pamidronate. Clin Endocrinol 43:531–536

CASE 25

A 13-year old patient presents with hypercalcemia and a six-month history of leukemia.

The pathologic effects of his leukemia that results in hypercalcemia include which one of the following mechanism?

A. Increased bone resorption induced by prostaglandin production
B. Interleukin-6-induced bone resorption
C. PTH-related protein-induced increase in bone resorption and reduction in calcium excretion
D. Tumor necrosis factor-induced activation of osteoblast proliferation
E. Transforming growth factor-β -induced increase in osteoclast activity

The correct answer is C. The pathophysiology underlying hypercalcemia of malignancy can be compared with its counterpart—primary hyperparathyroidism. Both syndromes are humoral in nature, with one being caused by PTH and the other by PTH-related protein (PYHrP). Both are associated with hypercalcemia, accelerated osteoclastic bone resorption, and reductions in renal phosphate reabsorption; both display increases in nephrogenous cAMP excretion as a result of the interaction of PTH or PTH-rP with the proximal tubular PTH/PTHrP receptor/adenyl cyclase complex.

Reference

Syed MA, Horwitz MJ, Tedesco MB, et al. (2001) Parathyroid hormone-related protein (1–36) stimulates renal tubular calcium reabsorption in normal human volunteers: Implications for the pathogenesis of humoral hypercalcemia of malignancy. J Clin Endocrinol Metab 86:1525–1531

Chapter 4
Nephrolithiasis

CASE 1

A seven-year old presents to the emergency room with pain radiating to the right testicle. The pain began as a dull ache in the right flank approximately six hours ago while he was sitting at his desk at school. The pain rapidly progressed increasing in intensity steadily over a period of one hour. It was subsequently associated with radiation along the inguinal canal into the groin and the right testicle. This is the first time the patient has experienced these symptoms. He does admit to some nausea and vomiting over the last several hours, but he denies chills, fever, dysuria, or urgency.

Upon examination, the vital signs are normal. He weighs 40 kg. Examination of HEENT is normal. The chest is clear to auscultation and percussion. The heart size is normal and there are no murmurs. The abdomen is soft, nontender, and slightly distended with hypoactive bowel sounds. There is no organomegaly, no masses, rebound, or guarding. No bruits are heard and there are no hernias. There is moderate costovertebral angle tenderness to palpation on the right side. There is no edema. Laboratory studies show Hb 14 g/dl; HC 44%, WBC 5600 cells/uml, sodium 140 mEq/l, potassium 4 mEq/l, chloride 105 mEq/l, bicarbonate 25 mEq/l, BUN 15 mg/dl, and creatinine 1.0 mg/dl. Urinalysis reveals pH 5.0, SG 1.016, 4+ blood, 1+ protein, no glucose, many RBCs, no casts, and multiple calcium oxalate crystals.

Which of the following studies is most likely to provide the correct diagnosis and should be done first in this situation?

A. Noncontrast-enhanced helical CT scan
B. Abdominal plain film
C. IVP
D. Ultrasonography

The correct answer is A. Noncontrast-enhanced helical CT scanning is the diagnostic method of choice for establishing the diagnosis of nephrolithiasis in most cases. The study can be combined with a flat plate to ensure that the stone is not radiolucent when there is a possibility of uric acid stones.

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The helical CT scan demonstrates a 3 mm stone in the right ureter. A similar finding was seen on the abdominal flat plate.

Which of the following is the likely clinical composition of his stone?

A. Calcium phosphate nephrolithiasis
B. Calcium oxalate nephrolithiasis
C. Uric acid nephrolithiasis
D. Cystine nephrolithiasis

The correct answer is B. The patient has hematuria, flank pain, a urine pH of 5, and calcium oxalate crystals in the urinalysis. The helical CT scan demonstrates a 3 mm stone in the right ureter—all consistent with calcium oxalate urolithiasis.

What would be the best management approach at this time for this patient (select all that apply)?

A. Urology consultation
B. Hospitalization
C. IV fluids
D. IV antibiotics
E. IV analgesics

The correct answers are B, C, and E. The patient needs hydration and ECF volume expansion to maintain urine flow. He cannot tolerate oral fluid, so IV therapy is indicated. The patient should also be treated with effective pain medications. IV NSAIDs are actually very effective in this situation.

The patient experienced significant pain relief after IV analgesics, and tolerated oral medications and fluids.

What orders would you write now (select all that apply)?

A. Hospitalization
B. Discharge to home
C. Low calcium diet
D. Maintain increased oral fluid intake.
E. Strain the urine.
F. Schedule a follow-up IVP for the following week.
G. Schedule a 24-hour urine collection for calcium and creatinine.

The correct answers are B, D, and E. The patient tolerated medications and fluids orally efficiently and has pain relief. He can now be managed expectantly at home with increased fluid intake to await stone passages. Straining the urine with gauze increases the likelihood that a small stone will be recovered for analysis.

The patient was discharged and passed the stone five days later. No evidence of residual stone was seen on follow-up abdominal flat plate or CT scan. Analysis of the stone revealed it to be composed of 100% calcium oxalate. He now returns to the clinic to receive the results of the x-rays and stone analysis and to discuss prognosis and therapy.

What is your recommendation to patient at this time (select all that apply)?

A. A complete metabolic work-up followed by appropriate treatment of any abnormalities and risk factors that are identified
B. Measurement of serum calcium and continuation of the high fluid intake but no other specific work-up or therapy because the likelihood of a second stone is less than 50% at 10 years
C. Both of the above
D. None of the above

The correct answers are A and B. The relatively indolent course plus the availability of nonoperative therapy (such as lithotripsy) for most symptomatic stones has led some physicians to recommend a limited evaluation and therapy of the patient with a single calcium stone. However, the decision whether or not to undergo evaluation and therapy should be shared by the physician and patient.

The patient's family elected to take a conservative approach and not have him undergo extensive testing or specific therapy. He did increase his fluid intake to approximately 2.5 liters per day for several years and then paid less attention to his intake. He was clinically stone-free for five years until six weeks ago, when he again experienced right-sided flank pain and hematuria and passed another small calcium oxalate. Follow-up IVP was normal and he was referred to the clinic for further evaluation. He is on no medications and his usual fluid intake is approximately 1.5 liters per day. He agrees now to undergo metabolic evaluation.

Which of the following studies should be included in this evaluation (select all that apply)?

A. 24-hour urine for calcium
B. 24-hour urine for uric acid
C. 24-hour urine for oxalate
D. 24-hour urine for citrate
E. 24-hour urine for cystine
F. 24-hour urine for creatinine
G. 24-hour urine for phosphorous
H. Serum calcium
I. Serum uric acid
J. Serum albumin
K. Serum creatinine
L. Serum electrolytes

The correct answers are A, B, C, D, F, H, J, K, and L. A metabolic workup for risk factors for calcium stone disease should include the following:

- Serum calcium concentration (risk factor = hypercalcemia)
- Serum albumin concentration (required to evaluate the serum calcium concentration)
- 24-hour urine calcium excretion (risk factor = hypercalciuria)
- 24-hour urine uric acid excretion (risk factor = hyperuricosuria)
- 24 hour urine oxalate excretion (risk factor = hyperoxaluria)
- 24-hour urine citrate excretion (risk factor = hypocitraturia)
- 24-hour creatinine excretion (required to evaluate completeness of the urine collections)

It is also useful to measure the serum electrolytes to rule out renal tubular acidosis as a cause of hypercalciuria, and to measure the serum creatinine so that the creatinine clearance can be estimated.

In order to maximize the sensitivity of these measurements, the values for the metabolic work-up were obtained as the mean of three, 24-hour urine collections, as follows:

serum: Ca^{++}: 9.8 mg/dl; Na^{+} 149 mEq/l; K^{+} 4.0 mEq/l; Cl^{-} 105 mEq/l; $COH3^{-}$ 25 mEq/l; BUN 12 mg/dl; Creatinine 1.0 mg/dl.

urine: Ca^{++}: 343 mg/day (normal $<$300 mg/day); Na^{+}: 226 mEq/day; oxalate 33 mg/day (normal $<$45 mg/day); citrate 256 mg/day (normal $>$320 mg/day); urate 678 mg/day (normal $<$ 800 mg/day); creatinine 1500 mg/day (normal 20 mg/kg/day).

What is the most appropriate therapeutic regimen for this patient at this time (select all that apply)?

A. Hydrochlorothiazide
B. Potassium citrate
C. Allopurinol
D. Low calcium diet
E. Moderate dietary sodium restriction
F. High protein diet
G. Water intake $>$2 liters per day

The correct answers are A, B, E, and G. The patient has hypercalciuria and hypocitraturia. Appropriate treatment therefore should include hydrochlorothiazide and potassium citrate. Moderate sodium restriction is necessary to allow thiazides to produce sustained ECF volume contraction and maximal reduction in urinary calcium excretion. Increased fluid intake will lower urinary solute excretion.

The patient was begun on hydrochlorothiazide, potassium citrate, increased fluid intake, and moderate sodium restriction. He returns two weeks later to review test results. Serum electrolytes are normal. The 24-hour urine values are sodium 205 mEq; calcium 275 mg; citrate 544 mg; oxalate 30 mg; creatinine 1450 mg, and uric acid 680 mg.

What do you recommend now?

A. Re-emphasize the need for sodium restriction
B. Add lasix
C. Add amiloride

The correct answer is A. The patient has not complied with the recommendation to utilize moderate sodium restriction. For this reason, the hypocalciuric response to hydrochlorothiazide is blunted. Thus, the patient should be instructed to adhere to sodium restriction.

The patient took his medication as instructed and maintained a high fluid intake and moderate sodium restriction. On this regimen, he remained stone-free for the next 10 years. He indicates that his brother is concerned about the possibility of an increased risk of calcium stones in the family.

Is there an increased risk for family members?

A. Yes
B. No

The correct answer is A. Yes, there is an increased likelihood of calcium stone disease in family members. The presence of a family history of nephrolithiasis, in about half of the individuals with hypercalciuria studied, indicates that an inherited genetic defect is at least one likely cause of this condition.

References

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Muldowney FP, Freaney R, Moloney MF (1982) Importance of dietary sodium in the hypercalciuria syndrome. Kidney Int 22:292–296

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Worster A, Preyra I, Weaver B, et al. (2002) The accuracy of noncontrast helical computed tomography versus intravenous pyelography in the diagnosis of suspected acute urolithiasis: a meta-analysis. Ann Emerg Med 40:280–286

CASE 2

A 15-year old boy with recurrent calcium oxalate nephrolithiasis is begun on hydrochlorothiazide and potassium citrate therapy. He asks you about the potential effects and/or complications of this therapy.

Which ONE of the following choices is MOST likely to be a result of treatment with 50 mg/day hydrochlorothiazide and 40 mg/day potassium citrate?

A. Hypokalemia
B. Metabolic alkalosis
C. Hpercitraturia secondary to intracellular acidosis
D. Hypochloremia
E. Increased urine pH

The correct answer is E. While hypocitraturia is a consequence of hypokalemia and the latter, along with a mild degree of metabolic alkalosis, is a common complication of thiazide therapy, the use of small doses of potassium citrate has been shown to eliminate this complication and only leads to an elevated urine pH.

Reference

Odvina CV, Preminger GM, Lindberg JS, et al. (2003) Long-term combined treatment with thiazide and potassium citrate in nephrolithiais does not lead to hypokalemia or hypochloremic metabolic alkalosis. Kidney Int 63:240–247

CASE 3

A 19-year old male with human immunodeficiency virus (HIV) presents with the acute passage of a kidney stone. The patient has been doing well on highly active anti-retroviral therapy (HAART) and has had no serious episodes of opportunistic infections. Indinavir had been one of the components of his therapy. Laboratory studies are all within normal limits. Spiral computed tomography reveals one radiodense stone in the left kidney.

Which ONE of the following choices represents the MOST likely chemical composition of his stone?

A. Calcium oxalate
B. Indinavir
C. Uric acid
D. Calcium phosphate
E. Ritonavir

The correct answer is A. In a study of 24 patients with HIV and nephrolithiais who had been on protease inhibitors, the patients formed many different types of stones that were attributable to underlying metabolic abnormalities rather than the use of protease inhibitors. While protease inhibitors, particularly indinavir, are known to induce kidney stone formation, a complete metabolic evaluation is warranted in HIV patients as a means of guiding treatment to prevent future stone episodes while avoiding the need to alter antiretroviral regimens.

Reference

Nadler RB, Rubenstein JN, Eggener SE, et al. (2003) The etiology of urolithiasis in HIV infected patients. J Urol 169:475–477

CASE 4

Which ONE of the following has been shown to contribute to hyperoxaluria in typical patients with calcium oxalate stone formation and hyperoxaluria compared with calcium oxalate stone formers who excrete normal amounts of oxalate?

A. Dietary oxalate intake
B. Ascorbic acid intake
C. Low 24-hour urine volume
D. Low dietary fiber intake
E. High calcium intake

The correct answer is B. In a large clinical study utilizing self-selected diets, multiple logistic regression analysis revealed that urinary oxalate excretion was significantly associated with dietary ascorbic acid, a metabolic source of oxalate, and fluid intake, and inversely related to calcium intake. Other factors were not relevant.

Reference

Siener R, Ebert D, Nicolay C, et al.. (2003) Dietary risk factors for hyperoxaluria in calcium oxalate stone formers. Kidney Int 63:1037–1043

CASE 5

A 10-year old boy with a long history of ulcerative colitis is referred to you because he passed a kidney stone for the first time one month ago. There is no family history of kidney stone formation, he is on no medication now, and is asymptomatic. His supine abdominal x-ray is negative for renal or urinary tract calcifications, and his serum electrolytes, calcium, phosphate, and creatinine are all within normal limits.

Evaluation of his urine is most likely to reveal which ONE of the following patterns compared with normal individuals?

A. Hypocitraturia, low urine pH, and hypocalciuria
B. Hyperuricosuria and low urine pH
C. Hyperoxaliuria and hypocalciuria
D. Hyperoxaliuria and hypercalciuria
E. Elevated urine pH, hypercalciuria, and hyperoxaliuria

The correct answer is A. Acid urine pH, hypocitraturia, and dehydration are strong risk factors for uric acid stone formation in bowel disease patients.

Reference

Parks JH, Worcester EM, O'Connor RC, et al. (2003) Urine stone risk factors in nephrolithiasis patients with and without bowel disease. Kidney Int 63:255–265

CASE 6

You find that the stone passed by a nine-year old male is 100% uric acid. His 24-hour urinary excretion of calcium, oxalate, and uric acid are within normal levels. Urine volume is 1700 ml/day. Serum chemistries were also within normal limits. He takes no medications and ingests a healthy diet.

Which ONE of the following chemical patterns is MOST likely to be seen after an oral acid load in this patient compared with a normal, non-stone former?

A. Lower initial urine pH, higher post-load pH, reduced ammonium excretion
B. Lower initial urine pH, lower post-load pH, reduced ammonium excretion
C. Lower initial urine pH, lower post-load pH, higher ammonium excretion

D. Lower initial urine pH, higher post-load pH, higher ammonium excretion
E. Higher initial urine pH, higher post-load pH, reduced ammonium excretion

The correct answer is B. Patients with uric acid stones have lower urinary pH and they excrete less of their acid as ammonium but have higher titratable acid and less citrate excretion in order to maintain acid-base balance. Despite their low baseline urinary pH, uric acid stone formers further acidify their urine after an acid load because of a severely impaired ammonia excretory response.

Reference

Sakhaee K, Adams-Huet B, Moe OW, et al. (2002) Pathophysiologic basis for normouricosuric uric acid nephrolithiasis. Kidney Int 62:971–979

CASE 7

Which ONE of the following risk factors for calcium oxalate stone formation characterizes the urine of patients with medullary sponge kidney (MSK) and recurrent nephrolithiasis?

A. Hypercalciuria
B. Hyperuricosuria
C. Hypocitraturia
D. Reduced urine volume
E. Increased magnesium excretion

The correct answer is C. Low urinary excretion of citrate and magnesium are the most typical metabolic disorders that distinguish MSK stone patients from idiopathic, calcium-stone forming patients. In addition, anatomic abnormalities such as ecstatic ducts, low levels of urinary inhibitors of stones seem to contribute to the pathogenesis of nephrolithiasis in patients with MSK.

Reference

Yagisawa T, Kobayashi C, Hayashi T, et al. (2001) Contributory metabolic factors in the development of nephrolithiasis in patients with medullary sponge kidney. Am J Kidney Dis 37:1140–1143

CASE 8

A 12-year old boy has had a history of recurrent kidney stone disease for the last seven years. His serum creatinine was normal until three years before presentation, when a value of 1.8 mg/dl was noted. Intravenous urography showed

a radioopaque stone in the left ureter and moderate nephrocalcinosis, but he had never had documented urinary tract obstruction. Serum calcium, phosphate, PTH, and bicarbonate were all normal, but serum creatinine was 2.4 mg/dl. Urinalysis at that time showed 1+ proteinuria, and fasting urine pH was 5.2. A 24-hour urine calcium excretion was 490 mg. No specific therapy was given except for a high fluid intake. One year later, the patient was found to have a serum creatinine of 5.6 mg/dl, progressive nephrocalcinosis, but again, no evidence of obstruction.

What is the most likely cause of this condition?

A. Renal tubular acidosis
B. Analgesic abuse nephropathy
C. Dental disease
D. Primary hyperoxaluria
E. Medullary sponge kidney

The correct answer is D. This case is an example of primary hyperoxaluria presenting as unexplained renal failure in later life. The primary hyperoxalurias are autosomal recessive disorders resulting from deficiency of hepatic alanine glyoxylate aminotransferase (PHI) or D-glycerate dehydrogenase/glyoxylate reductase (PHII). Marked hyperoxaluria results in urolithiasis, renal failure, and systemic oxalosis. While it is uncommon to present later in life, it is well documented that it can occur. Incomplete RTA will not lead to renal failure in the absence of obstructive uropathy. Analgesic abuse is possible in this case, but radiopaque stones are not characteristics of that entity. Dent's disease produces renal failure and kidney stones but is associated with hypercalciuria. Medullary sponge kidney does not produce renal failure.

At what serum uric acid level does hyperuricemia occur?

A. 6.0 mg/dl
B. 6.8 mg/dl
C. 7.5 mg/dl
D. 8.4 mg/dl

The correct answer is B. Hyperuricemia is defined as a serum uric acid concentration $\geq$6.8 mg/dl.

What is the most common cause of hyperuricemia?

A. Inability to excrete sufficient uric acid
B. Overproduction of uric acid
C. Ingestion of a purine-rich diet
D. Alcohol abuse

The correct answer is A. The most common cause of hyperuricemia is a defect in transport systems within the kidney that prevents the kidney from excreting enough uric acid. Almost all uric acid is filtered in the glomerulus. Immediate reabsorption takes place in the proximal convoluted tubule. About half the original filtered load is then secreted. This is followed by reabsorptiom, with the final excretion of uric acid being about 10% of the originally filtered amount.

Which of the following conditions is associated with hyperuricemia?

A. Renal insufficiency
B. Hypertension
C. Cardiovascular disease
D. All of the above

The correct answer is D. A number of medical conditions can be associated with hyperuicemia, including renal insufficiency, IgA nephropathy, kidney stones, and hypertension.

References

Igarashi T (1993) Normal serum uric acid concentrations for age and sex and incidence of renal hypourecemia in Japanese school children. Ped Nephrol 7:239–240

Johnson RJ, Kivlighn SD, Kim YG, et al. (1999) Reappraisal of the pathogenesis and consequences of hyperuricimia in hypertension and cardiovascular disease, and renal disease. Am J Kidney Dis 33: 225–234

Maesaka JK, Fishbane S (1998) Regulation of renal urate excretion: A critical review. Am J Kidney Dis 32:917–933

Milliner DS, Wilson DM, Smith LH (2001) Phenotypic expression of primary hyperoxaluria: Comparative features of Types II and I. Kidney Int 59:31–36

CASE 9

Rasburicase catalyzes uric acid into a more soluble, excretable form of allantoin and is widely used in patients about to undergo chemotherapy for a hematologic malignancy and who are allergic to allopurinol.

Which of the following adverse effects is associated with rasburicase therapy?

A. Anaphylaxis
B. Hemolysis
C. Methemoglobinemia
D. All of the above
E. None of the above

The correct answer is A. The use of Rasburicase may carry the risk of anaphylaxis, hemolysis, and methemoglobinemia.

Reference

Coiffer B, Mounier N, Bologna S, et al. (2003) Efficacy and safety of rasburicase (recombinant uricoxidase) for the prevention and treatment of hyperuricemia during chemotherapy of aggressive non-Hodgkin's lymphoma: results of the GRAAL1 study. J Clin Oncol 21:4402–4406

CASE 10

A 14-year old boy presents with a seven-year history of cystinuria with multiple stone events. He is now on a regimen of tiopronin (1 g/day), and a high fluid intake (3 liters/day). Measurement of 24-hour urine collection reveals a volume of 2.8 liters, pH 7.0, sodium 105 mEq, and cystine excretion of 1250 mg. Despite this treatment, the patient has continued to form approximately one stone per year.

Which one of the following approaches would increase the efficacy of this patient's treatment?

A. Direct measure of cystin solubility in day and night urine collections
B. Additional potassium citrate to raise pH to 8.0
C. Reduce dietary sodium to 70 mEq/day
D. Add acetylcystein
E. Add captopril

The correct answer is A. Clinical management of cystinuria can be improved by direct measurement of cystin solubility because it varies widely at any given pH. Increasing 24-hour collection pH with sodium bicarbonate additionally improves accuracy of supersaturation measurement by recovering crystallized cystin. Cystin solubility increases by up to three-fold in an alkaline urine, but one generally needs to achieve values higher than urine pH of 7.2. Reducing dietary sodium intake to 50 mEq/day or less is effective, but adherence to such a strict regimen is unlikely. There are studies advocating the use of acetylcystein, but the cystein may be released from the compound and actually lead to increased cystein excretion rather than achieving a more soluble mixed disulfide. The effects of capropril have been inconsistent as a therapy of cystinuria.

References

Nakagawa Y, Asplin JR, Goldfarb DS, et al. (2000) Clinical use of cystin super saturation measurements. J Urol 164:1481–1485

Fjellstedt E, Denneberg T, Jeppsson JO (2001) Cystin analyses of separate day and night urine as a basis for management of patients with homozygous cystinuria. Urol Res 29:303–310

CASE 11

A five-year old boy presents with a long history of urinary difficulties that began in infancy with urinary reflux and a congenital solitary kidney. His parents have been obsessed with their son's health ever since and have been using a variety of dietary supplements to increase his strength and endurance. He has developed two radiolucent stones in the past year. Urine studies reveal no hypercalciuria, a urine pH of 7.5, and no hyperuricosuria.

Which of the following alternative medications could contribute to stone formation in this patient?

A. Oalang tea
B. Cat's claw
C. Ma-Haung extract (ephedrine)
D. Star fruit
E. Creatine

The correct answer is C. Ma-Huang extract, a popular alternative herbal preparation, is rich in ephedrine and is also used as a weight-loss preparation. Ephedrine is a constituent of about .06% of all stones assayed. Cat's claw has been associated with a lupus-like syndrome. Oolong tea is rich in theophylline and has been reported to induce hyponatremia when consumed in very large quantities. Creatine has been associated with acute tubular necrosis. Star fruit is very rich in oxalate and has been reported to induce acute renal failure if consumed in large quantities by volume-depleted and dehydrated individuals.

Reference

Powell T, Hsu FF, Turk J, et al. (1998) Ma-huang strikes again: ephedrine nephrolithiasis. Am J Kidney Dis 32:153–159

CASE 12

A 15-year old boy patient presents with his second kidney stone. Some analysis in the past had revealed calcium oxalate stone, but on this occasion (two years after the first stone passage) the stone had not been saved for analysis. Hypercalcemia and renal tubular acidosis had been ruled out in the past, and you decide to perform an evaluation for the presence of risk factors for recurrent calcium oxalate stone formation.

Which of the following statements regarding the workup of recurrent urolithiasis, in a patient such as the one described, is correct?

A. Patient should be placed on a specific calcium diet to accurately assess whether they are hypercalciuric.
B. Patients must be placed on a specific sodium intake level to assess the presence of hypercalciuria.
C. Serum PTH should be measured to assess the possibility of hyperparathyroidism.
D. A single, random collection of 24-hour urine for calcium, uric acid, pH, total volume, and sodium is sufficient to determine risk factors.
E. Urine should be cultured for nonbacterial species.

The correct answer is D. A single stone risk analysis is sufficient for the simplified medical evaluation of urolithiasis. They reached this conclusion by retrospectively analyzing stone risk data on 24-hour urine samples obtained during random and restricted diets in 225 patients recurrent urolithiasis. Restricting dietary calcium will not help in defining etiology because this might contribute to the patient's stone propensity if he is habitually on a very high calcium intake. If he is on a very low calcium intake, it could also result in increased stone formation by inducing hyperoxaluria. In either case, identifying the potential role of diet would be useful and would be obscured by a salt diet. PTH assays are not helpful unless the patient is hypercalcemic. A small fraction of patients with recurrent nephrolithiasis will have renal wasting of calcium, and may have secondary hyperparathyroidism. The role of nanobacter species in the pathogenesis of kidney stones was briefly favored as an important factor, but has since been discarded based on new information suggesting the finding was likely artifactual.

Which of the following statements regarding the collection of 24-hour urine to ascertain the etiology of kidney stone formation is correct?

A. Patients with a history of kidney stone formation excrete more oxalate than age-matched controls.
B. Patients with a history of kidney stone formation do not excrete more oxalate than age-matched controls.
C. Patients with a history of kidney stone formation excrete more uric acid than age-matched controls.
D. About 20% of normal individuals have a urinary calcium excretion in the hypercalciuric range (>4 mg/kg/day).
E. Patients with a history of kidney stone formation excrete less citrate than age-matched controls.

The correct answer is D. A careful epidemiologic study (Curhan et al.. 2001) using three large groups showed that while mean 24-hour urine calcium excretion was higher (and urine volume was lower) in cases other than the control groups in two of the very large cohorts, urine oxalate and citrate did not differ. Among women,

urine uric acid was similar in cases and controls but was actually lower in cases in men. The frequency of hypercalciuria was higher among the cases in three separate cohorts but 27%, 17%, and 14% of the controls, respectively, also met the definition of hypercalciuria. The frequency of hypercalciuria did not differ between cases and controls.

References

Curhan GC, Wilett WC, Speizer FE, et al. (2001) Twenty-four-hour urine chemistries and the risk of kidney stones among women and men. Kidney Int 59:2290–2298

Pack CY, Peterson R, Poindexter JR (2001) Adequacy of a single stone risk analysis in the medical evaluation of urolithiasis. Urol 165:378–381

CASE 13

A 19-year old man is referred for evaluation of a rising serum creatinine and hypertension. He has a history of intravenous drug abuse and unprotected sex. He is HIV and hepatitis C seropositive. He has been treated with highly active anti-retroviral therapy (HAART), including stavudine, lamivudine, and indinavir. His most recent serum creatinine was 3.1 mg/dl as compared with 2.9 mg/dl three month earlier. Urine dipstick is negative for blood or protein, and renal ultrasound examination shows mildly reduced renal size without any calcifications or nephrolithiais. Microscopic examination of the urine reveals 20 to 30 WBC/hpf without hematuria. Occasional crystals were seen.

What is the most likely cause of his renal disease?

A. Collapsing FSGS secondary to human immunodeficiency virus (HIV) nephropathy
B. Vasculitis secondary to hepatitis C nephropathy
C. Tubulointerstitial fibrosis with intratubular crystals secondary to indinavir nephropathy
D. Heroin nephropathy
E. Tuberculous nephritis

The correct answer is C. Indinavir is extremely insoluble at physiologic pH levels, is lithogenic, and is thought to cause 3% of kidney stones. Among the risk factors of age, weight, duration of indinavir use, CD4 count, serum creatinine level, liver function tests, urine pH, and urinary specific gravity, only increasing age is a variable that is a statistically significant predictor of indinavir urolithiaisis. Hepatitis C would be expected to produce a proteinuric nephropathy or a glomerulonephritic picture. Collapsing FSGS or heroin-associated nephropathy would also be expected to be associated with marked proteinuria. Tuberculous nephritis rarely presents as a form of renal insufficiency.

Reference

Fogo A (2000) Indinavir nephropathy. Am J Kidney Dis 36: (4) E22

CASE 14

An otherwise healthy 12-year old boy has recurrent calcium oxalate stones. He is on no medications and has no history of gastrointestinal or urinary tract disease. Serum electrolytes are normal. Serum calcium and phosphate are repeatedly normal. A 24-hour urinary evaluation reveals: sodium 358 mEq, potassium 78 mEq, calcium 350 mg, oxalate 42 mg. citrate 200 mg, urate 720 mg, creatinine 800 mg, and volume 1100 ml.

All of the following therapies would be useful except:

A. Hydrochlorothiazide (50 mg/day)
B. Potassium citrate
C. Low sodium diet
D. Sodium citrate
E. Increased fluid intake

The correct answer is D. Sodium citrate will increase urinary citrate excretion and cause alkaline urin,e but will also increase calcium excretion by increasing sodium excretion. Potassium citrate will increase urinary pH without increasing calcium excretion. The thiazide diuretic and low sodium diet help to prevent new stone formation by reducing urinary calcium excretion.

Reference

Coe FL, Parks JH, Asplin JR (1992) The pathogenesis and treatment of kidney stones. N Engl J Med 327:1141–1152

CASE 15

A 14-year old male enters the emergency room because of flank pain, hematuria, and nausea. He has had calcium oxalate kidney stones in the past. You order an imaging study to determine whether kidney stones are present.

Which ONE of the following statements regarding imaging of the urinary tract under these circumstances is correct?

A. An unenhanced helical computed tomography (CT) scan is more accurate than an intravenous urogram.

B. An intravenous urogram has better sensitivity and specificity than an unenhanced helical CT.
C. An ultrasound study combined with a flat plate of the abdomen allows the most rapid diagnosis of stones.
D. The direct and indirect costs of an intravenous urogram are 50% less than an unenhanced helical CT.
E. The intravenous urogram results in higher radiation doses than an unenhanced helical CT.

The correct answer is A. Sensitivity and specificity of unenhanced helical computed tomography (UHCT) and intravenous urography (IVU) is 94.1 and 94.2%, and 85.2 and 90.4%, respectively. Time delay between access to the emergency room and start of the imaging procedure was 32 hours and 7 minutes for the UHCT, and 36 hours and 55 minutes for the IVU. The UHCT took an average in-room time of 23 minutes vs. 1 hour and 21 minutes for the IVU. The direct costs of UHCTs and IVUs are nearly identical (310/309), but indirect costs are much lower for UHCTs because it saves examination time and when performed immediately, an initial abdominal plain film (KUB) and sonography are not necessary. The mean applied radiation dose was 3.3 mSv for IVU, and 6.5 mSv for UHCT.

References

Pfister SA, Deckart A, Laschke S, et al. (2003) Unenhanced heical computed tomography vs. intravenous urography in patients with acute flank pain: accuracy and economic impact in a randomized prospective trial. Eur Radiol 13: 2513–2520

Worster A, Preyra I, Weaver B, et al. (2002) The accuracy of noncontrast helical computed tomography versus intravenous pyelography in the diagnosis of suspected acute urolithiasis: a meta-analysis. Ann Emerg Med 40:280–286

CASE 16

A 13-year old girl has a strong family history of kidney stones but she has not formed stones herself. She wishes to take oral calcium supplements to prevent osteoprosis and questions you about the timing of such therapy.

Which ONE of the following statements about the use of calcium supplements in this patient is correct?

A. If she takes the supplements at bedtime, her risk of kidney stones will increase.
B. If she takes the supplements at bedtime, the urinary calcium will be lower.
C. If she takes the supplements at bedtime, urinary oxalate will fall.
D. If she takes the supplements with meals, her urinary calcium will not increase.
E. If she takes the supplements with meals, urinary oxalate will be unchanged.

The correct answer is A. While epidemiologic data suggest that increased dietary calcium intake does prevent kidney stone formation; the use of calcium supplements has a less clear effect. When supplements are taken by patients at bedtime, the data suggest that the risk of stone formation may actually increase whereas intake with meals has no such deleterious action on stone risk. Increased calcium intake in the form of supplements will increase urinary calcium excretion, but if taken with meals will lower urinary oxalate excretion.

Which ONE of the following statements regarding the heritability of nephrolithiasis is correct?

A. First-degree relatives of patients who have formed stones are three times more likely to form a stone than the general population.
B. Spouses of patients who form stones have twice the risk of forming stones as the general population.
C. Most studies suggest that the heritability of nephrolithiasis is monogenetic.
D. 90% of stone formation can be attributed to genetic factors.
E. In studies where inheritance of stone formation risk has been found, the pattern of inheritance is typically x-linked.

The correct answer is A. The available data suggest that the mode of inheritance is complex and polygeneic, but if anything, nephrolithiasis has an autosomal dominant pattern. Approximately half of an individual's liability to renal stone disease is genetic and half is environmental. There is little evidence that spouses are at increased risk.

References

Domrongkitchairporn S, Sopassathit W, Stitchantrakul W, et al. (2004) Schedule of taking calcium supplements and the risk of nephrolithiasis. Kidney Int 65:1835–1841

Griffin DG (2004) A review of the heritability of idiopathic nephrolithiasis. J Clin Pathol 57:793–796

CASE 17

A 16-year old female has passed three kidney stones, each composed of calcium oxalate. She has been thoroughly evaluated and found to have idiopathic hypercalciuria. She is concerned about developing osteoporosis and wants your advice about her prognosis and recommendations for preventive therapy, including dietary advice.

Which ONE of the following statements describes the risk factors for osteoporosis given her history of hypercalciuria?

A. Consuming a high-calcium diet will exacerbate her risk of osteoporosis.
B. Kidney stone formation is irrelevant to the risk of osteoporosis.

C. Serum calcitriol levels will help predict the risk of osteoporosis.
D. Excessive dietary protein intake will lead to reduced bone density.
E. Thiazide diuretics will reduce hypercalciuria and reduce bone mineral mass.

The correct answer is D. The data suggest that stone formers have tended to avoid calcium in their diets and this likely has contributed to osteoporosis in the past. Consuming an adequate calcium diet should not lead to exacerbation of osteoporosis risk. Stone formation does seem to increase risk of osteoporosis as urine calcium varies inversely with bone mineral density in stone formers. Vitamin D levels, however, do not appear to correlate with risk. Thiazides tend to increase bone mineral mass in a number of studies. The higher acid loads of high protein diets have been shown to produce negative calcium balance. In this patient, higher dietary protein intake was likely associated with lower bone density in stone formers.

Reference

Asplin Jr, Bauer KA, Kinder J, et al. (2003) Bone mineral density and urine calcium excretion among subjects with and without nephrolithiasis. Kidney Int 63:662–669

CASE 18

A 14-year old male has a history of passing five kidney stones, two of which were analyzed and found to be 100% calcium oxalate. He is known to excrete 55 mg oxalate per day (normal <40 mg/day).

Which ONE of the following statements BEST describes the likely impact of taking 1 g/day ascorbate in this patient?

A. Little impact, because >90% of increased urinary oxalate seen in stone-formers with hyperoxaluria is due to ascorbate oxalate
B. Little impact, because ascorbate does not contribute to 20% increase in urinary oxalate excretion
C. 20% increase in urinary oxalate excretion
D. 100% increase in urinary oxalate excretion
E. A rise in oxalate excretion is unlikely because only 10% of stone-formers have a genetic characteristic that leads to increased oxalate production from ascorbate ingestion.

The correct answer is C. Ascorbate supplementation increases urinary total oxalate levels by about 20%. About 80% of urinary oxalate derives from endogenous metabolism. The majority of stone formers appear to respond to an increased ascorbate intake with a rise in urinary oxalate excretion.

Reference

Chai W, Liebman M, Kynast-Gales S et al.. (2004) Oxalate absorption and endogenous oxalate synthesis from ascorbate in calcium oxalate stone formers and non-stone formers. Am J Kidney Dis 44:1060–1069

CASE 19

A 12-year old boy with recurrent nephrolithiasis is sent to you for evaluation. Evaluations reveal normal urinary acidifying activity and no evidence of metabolic acidosis. Serum electrolytes and creatinine are all within the normal range. Serum calcium is 9.2 mg/dl, albumin 4.0 g/dl, urine calcium 210 mg/day, urine phosphate 800 mg/day, urine oxalate 80 mg/day (normal <40 mg/day), and urine pH 5.2.

Which ONE of the following statements regarding this patient is correct?

A. His stones should be analyzed because they are likely to contain a combination of two calcium oxalate crystals (calcium oxalate monohydrate and calcium oxalate dehydrate).
B. His disorder likely stems from high dietary oxalate.
C. He should receive an ammonium chloride test for maximal urinary pH.
D. He should undergo mutation analysis of the gene coding for alanine glyoxalate aminotransferase to help guide therapy.
E. He should undergo plasma glycolate determination.

The correct answer is D. It is important to not only recognize the possibility of primary hyperoxalluria in a young person with high urinary oxalate excretion but also to genotype patients with this disorder because early detection of Gly170Arg and Phe152Ile mutations in Type I primary hyperoxaluria has important clinical implications. These mutations are associated with pyridoxine responsiveness, and renal function can be preserved if treatment with prydoxine, high fluid intake, and potassium citrate are initiated before renal insufficiency develops. Prydoxine is effective because it is a coenzyme of AGT and promotes the conversion of glyoxylate to glycin rather than to oxalate.

Reference

Hoppe B, Lehmann E (2004) Diagnostic and therapeutic strategies in hyperoxaluria: a plea for early intervention. Nephrol Dial Transplant 19: 39–42

Chapter 5
Hypertension

CASE 1

Which ONE of the following is the most accurate statement regarding cardiovascular outcomes in high risk people?

A. Lowering BP (BP) with a combination of drugs that includes an angiotensin-converting enzyme (ACE) inhibitor is superior to using any other agents, even if the BP is close to, but not at, goal levels.
B. Lowering BP with any combination of agents will reduce cardiovascular risk if the BP is at goal levels.
C. Use of a diuretic/ß-blocker combination is the only therapy that has been shown in clinical trials to effectively reduce cardiovascular risk regardless of the BP achieved.
D. Risk for cardiovascular events plateaus at BP levels above 180 mmHg.
E. A J-shaped curve relative to the occurrence of cardiovascular events exists for BP-lowering in people under the age of 50 years.

The correct answer is B. Numerous clinical trials have shown that an average of two to three different antihypertensive medications may be needed to achieve goal BP. Thus, combinations that include agents that block the renin-angiotensin–ldosterone system—such as, ACE inhibitors, angiotensin-receptor blockers (ARB), or beta-blockers, coupled with diuretics and calcium channel blockers—are usually adequate to achieve the goal BP. Occasionally, alpha-blockers or other agents are needed, especially in those who have isolated systolic hypertension or require a lower BP goal.

References

Bakris GL (2001) A practical approach to achieving recommended BP goals in diabetic patients. Arch Intern Med 161:2662–2667

Douglas JG, Bakris GL, Epstien M, et al. (2003) Management of high BP in African Americans: Consensus statements of the hypertension in African Americans Working Group of the International Society on Hypertension in Blacks. Arch Intern Med 163:525–541

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CASE 2

Which ONE of the following BP goals is currently recommended by Joint National Committee VII(JNC-7) and other guidelines committees for people with chronic kidney disease or diabetes?

A. <140/90 mmHg
B. <130/85 mmHg
C. <130/80 mmHg
D. <125/75 mmHg
E. <120/60 mmHg

The correct answer is C. This is the BP goal recommended by the JNC-7 for anyone with kidney disease or diabetes. For people with kidney disease or diabetes, a systolic BP ≥130 mmHg should be treated with an agent that blocks the renin-angiotensin-aldosterone system. Lifestyle modifications should also be initiated in this group.

Reference

Chobanian AV, Bakris GL, Black HR, et al. (2003) The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High BP. The JNC-7 Report. JAMA 289:2560–2571

CASE 3

All of the following antihypertensive drug classes have been shown to reduce BP, risk of heart failure, and other risk factors for renal disease progression such as proteinuria, EXCEPT:

A. Angiotensin-converting enzyme (ACE) inhibitors
B. Diuretics
C. Dihydropyridine calcium channel blockers (CCB)
D. Angiotensin receptor blockers (ARBs)
E. β-blockers

The correct answer is C. All classes of drugs listed reduce BP, but the dihydropyridine calcium channel blockers such as amlodipine, nifedipine, etc., have not been shown to slow the progression of Stages 3 and 4 nephropathy. However, the concomitant use with ACE inhibitors or ARB does not offset the benefits of the latter two agents. By further lowering the BP, the addition of dihydropyridine calcium channel blockers to ACE inhibitors or ARB's reduces the risk of stroke—a consistent observation in all comparative studies with these agents.

Reference

Wright JT, Bakris GL, Greene T, et al. (2002) Effect of BP lowering and antihypertensive drug class on progression of hypertensive kidney disease.: results from the AASK trial. JAMA 288:2421–2431

CASE 4

A 13-year old boy presents for a second opinion regarding his difficulty in controlling his BP. He has taken an ACE inhibitor and an ARB at maximal doses, but experienced only 8 to 10 mmHg reduction in systolic BP. He is currently on maximal doses of a CCB and an ACE inhibitor with a sitting BP of 148/92 mmHg.

Which ONE of the following genotypes might help predict an appropriate antihypertensive drug class to achieve the BP goal for this patient?

A. ACE gene
B. Angiotensinogen gene
C. Aldosterone syntheses gene
D. 11β-OH steroid dehydrogenase, Type 2 gene
E. Alpha-adducin gene

The correct answer is E. In an analysis of almost 1,000 patients, it was noted that carriers of the adducine variant had a lower risk for cardiovascular event or stroke when they received diuretic therapy compared to other antihypertensive drugs. It was also noted that those with the adducine variant had greater reductions in BP in response to a diuretic compared to other therapies. None of the other genotypes listed have been associated with this type of relationship to BP response and outcomes with a particular class of agents.

Reference

Psaty BM, Smith NL, Heckbert SR, et al. (2002) Diuretic therapy, the alpha-adducin gene variant, and the risk of myocardial infarction or stroke in persons with treated hypertension. JAMA 287:1680–1689

CASE 5

A 17-year old African-American woman has a BP of 142/89 mmHg, a body mass index (BMI) of 26 Kg/m^2, and a serum creatinine of 1.0 mg/dl. She walks about 20 minutes, three times weekly. She states that she is trying to comply with this program but is under stress at home and plans to move. She consumes a diet high in sodium and low in potassium.

She could benefit from which ONE of the following approaches?

A. Start a low-sodium diet and change her exercise program to include weight-lifting.
B. Start a high-potassium diet, 60 mEq/day (3.5 g) sodium diet, and increase exercise to 30 minutes sessions, five times weekly.
C. Start a 1200 calorie/day weight-loss diet, and add an ACE inhibitor to her regimen.
D. Re-evaluate her BP measurements six months after her move.
E. Recommend vigorous one-hour exercise six days per week, and a high potassium diet al.one.

The correct answer is B. This patient is overweight ,but not obese, and her sodium intake is quite high. The best answer for her BP control includes a diet high in potassium and low in sodium. The Diabetes Prevention Study demonstrated that exercise for 30 minutes, five times per week, was associated with weight loss and BP reduction. This patient should increase her exercise time accordingly to meet this standard.

References

The Diabetes Prevention Program (DDP): description of lifestyle intervention. Diabetes Care 25:2165–2171

Sacks FM, Svetky LP, Vollmer WM, et al. (2001) Effects on BP of reduced dietary sodium and the Dietary Approaches to stop Hypertension (DASH) diet. DASH-Sodium Collaborative Research Group. N Engl J Med 344:3–10

CASE 6

A 15-year old African American girl with a BMI of 35 kg/m2, and BP of 146/90 mmHg is referred to you for new-onset microalbuminuria (59 mg/g creatinine; normal <20 mg/g). She has been on antihypertensive medications (50 mg/day of metoprolol) for the past three years. Before that time, she had never been told she was hypertensive. On this visit, you note all laboratory tests are normal except her fasting blood glucose of 124 mg/dl. Her current BP is 149/92 mmHg, and pulse is 68 and regular.

Which ONE of the following is the BEST management approach for this patient?

A. Stop the ß-blocker and start an ACE inhibitor/diuretic and titrate to BP goal.
B. Tell her to lose weight and put her on a 1200-calorie/day diet.
C. Increase metoprolol to achieve BP goal.
D. Add an ACE inhibitor to current regimen.
E. Recommend an exercise program for weight loss.

The correct answer is A. Based on her cardiovascular risk factor profile, her current BP, the fact that she is African American, and the fact that she has normal kidney function, the ideal therapy for her would be an ACE inhibitor with a diuretic. Her BP is not well-controlled. This, taken together with data from clinical trials, would support the use of combination therapy and changing to a different blocker of the renin-angiotensin system. Other choices such as adding a beta-blocker are not pharmacologically rational approaches.

References

Wright JT, Bakris GL, Greene T, et al. (2002) Effect of BP lowering and antihypertensive drug class on progression of hypertensive kidney disease.: results from the AASK trial. JAMA 288:2421–2431

Douglas JG, Bakris GL, Epstien M, et al. (2003) Management of high BP in African Americans: Consensus statements of the hypertension in African Americans Working Group of the International Society on Hypertension in Blacks. Arch Intern Med 163:541–541

CASE 7

An 18-year old African American woman with an estimated glomerular filtration rate (GFR) of 100 ml/min, microalbuminuria of 130 mg/g creatinine (normal $<$20 mg/g), body mass index (BMI) of 29 kg/m^2, and BP of 152/90 mmHg is referred to you for BP control. She is currently on a low-sodium diet, which she claims to follow, and you confirm by a 24-hour urine sodium of 86 mEq. She is currently on 10 mg/day of amlodipine.

Which ONE of the following treatment regimens will most likely achieve a goal BP of $<$130/85 mmHg?

A. Add loop diuretic twice daily
B. Add an angiotensin-receptor blocker
C. Increase dose of amlodipine to 20 mg/day
D. Stop amlodipine and use non-dihydropyridine calcium channel blocker with diuretic
E. Add a combination of thiazide diuretic and ACE inhibitor and titrate to the maximum doses of both diuretic and ACE inhibitor over the next two months.

The correct answer is E. Based on current recommendations, this patient is more than 20/10 mmHg above the BP goal and therefore requires combination therapy. She does not have intractable edema, and has Stage 2 chronic kidney disease. Based on published guidelines for people with less than Stage 3 nephropathy, a thiazide diuretic should be part of the initial drug therapy. Therefore, a loop diuretic would be inappropriate. Moreover, a renin-angiotensin system blocker also needs to be part of the antihypertensive regimen.

Reference

Chobanian AV, Bakris GL, Black HR, et al. (2003) The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High BP. The JNC-7 Report. JAMA 289:2560–2571

CASE 8

A 19-year old male has a BP of 172/104 mmHg, a body mass index of 30 kg/m2, normal renal function, microalbuminuria, and a family history of cardiovascular disease.

Which ONE of the following initial therapies would be best for this patient?

A. Start with thiazide diuretic therapy, and observe.
B. Start with an ACE inhibitor or ARB and titrate the dose to maximize its effect on BP, and observe.
C. Start with a thiazide diuretic, quickly add a β-blocker, and titrate doses over the next two months.
D. Start with a combination of thiazide diuretic and an ACE inhibitor, ARB, or β-blocker, and titrate doses over the next two months.
E. Start with an ACE inhibitor/ARB combination, and titrate doses over the next two months.

The correct answer is D. Based on the available guidelines, the use of a combination of drugs as first-line therapy should be strongly considered in this patient. Generally speaking, the maximum BP reduction for a single agent is 13 to 17 mmHg, and this person is more than 30 mmHg above his goal BP. Also, based on published guidelines for people with less than Stage 3 nephropathy, a thiazide diuretic should be part of the initial combination of drugs prescribed.

Reference

Chobanian AV, Bakris GL, Black HR, et al. (2003) The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High BP. The JNC-7 Report. JAMA 289:2560–2571

CASE 9

A 14-year old boy with ESRD is dialyzed on the morning shift, at which his systolic BP (SBP) is consistently between 150 to 170 mmHg. After each treatment, his final SBP remains above 140 mmHg. A 24-hour BP monitor demonstrates that his average BP during the day is 148/72 mmHg. At night, it averages 144/78 mmHg.

He currently receives all his medications (ACE inhibitor, CCB, and ß-blocker) in the morning, but he does not take them on the morning of dialysis.

Which ONE of the following choices MOST accurately describes his cardiovascular risk?

A. He is at the same risk as the average ESRD patient.
B. He is at much higher risk than those ESRD patients whose BP manifests a night time dip (a nocturnal decline in BP).
C. His most likely time to have a cardiovascular (CV) event is in the late evening.
D. His prognosis will not improve if he is converted to a dipper.
E. There is no known therapy that will convert him to a dipping status.

The correct answer is B. Studies have shown that dialysis patients, like those *non-dippers* with normal renal function (i.e., those failing to decrease their normal SBP by at least 20 mmHg), have a higher risk of CV events and death than do *dippers*.

Reference

Liu M, Takahashi H, Morita Y, et al. (2003) Non-dipping is a potent predictor of cardiovascular mortality and is associated with autonomic dysfunction in hemodialysis patients. Nephrol Dial Transplant 18:563–569

CASE 10

A 17-year old obese male (BMI of 31 kg/m^2) receiving dialysis treatment is noted to have fluctuating BP such that he is severely hypertensive (200/90 mmHg) at the beginning of dialysis. Systolic BP drops to 130 mmHg during therapy, but he is always asleep when this happens. He is currently on four antihypertensive medications, including an ACE-inhibitor, a CCB, a ß-blocker, and minoxidil. When awakened, his systolic BP increases by at least 20 mmHg.

Which ONE of the following would be the most appropriate management of this patient?

A. Continuous positive airway pressure (C-PAP) mask
B. Nocturnal oxygen
C. Adding quanethidine
D. Benzodiazepines for sleep
E. Weight loss and benzodiazepine

The correct answer is A. This patient has a high probability of having sleep apnea, a disorder that is quite common in dialysis patients. He should be evaluated for this possibility. Central to effective treatment is the provision of C-PAP to improve

air exchange. This therapy has been shown to reduce elevated BP by as much as 20–30 mmHg systolic in compliant patients.

References

Fletcher EC (2003) Sympathetic over activity in the etiology of hypertension of obstructive sleep apnea. Sleep 26:15–19

Richert A, Ansarian K, Baran AS (2002) Sleep apnea and hypertension: pathophysiology mechanisms. Semin Nephrol 22:71–77

CASE 11

A 16-year old boy with Type 2 diabetes on well controlled diet for three years (HB AIc 5.8%, serum creatinine 1.6 mg/dl) is referred for BP control. His BP is 152/86 mmHg. He follows his diet and walks approximately 30 minutes, 4 times weekly. His BMI is 29 k/m^2. He has microalbuminuria (154 mg/g creatinine) and was recently switched to high-dose ACE inhibitor monotherapy (lisinopril 40 mg/day) with a BP of 142/84 mmHg and a regular pulse of 72.

Which ONE of the following is the most appropriate next step to achieve his BP goal?

A. Add a thiazide diuretic
B. Observe until the next visit in six months
C. Add an ARB for microalbuminuria
D. Add a β-blocker because he has high cardiovascular risk
E. Increase his exercise time

The correct answer is A. Based on the JCN-7 guidelines; a thiazide diuretic should be one of the first two agents prescribed for BP control in people without renal disease. Thiazides may also be used in patients with renal disease if they have less than Stage 3 chronic kidney disease.

Reference

Chobanian AV, Bakris GL, Black HR, et al. (2003) The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High BP. The JNC-7 Report. JAMA 289:2560–2571

CASE 12

A 16-year old Caucasian female presented to the emergency room with severe hypertension and evidence of neurologic deficits. Her BP was 210/120 mmHg, pulse was 88 beats/min, and she had a regular and continuous bruise over her left lateral

abdominal area. Her serum creatinine level was 1.6 mg/dl, potassium 3.9 mEq/l, sodium 139 mEq/l, chloride 104 mEq/l, and bicarbonate 24 mEq/l. A chest x-ray was normal. She was given 10 mg of sublingual nifedipine and started on intravenous nitroprusside. She died suddenly in the process of being transferred to the intensive care unit (ICU).

Which of the following choices describes what should have been the best approach for this patient's management?

A. Nothing different should have been done, because she had a fatal cardiac arrhythmia.
B. IV fenoldopam should have been substituted for nitroprusside because of her renal insufficiency.
C. Both intravenous labetalol and intravenous fenoldopam should have been used.
D. Intravenous diuretics should have been used initially to help unload the heart.
E. Her systolic BP should have been maintained above 140 mmHg because of possible stroke extension.

The correct answer is C. It is clear from the physical examination that the patient has an abdominal aneurysm and renal insufficiency. Attempting to lower this patient's pressure with vasodilators that will cause reflex tachycardia could result in further stress to the aortic wall and rupture of the aneurysm, which is exactly what happened to this patient. Use of IV β-blockers is ideal therapy in patients with a selective dopamine-1 receptor agonist to vasodilate without increasing heart rate.

References

Mansoor GA, Frishman WH (2002) Comprehensive management of hypertensive emergencies and urgencies. Heart Dis 4:358–371
Elliot WJ (2001) Hypertensive emergencies. Crit Care Clin 17:435–451

CASE 13

A 13-year old boy with Stage 3 chronic kidney disease, and long-standing renal vascular hypertension was admitted overnight with a left hemiparesis. Initial studies demonstrate no intracranial hemorrhage. Admitting BP was 188/109 mmHg.

Which ONE of the following therapeutic goals is MOST appropriate regarding BP control in this patient?

A. BP should be lowered quickly during the first 24 to 48 hours to reduce the risk of stroke extension.
B. BP should be reduced quickly to prevent myocardial events.
C. There are no special guidelines, because no data is available.

D. You should never reduce BP below 150 mmHg.
E. BP should be reduced gradually over the first 48 hours (150/90 mmHg), and then proceed to achieve systolic BP goal between 135 and 140 mmHg after the first week.

The correct answer is E. It is generally well-accepted that BP should be reduced in patients with a recent stroke to levels below 160 mmHg. It may then be gradually reduced to 140 mmHg over the first week following a stroke. After stability has been achieved, the BP may be gradually lowered further in some patients to values not less than 135–140 mmHg.

Reference

Brown RD (2003) Treatment of hypertensive patients with cerebrovascular disease. In; Izzo J and Black HR (eds): Hypertension Primer. Lippincott, Williams and Wilkins Dallas, pp.476–477

CASE 14

You evaluate an 18-year old male with a history of Type 2 diabetes and hypertension for newly identified microalbuminuria and a stable serum creatinine of 1.2 mg/dl. His BP is 138/82 mmHg, and he is not orthostatic. He currently receives a low-dose ACE inhibitor and 12.5 mg/day hydrochlorothiazide.

Which ONE of the following is the most appropriate management for this patient to ensure maximal cardiovascular and renal risk reduction?

A. Stop his ACE inhibitor and substitute an ARB because he has Type 2 diabetes.
B. Increase his medication because his systolic BP is not at goal.
C. Increase his BP because neither his systolic nor diastolic BP is at goal.
D. Add another agent because his goal BP is $<$125/75 mmHg.
E. He is at goal, therefore, the dose of ACE inhibitor should be increased to 80 mg/day to normalize microalbuminuria.

The correct answer is B. If the patient is euvolemic, his medication should be increased because he is not at the desired BP goal of $<$130/85 mmHg.

Reference

Chobanian AV, Bakris GL, Black HR, et al. (2003) The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High BP. The JNC-7 Report. JAMA 289:2560–2571

CASE 15

A 19-year old male presents for a second opinion regarding his kidney disease. He has had a long history of poorly controlled hypertension and suffered a stroke with a small residual defect about one year ago.

Which ONE of the following is the best predictor of cardiovascular morbidity and progression of renal disease?

A. Mean arterial pressure
B. Diastolic pressure
C. Pulse pressure
D. Systolic pressure
E. Systolic and diastolic pressures are equally important.

The correct answer is D. Based on current recommendations, systolic BP is the best predictor of renal disease progression.

Reference

Klag MJ, Whelton PK, Randall BL, et al. (1996) BP and end-stage renal disease in man. N Engl J Med 334:13–18

CASE 16

A 17-year old girl presents for a second opinion regarding her BP control and medicine regimen. She was told that she has renal insufficiency, but she feels fine. Her physical examination is unremarkable, and she currently receives an ACE inhibitor, thiazide diuretic, and non-dihdropyridine calcium antagonist for her BP control. Her sitting BP is 146/84 mmHg, with an abnormal pulse of 78. Laboratory tests demonstrate serum potassium of 3.5 mEq/l, and serum creatinine of 1.4 mg/dl. A 24-hour urine contains 108 mEq of sodium (adequate urine collection).

Which ONE of the following antihypertensive medications would help reduce mortality by inhibiting fibrosis of the heart and helping achieve her BP goal.

A. An ARB
B. A long-acting β-blocker
C. An aldosterone receptor antagonist
D. Hydralazine
E. Clonidine

The correct answer is C. In this patient, low potassium is a clear contributor to persistent hypertension. Potassium channels lend to close when hypokalemia is present,

causing vasoconstriction that leads to a sustained elevation in BP. This patient needs potassium supplementation, either in the form of potassium tablets or an ARB.

Reference

Tobian L (1997) Dietary sodium chloride and potassium have effects on the pathophysiology of hypertension in humans and animals. Am J Clin Nutr 65:606S–611S

CASE 17

A 12-year old girl presents with a BP of 194/116 mmHg. Her baseline laboratory values include BMI of 23 kg/m2, HbAIc of 5%, microalbuminuria of 320 mg/ g creatinine, serum creatinine of 1.0 mg/dl, BUN of 33 mg/dl, bicarbonate of 24 mEq/L, and potassium of 3.8 mEq/L. Urinalysis is otherwise normal. Echocardiogram (EKG) shows left ventricular hypertrophy with no evidence for the coarctation of the aorta. She is receiving an ACE inhibitor, a CCB, and thiazide diuretic for BP management.

Which ONE of the following would be appropriate as a next step in her evaluation?

A. Perform an ultrasound to assess kidney size
B. Check a 24-hour urinary aldosterone level
C. Restrict her sodium intake and add a loop diuretic
D. Perform magnetic resonance angiography (MRA) to assess renal arteries.
E. Add clonidine

The correct answer is D. This patient has severe hypertension. The clinical and laboratory findings suggest renal vascular hypertension. The best choice for a study would be an MRA.

Reference

Schoenberg SO, Knopp MV, Londy F, et al. (2002) Morphologic and functional magnetic resonance imaging of renal artery stenosis: a multireader tricenter study. J Am Soc Nephrol 13:158–169

CASE 18

A nine-year old girl presents to the emergency room with acute onset of severe headache and a BP of 180/85 mmHg. She is given 10 mg of sublingual nifedipine twice over one hour, with a reduction in pressure to 150/80 mmHg. At this time, her only complaint is that she feels tired. Her physical examination is unremarkable other than a round face and short stature. An echocardiogram is normal.

Additional evaluation includes a renal ultrasound, urinalysis, BUN and creatinine, plasma cortisol, and a 24-hour urine for metanephrines and cathecolamines—all of which are within the normal range. Serum sodium is 142 mEq/L, potassium 3.1 mEq/L, chloride 92 mEq/L, and bicarbonate 29 mEq/L. A random urine chloride is 89 mEq/L. She is placed on 20 mg/day of enalepril, 25 mg/day of hydrochlorothiazide, 10 mg/day of amlodipine, and 60 mEq of potassium daily. One month later, she presents with chest pain and a BP of 175/83 mmHg.

Which ONE of the following laboratory tests would provide the greatest likelihood of making a correct diagnosis?

A. Renal angiogram
B. Peripheral plasma renin-to-aldosterone ratio
C. Dexamethasone suppression test
D. 24-hour urinary aldosterone
E. Thyroid function studies

The correct answer is D. This patient has systolic hypertension associated with hypokalemic metabolic alkalosis with normal renal function. Given the patient's history and existing laboratory studies, the most likely diagnosis is either primary hyperaldosteronis or pseudo-hyperaldosteronism (Liddel syndrome). The most sensitive and specific test to rule out primary aldosteronism is a 24-hour urinary aldosterone level. Other tests, such as plasma renin or aldosterone, have many problems and their value in this setting has not been validated.

Reference

Young WF, Jr (2002) Primary aldosteronism: management issues. Ann NY Acad Sci 970:61–76

CASE 19

Which ONE of the following choices most accurately describes the role that ambulatory BP monitoring (ABPM) would play in a patient with white coat hypertension (select all that apply)?

A. Average BP readings $<140/90$ mmHg would confirm the presence of *office* or *white coat* hypertension.
B. Failure to lower nocturnal BP would signify higher risk of left ventricular hypertrophy.
C. The difference between day and night BP measurements would guide the choice of antihypertensive therapy.
D. Home BP reading can accurately predict *white coat* hypertension.
E. Persistent elevations in night-time readings of BP require the exclusion of sleep apnea as a cause for hypertension.

The correct answers are B and E. Sleep apnea interferes with the nocturnal fall in BP. Lack of nocturnal fall in BP predicts risk of left ventricular hypertrophy. ABPM BP readings are lower than those obtained under office conditions, and normal levels are below 135/85 mmHg, not 140/90 mmHg. The use of ABPM defines *white coat hypertension* rather than home BPs, and the specific range of day-night variability does not guide specific drug therapy.

References

Bur A, Herkner H, Vlcek M, et al. (2002) Classification of BP levels by ambulatory BP in hypertension. Hypertension 40:817–822

Logan AC, Perlikowski SM, Mente A (2001) Prevalence of unrecognized sleep apnea in drug-resistant hypertension. J Hypertension 19:2271–1177

CASE 20

A six-year old girl has been hospitalized twice in the last six months with symptoms of congestive heart failure. An MR angiogram showed complete occlusions of the right renal artery and high grade stenosis (>90% narrowing of the left renal artery). Current medications include ramipril 5 mg daily and furosemide 40 mg daily. Physical examination shows BP 155/80 mmHg, pulse 64 beats/min, lungs with occasional rhonchi, third heart sound appreciated, and a 2+ peripheral edema noted. Laboratory studies show hemoglobin 12 g/dl, serum creatinine 1.0 mg/dl, Na 139 mEq/l, K 3.9 mEq/l, and normal urinalysis.

Which ONE of the following recommendations would be most appropriate for this patient's care?

A. Stenting of the left renal artery
B. Laparoscopic nephrectomy of the right kidney
C. Withdrawal of angiotensin-converting enzyme inhibitor
D. Improve BP to <120/80 mmHg before any surgical procedure
E. Bilateral nephrectomy followed by renal replacement therapy

The correct answer is A. Stenting of the left renal artery reflects the benefit of renal revascularization when renal stenosis affects the entire functioning mass for patients with recurrent congestive heart failure. ACE inhibitors have established survival benefits and should be continued, not stopped. Unilateral nephrectomy of the occluded kidney might lower BP levels, but low BPs are counterproductive and may worsen fluid retention when the remaining kidney has high-grade vascular disease.

Reference

Gray BH, Olin JW, Childs MB (2002) Clinical benefit of renal artery angioplasty with stenting for the control of recurrent and refractory congestive heart failure. Vas Med 7:275–279

CASE 21

A seven-year old African-American girl is admitted to the hospital with confusion and BP readings of 185/112 mmHg. She has had no previous medical conditions. There is no history of trauma or drug use. Medications include enalepril (20 mg/day) and hydrochlorothiazide (25 mg/day). Upon examination, she is arousable but unable to converse. No focal neurologic deficits were noted. BP is 185/120 mmHg, pulse is 100 beats/min, and BMI is 18 kg/m^2. Lungs have coarse rhonchi, and trace peripheral edema is noted. Laboratory studies show serum creatinine 1.6 mg/dl, Na 130 mEq/l, K 4.8 mEq/l, and urinalysis showed 2+ proteinuria.

Which ONE of the choices offers the most appropriate therapeutic goal for this patient?

A. Controlled BP reduction to below 130/80 mmHg
B. Pulse rate reduction to less than 60 beats/min
C. Controlled BP reduction to 150/90 mmHg
D. Combined ACE-inhibition with angiotensin-receptor blockade
E. Combined ACE inhibition with non-dihydropyridine calcium antagonist therapy to lower proteinuria and BP to <120/80 mmHg

The correct answer is C. This patient has clear signs and symptoms related to her hypertension along with renal insufficiency. Given her history, it would be unwise to lower her BP to levels well below 140/90 mmHg because that might precipitate further cerebral ischemia. There is no evidence of an aneurysm, thus, reduction of pulse is unnecessary. Lowering BP to just above 140/90 mmHg is generally believed (in the acute stages of neurological symptoms related to hypertension) to provide alleviation of symptoms while not furthering ischemia. Combination therapies focus on changes in proteinuria and progression of kidney disease, and thus do not directly deal with the acute management of this patient.

Reference

Leonardi-Bee J, Bath PM, Phillips SJ et al. (2002) BP and clinical outcomes in the International Stroke Trial. Stroke 33:1315–1320

CASE 22

A nine-year old female has renal failure from glomerulonephritis and receives a kidney transplant from a living related donor. She is treated with cyclosporine, mycophenolate mofetile, and prednisone. One year after the transplant, her serum creatinine is 1.3 mg/dl. Her BP had been well-controlled before the transplant, and now requires additional BP medication to maintain her systolic BP at levels between 134 and 138 mmHg.

Which ONE of the following statements is TRUE about this patient's cardiovascular risk?

A. Her cardiovascular risk is increased because she requires more antihypertensive medication to control her BP.
B. Her cardiovascular risk is increased because she takes calcineurin inhibitors, which are independent cardiovascular risk factors.
C. Her cardiovascular risk is decreased relative to people whose grafts fail.
D. Her cardiovascular risk is decreased relative to the general population.

The correct answer is C. Cardiovascular risk is lower for individuals with functioning renal allograft, as compared to those that fail. Cardiovascular risk is not as low as the general population, making D incorrect. A is incorrect because the specific antihypertensive requirements do not predict cardiovascular risk, nor does the use of calcineurin inhibitors per se.

Reference

Dimeny EM (2002) Cardiovascular disease after renal transplantation. Kidney Int 61:S78–S84

CASE 23

A 16-year old African American female with a body mass index of 35 kg/m^2 and BP of 138/86 mmHg is referred to you for albuminuria—370 mg/g creatinine (normal <30 mg/g). For the past two years, she has been receiving metoprotol 50 mg/day, and before that she had never been told she was hypertensive. On this visit, you note all laboratory tests are normal except for her fasting glucose of 124 mg/dl. Her current BP is 152/92 mmHg, and her pulse is 68 beats/min and regular.

Which ONE of the following choices provides for the patient's BEST management?

A. Tell her to lose weight and put her on a 1200 calorie/day American Diabetic Association diet.
B. Stop the β-blocker and begin an ACE inhibitor/diuretic combination and titrate to BP goal.
C. Increase metoprolol and titrate to BP goal.
D. Add an ACE inhibitor to her current regimen.
E. Recommend an exercise for weight loss.

The correct answer is B. Clearly, this patient is obese and has impaired glucose tolerance. Moreover, she has hypertension and is being treated with a drug at a very low dose—given her body size—that worsens glucose tolerance. Getting her to lose weight will take a long time, and even if successful will increase her *total BP load*

over time. Increasing the dose of metoprolol will increase the likelihood of diabetes and worsen her morbidity. Adding an ACE inhibitor to an under-dosed beta blocker such as metoprolol does not alleviate the risk for diabetes development and, while it may improve BP, it will not have the same effect as a drug combination that is well-documented in having additional BP- lowering effects in such patients.

Reference

Bakris GL, Gaxiola E, Messerli FH (2003) Clinical outcomes in the diabetes cohort of the INVEST. Hypertension 44:637

CASE 24

Which ONE of the following statements is TRUE regarding BP reduction in hypertensive patients with normal renal function who are consuming a high-potassium, low-sodium (60 mEq/day) diet—the Dietary Approaches to Stop Hypertension (DASH) diet?

A. They will decrease their systolic BP by >20 mmHg within a few months.
B. They will decrease their systolic BP by 12 to 14 mmHg within a few months.
C. The diet has little effect on systolic BP but decreases diastolic BP by >10 mmHg within a few months.
D. The diet is not well-tolerated and thus no significant BP response is noted.
E. This diet increases the need for diuretics because of the high potassium load.

The correct answer is B. A review of the DASH diet studies indicates that the greatest benefit was seen among African-American women who were hypertensive, and the least significant effect on BP reduction in normotensive Caucasian women. The DASH diet lowers BP but not weight or glucose control.

Reference

Sacks FM, Svetkey LP, Vollmer WM, et al. (2001) Effects on BP of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. DASH-sodium Collaborative Research Group. N Engl J Med 344:3–10

CASE 25

A 17-year old male with Type 2 diabetes has a BP of 148/82 mmHg and a baseline serum creatinine of 1.2 mg/dl. He is referred to you because of an abrupt increase in serum creatinine to 2.8 mg/dl after starting on an ACE inhibitor for his BP management. Upon physical examination, you note that his BP is now 128/74 mmHg, his serum potassium concentration is 4.6 mEq/l, and he has no other complaints.

Which ONE of the following statements is TRUE regarding his condition?

A. He is likely to have renal artery stenosis and should be evaluated.
B. The ACE inhibitor should be stopped because it has reduced his renal function.
C. His prognosis for an adverse renal outcome is better than some whose creatinine did not increase as much and whose BP is not at goal.
D. It is clear that his kidney can not tolerate lower pressure, so that dose of the ACE inhibitor should be reduced.
E. An ARB should be substituted for the ACE inhibitor because it may not affect serum creatinine values.

The correct answer is C. Abrupt elevations in serum creatinine in patients with pre-existing renal insufficiency treated with ACE inhibitor are fairly common. This is driven, in this case, by the magnitude of BP reduction as much as it is by an ACE inhibitor itself. Stopping ACE inhibitors based on these findings would be a mistake because long-term follow-up studies extending over six years show clear benefits in people who manifest this type of renal/BP response. It is recommended that a rise of 30–35% in serum creatinine be allowed in people with starting serum creatinine values up to 3 mg/dl because they will have slower declines in kidney function. If treatment were continued and serum creatinine continued to climb irrespective to BP value, then volume depletion, not renal arterial disease, would be the most common diagnosis.

Reference

Barkis GL, Weir MR (2000) Angiotensin-converting enzyme inhibitor-associated elevations in serum creatinine: is this a cause for concern? Arch Intern Med 160:685–693

CASE 26

A 15-year old female with an estimated GFR of 64 ml/min, microalbuminuria, body mass index of 29 kg/m^2, and a BP of 164/90 mmHg is referred to you for BP control. She is currently on low-sodium diet, which she claims to follow and you confirm this with a 24-hour urine sodium excretion of 86 mEq/day. She is currently receiving 2.5 mg/day amlodipine. Her systolic BP goal is <130 mmHg, and when amlodipine was titrated to 10 mg/day, her systolic BP remained at 152 mmHg.

Which ONE of the following treatment regimens will most likely achieve a BP goal of <130 mmHg in this patient?

A. Add a loop diuretic with twice-daily dosing.
B. Add an ACE inhibitor/thiazide diuretic combination and titrate to the maximum dose of both diuretic and ACE inhibitor.

C. Add an ACE and titrate to the maximum dose.
D. Increase dose of amlodipine to 20 mg/day.
E. Stop amlodipine and use non-dihydropyridine CCB with a diuretic.

The correct answer is B. Given the history on this patient, she will not do well with monotherapy alone. Moreover, she will need combination therapy as recommended by kidney disease outcomes quality initiative blood pressure (KDOQI-BP) guidelines and the JNC-7 because she has Stage 2 hypertension and kidney disease with microalbuminuria. Prospective studies have shown that if you have Stage 2 hypertension, combination therapy will be needed to achieve the goal.

Reference

K/DOQI clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease. Am J Kidney Dis 43:1–290

CASE 27

A 17-year old male has a BP of 172/104 mmHg, a BMI of 30 kg/m^2, normal renal function, microalbuminuria, and a family history of cardiovascular disease.

Which ONE of the following initial therapies would be BEST for this patient?

A. Start with thiazide diuretic and observe
B. Start with an ACE inhibitor or angiotensin-receptor-blocker (ARB), and titrate the dose to maximize its effect on BP and observe
C. Start with a thiazide diuretic and quickly add a β-blocker within a month
D. Start with a combination of a thiazide diuretic and either an ACE inhibitor, ARB, or β-blocker and titrate doses over the next two months.
E. Start with an ACE inhibitor/ARB combination and titrate doses over the next two months.

The correct answer is D. This patient has Stage 2 hypertension. Starting with a combination of a thiazide and an angiotensin-system blocker gives a better likelihood of achieving BP goal and reducing cardiovascular risk than starting with monotherapy.

Reference

Bakris GL, Weir MR (2003) Achieving goal BP in patients with Type 2 diabetes: conventional versus fixed-dose combination approaches. J Clin Hypertens 5:202–209

CASE 28

In a hypertensive patient with stroke, which ONE of the following therapeutic approaches would be BEST?

A. Reduce BP to <140/90 mmHg during the first 24 hours to reduce risk of stroke extension.
B. Reduce BP to <140/90 mmHg during the first 48 hour to prevent myocardial event.
C. Reduce BP to 150/90 mmHg gradually over the first 48 hours and achieve goal BP after the first week.
D. There are no special guidelines because no data are available.
E. You should never reduce systolic BP in such patients below 150 mmHg.

The correct answer is C. It is unclear to exactly what level BP should be reduced in stroke patients, but what is clear is that it should not be below 140/90 mmHg within at least the first 3 to 4 days of the stroke to avoid a cerebral *steal* phenomena. Reducing the BP to <140/90 mmHg may extend the stroke and prolong the morbid event.

Reference

Leonardi-Bee, Bath PM, Phillips SJ, et al. (2002) BP and clinical outcomes in the International Stroke Trial. Stroke 33:1315–1320

CASE 29

A 15-year old male indicates that his BP during the past year routinely stayed above 150/90 mmHg despite limitation of sodium intake and regular exercise. Antihypertensive therapy for the past four years consisted of thiazide diuretics with BP readings that averaged approximately 134/82 mmHg. Current medications include amiloride/hydrochlorothiazide (5/50 mg daily); ramipril (10 mg daily), and diltiazem (240 mg daily). On examination, the pertinent findings were BP 156/98 mmHg; pulse 72 beats/min; weight 81 kg and BMI 28 kg/m^2. No ankle edema noted. Serum creatinine was 1.4 mg/dl; Na 146 mEq/l; K 3.4 mEq/l, electrocardiogram showed left ventricular hypertrophy and urinalysis trace protein.

Which ONE of the following studies is most likely to clarify the reason for his resistance to therapy?

A. GFR by iothalamate clearance
B. Left ventricular mass (LVM)
C. Plasma aldosterone:renin ratio

D. Plasma catecholamines
E. Urinary albumin:creatinine ratio

The correct answer is C. The elevated serum sodium and low potassium levels reflect a high probability of mineralocorticoid effect, which would explain the recent development of resistant hypertension. Therefore, measurement of aldosterone and renin are most likely to reveal this disturbance. Measurement of GFR, LVM, cathecolamines, and microalbuminuria would not explain the electrolyte changes and are far less likely to add useful information regarding identifying the cause of treatment resistance, making A, B, D, and E incorrect.

Reference

Mulatero P, Stowasser M, Loh KC (2004) Increased diagnosis of primary aldosteronism, including surgically correctable form, in centers from five continents. J Clin Endocrinol Metab 89:1045–1050

CASE 30

Smoking increases arterial BP and accelerates vascular injury by which ONE of the following mechanisms?

A. Promoting endothelial dysfunction
B. Retention of sodium
C. Increased aldosterone production
D. Activation of the adducing gene
E. Three-fold increase in plasma catecholamines

The correct answer is A. Tobacco smoking is a potent promoter of endothelial dysfunction and activates vasoconstriction by inhibition of endothelium-dependent vasodilatation.

Reference

Ritz E, Benck U, Franek E, et al. (1998) Effects of smoking on renal hemodynamics in healthy volunteers and in patients with glomerular disease. J Am Soc Nephrol 9:1798–1804

Chapter 6
Acute Renal Failure

CASE 1

An 18-year old man receiving treatment for HIV infection presents with severe myalgias. His serum creatinine is 2.1 mg/dl, with a creatinine phosphokinase of 7,400 U/L. His urinalysis is strongly positive for blood on dipstick, but he has only two to four red blood cells per high-power field.

Which ONE of the following medications is MOST likely to be associated with his acute renal failure (ARF)?

A. Acyclovir
B. Adefovir
C. Cidofovir
D. Foscarnet
E. Zidovudine

The correct answer is E. Rhabdomyolysis is seen with increased frequency in association with HIV infection. Several factors contribute to this, including a high rate of alcohol and substance abuse in this population, muscle involvement, and direct drug toxicity. Although myopathy is a common complication of HIV infection, it usually does not produce severe enough muscle injury to cause myoglobinuric ARF. The antiretroviral drug, zidovudine, has been associated with severe myopathy and rhabdomyolysis as a result of mitochondrial DNA depletion in myocytes. None of the other listed agents are associated with rhabdomyolysis.

Reference

Perazella MA (2000) Acute renal failure in HIV-infected patients: A brief review of common causes. Am J Med Sci 319:385–391

F. Assadi, *Clinical Decisions in Pediatric Nephrology.*

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CASE 2

Which ONE of the following statements regarding treatment with loop-acting diuretics in acute renal failure (ARF) is true?

A. Increased urine output decreases the need for dialysis.
B. Diuretic therapy decreases mortality.
C. Diuretic therapy decreases the duration of renal failure.
D. Diuretic therapy may be associated with severe hypokalemia.
E. The benefit of diuretic therapy is augmented by simultaneous administration of dopamine.

The correct answer is D. Loop diuretics are frequently used in the management of patients with ARF. Because nonoliguric ARF has a better prognosis than oliguric ARF, it has been suggested that *converting* a patient from an oliguric to nonoliguric state improves outcomes. Increasing urine flow may *wash out* obstructing intraluminal cellular debris and casts, thereby reversing one of the mechanisms of renal dysfunction. In addition, by decreasing active transport in the thick ascending Loop of Henle, loop diuretics may decrease energy requirements and protect cells in a region of compromised perfusion. Clinical studies, however, have not supported these arguments. In randomized controlled trials, diuretic therapy was not associated with any improvement in mortality, decrease in the duration of ARF, or alteration in the need for dialysis therapy. There is no evidence of augmentation of benefit with concomitant administration of dopamine. Diuretic therapy may, however, result in kaliuresis and hypokalemia.

References

Kellum JA (1998) Use of diuretics in the acute care setting. Kidney Int 66:S67–S70
Brown CB, Ogg CS, Cameron JS (1981) High dose furosemide in acute renal failure: A controlled trial. Clin Nephrol 15:90–96

CASE 3

A seven-year old boy develops multisystem organ failure with ARF in the setting of Klebsiella pneumonia and sepsis. His BP is 87/50 mmHg, with a heart rate of 96 beats/min with 6 μg/kg/min continuous infusion of dopamine. He is mechanically ventilated and has a PO_2 of 74 torr while receiving 60% inspired oxygen. His pulmonary capillary occlusion pressure is 22 mmHg. His urine output is <5ml/h. Laboratory data include a creatinine of 4.3 mg/dl, BUN of 92 mg/dl, potassium of 5.3 mEq/L, and a bicarbonate of 19 mEq/L. You decide to begin renal replacement therapy (RRT).

Which ONE of the following statements comparing modalities of RRT is correct?

A. Continuous arteriovenous hemodiafiltration (CAVHDF) is associated with improved survival compared with intermittent hemodialysis.
B. Continuous venovenous hemodialysis (CVVHD) provides better solute control than continuous venovenous hemofiltration (AVVH).
C. Sustained low-efficiency dialysis (SLED) and extended daily dialysis (EDD) are associated with improved survival compared with intermittent hemodialysis.
D. CVVH is associated with improved survival as compared with peritoneal dialysis.
E. Sustained SLED and EDD are associated with improved survival as compared with continuous CVVH.

The correct answer is D. In a recent study in patients with infection-associated ARF, the mortality rate in patients treated with peritoneal dialysis was 47% as compared to a mortality rate of 15% in patients treated with CVVH. In studies comparing chronic RRT (CRRT) to intermittent hemodialysis, no consistent survival benefit has been observed for CRRT. In the largest randomized controlled trial, CRRT was associated with a higher mortality, although the study was flawed by unbalance randomization that resulted in a higher acuity of illness in the CRRT group. There are no data to compare outcomes of SLED or EDD to outcomes with intermittent hemodialysis, or any from of CRRT. Although the mechanism of solute removal differs between CVVH (predominantly convective clearance) and CVVHD (predominantly diffusive clearance), similar degrees of solute control for urea and other low molecular weight solutes can be achieved with either modality.

References

Kellum JA, Angus DC, Johnson JP, et al. (2002) Continuous venous intermittent renal replacement therapy: a meta-analysis. Intensive Care Med 28:29–37

Mehta R, McDonald B, Gabbai F, et al. (2001) A randomized clinic trail of continuous versus intermittent dialysis for acute renal failure. Kidney Int 60:1151–1163

Phu NH, Hien TT, Mai NTH, et al. (2002) Hemofiltration and peritoneal dialysis in infection-associated acute renal failure in Vietnam. N Engl J Med 347:895–902

CASE 4

A six-year old boy develops multisystem organ failure and ARF after a motor vehicle accident in which he sustains severe trauma. His BP is 80/47 mmHg with 0.07 μg/kg per min of norepinephrine. He is intubated and mechanically ventilated and has an oxygen saturation of 98% in a FIO2 of 0.40. His urine output is 15 ml/h. Laboratory studies demonstrate a serum creatinine of 2.9 mg/dl, BUN of 49 mg/dl,

potassium of 4.8 mEq/L, and bicarbonate of 22 mEq/L. The critical care attending physician asks if you should initiate RRT.

Which ONE of the following statements regarding the timing of RRT initiation is correct?

A. In a randomized controlled trial, early RRT initiation (BUN,60 mg/dl) was associated with a 25% reduction in mortality.
B. In a randomized controlled trial of early versus late initiation of RRT, early RRT initiation resulted in no change in mortality.
C. In a retrospective analysis of patients with ARF, early initiation of RRT did not change mortality.
D. In a retrospective analysis of patients with ARF, early initiation of RRT reduced mortality by 25%.
E. In a retrospective analysis of patients with ARF, early initiation of RRT reduced mortality by 50%.

The correct answer is E. There is very limited data regarding the timing of renal therapy initiation in ARF. In a single retrospective analysis, the survival in patients initiated on RRT with a BUN < 60 mg/dl was 39% as compared to a survival of only 20% in patients in whom RRT was not initiated until BUN was > 60 mg/dl. No randomized controlled trials have been conducted to evaluate this question.

Reference

Kaarsou SA, Jaber BL, Pereira GJG (2000) Impact of intermittent hemodialysis variables on clinical outcomes in acute renal failure. Am J Kidney Dis 35:980–991

CASE 5

Which ONE of the following statements regarding the use of low-dose dopamine (< 2 μg/kg/min) in the treatment of ischemic acute tubular necrosis (ATN) is correct?

A. Decreases the mortality in ATN
B. Decreases the percentage of patients who are oliguric
C. Decreases the likelihood of needing RRT
D. Decreases the duration of ATN
E. None of the above

The correct answer is E. When infused at low doses (0.5 to 2 μg/kg/min), dopamine increases plasma flow, glomerular filtration rate, and renal sodium excretion through activation of dopaminergic receptors. At higher doses, dopamine binds to adrenergic receptors, resulting in vasoconstriction and inotropic effects. Infusions

of low-dose dopamine have been used, and still are widely used, to increase urine output and to prevent or treat ATN among oliguric, critically ill patients. The ability of dopamine to achieve these goals is largely anecdotal, however, and has not been supported in rigorous clinical trials. In both a large, randomized trial of low-dose dopamine in critically ill patients with early evidence of ATN, and in a meta-analysis of 17 earlier studies, low-dose dopamine was not associated with any benefit with regard to development of oliguria, duration of ATN, need for RRT, or mortality.

References

Kellum JA, Decker JM (2001) Use of dopamine in acute renal failure: A meta-analysis. Cri Care Med 29:1526–1531

Australian and New Zealand Intensive Care Society Clinical Trials Group (2000) Low-dose dopamine in patients with early renal dysfunction: a placebo-controlled randomized trial. Lancet 356:2139–2143

CASE 6

Which ONE of the following agents increases the mortality rate when used in the treatment of ARF?

A. Arterial natriuretic peptide
B. Dopamine
C. Insulin-like growth factor-I
D. N-acetylcysteine
E. Thyroxin

The correct answer is E. Thyroxin has been shown to shorten the course of ARF in experimental models of ischemic and nephrotoxic renal injury. In a clinical trial, however, administration of thyroxin in critically ill patients with ARF had no effect on the clinical course of ARF. Mortality rates, however, were significantly higher in the patients treated with thyroxin than in patients receiving placebo with mortality correlating with the degree of suppression of TSH. Although none of the other agents have been demonstrated to be efficacious in improving the outcome of patients with incipient or established ARF, they have not been associated with increased mortality.

Reference

Acker CG, Singh AR, Flick RP, et al. (2000) A trial of thyroxin in acute renal failure. Kidney Int 57:293–298

CASE 8

A 19-year old woman with HIV infection, treated with active anti-retroviral therapy (HAART), presents with nausea, vomiting, and abdominal and flank pain. Her serum creatinine is 2.8 mg/dl (baseline value was 0.7 mg/dl two weeks previously). Urine microscopy is remarkable for rectangular plate-like and needle-shaped crystals.

Which ONE of the following medications is most likely to have caused her ARF?

A. Adfovir
B. Indinavir
C. Nevriapine
D. Ritonavir
E. Zidovudine

The correct answer is B. This patient presents with crystal-related ARF with indinavir. Indinavir sulfate forms needle-shaped crystals that may aggregate to form rectangular plates or rosettes. The actual renal failure may develop as a result of intratubular deposition with tubulointerstitial nephritis or with nephrolithiais. None of the other drugs listed are associated with crystal-induced ARF.

References

Perazella MA, Kashgarian M, Cooney E (1998) Indinavir nephropathy in an AIDS patient with renal insufficiency and pyuria. Clin Nephrol 50:194–196

Gagnon RF, Tsoukas CM, Walters AK (1998) Light microscopy of indinavir urinary crystals. Ann Intern Med 128:321

CASE 9

A 16-year old boy with a history of intravenous drug abuse is admitted with a two-week history of fever and malaise. Blood cultures on admission are positive for coagulase-negative staphylococcus, and an echocardiogram demonstrates vegetation on his aortic valve. His serum creatinine is 1.1 mg/dl. He is started on antibiotic therapy with vancomycin and gentamycin, his blood cultures resolve, and he is discharged to home to complete a four-week course of intravenous antibiotics. He is readmitted two weeks later with recurrent fevers, having been noncompliant with his outpatient antibiotic regimen. Blood cultures are again positive for coagulase-negative staphylococcus. His serum creatinine is now 2.4 mg/dl. Urinalysis reveals hematuria with some dysmorphic red blood cells but without any casts noted. Serum complement levels are slightly reduced below the lower limits of normal.

Which ONE of the following choices provides the MOST appropriate management for his ARF?

A. Continue current antibiotic therapy
B. Discontinue aminoglycoside antibiotic
C. Discontinue vancomycin
D. Begin a tapering dose of oral prednisone
E. Begin intravenous methylprednisolone

The correct answer is A. This patient presents with a syndrome most consistent with endocarditis-associated glomerulonephritis. Although red blood cell cats were not seen on urinalysis, there is hematuria with dysmorphic red blood cells suggesting glomerular bleeding. The low serum complement levels are suggestive of an immune complex disease. The treatment of endocarditis-associated glomerulonephritis is treatment of the underlying infection. The use of combination therapy with vancomycin and gentamicin to achieve more rapid sterilization of blood cultures is appropriate. Steroid therapy is not indicated, especially in the setting of active infection.

Reference

Majumdar A, Chowdhary S, Ferreira MA, et al. (2000) Renal pathological findings in infective endocarditis. Nephrol Dial Transpl 15:1782–1787

CASE 10

Which ONE of the following interventions has been proven to decrease the risk of severe (dialysis-requiring) ARF after radiocontrast administration?

A. Dopamine
B. Fenoldopam
C. Mannitol
D. N-acetylcysteine
E. None of the above

The correct answer is E. None of the agents listed have been associated with a decreased risk of severe radio contrast nephropathy (RCN). Clinical trails have not uniformly demonstrated benefit—and have suggested possible harm—rom the use of low-dose dopamine to prevent RCN. Fenoldopam, a selective dopamine-receptor agonist, has been suggested as a protective agent based on case-series, but this has not been confirmed in randomized clinical trials. Mannitol has also been widely used to prevent RCN—however, multiple studies have found minimal protective effect, and actually increased RCN in diabetic patients. Several randomized controlled trials of N-acetylcystein (NAC) have been published showing a fall in serum creatinine

in patients treated with NAC as compared to an increase in serum creatinine in controls. While this data has suggested a potential role for NAC in the prevention of RCN, all of these studies were underpowered and did not include any patients who developed severe renal failure.

References

Briguori C, Manganelli F, Scarpato P, et al. (2002) Acetylcystein and contrast agent-associated nephrotoxicity. J Am Coo Cardiol 40:298–303

Murphy SW, Barrett BJ, Parfrey PS (2000) Contrast nephropathy. J Am Soc Nephrol 11:177–182

CASE 11

A five-year old girl with a history of mitral valve prolapse and no history of renal disease develops streptococcus viridans endocarditis. She is placed on intravenous ampicillin and gentamicin. Two weeks into her course of therapy, she develops worsening shortness of breath and lower extremity edema. Upon examination, she has an erythematous maculopapular rash across her legs and lower abdomen. Laboratory studies demonstrate a serum creatinine of 1.6 mg/dl. The leukocyte count is 9800/mm^3, with 4% eosinophils. Urinalysis demonstrates microscopic hematuria and pyuria. The urine stain for eosinophils is negative.

Which ONE of the following treatment options would be most appropriate in this patient?

A. Discontinue gentamicin, continue ampicillin
B. Discontinue gentamicin and ampicillin, begin vancomycin
C. Discontinue gentamicin and ampicillin, begin vancomycin and oral prednisone
D. Continue current antibiotics without change
E. Continue current antibiotics and begin intravenous methylprednisolone

The correct answer is B. The most likely diagnosis for this patient's ARF is allergic interstitial nephritis (AIN), with ampicillin being the most likely offending agent. The characteristic features of AIN that are present include the erythematous maculopapular rash, microscopic hematuria, and pyuria. Although eosinophilia is frequently associated with AIN, and her percentage of eosinophil is slightly elevated, her absolute eosinophil count is not elevated (<400/mm^3). Although eosinophilia has been suggested as a key diagnostic feature in AIN, its true diagnostic value is that it is present in only 2/3 of patients with AIN. Aminoglycoside nephrotoxicity is a less likely diagnosis; it is not associated with cutaneous manifestations, and would be expected to be associated with many tubular epithelial cells and granular casts in urine microscopy. The urine sediment does not suggest endocarditis-associated GN.

The primary treatment of acute interstitial nephritis (AIN) is discontinuation of the offending agent. Thus, choices A, D, and E are incorrect. There is no convincing

evidence for the treatment of AIN with steroids, and they are relatively contraindicated in the presence of acute infection. Choice C is therefore inappropriate. The optimal therapy is therefore to discontinue the ampicillin and begin an alternative antibiotic agent to treat endocarditis (choice B).

Reference

Roseert J (2001) Drug-induced interstitial nephritis. Kidney Int 60:804–817

CASE 12

A four-year old has his legs pinned under a pile of rubble in an earthquake event. He is extricated after five hours. Upon arrival in the emergency room, he is found to have a creatinine phosphokinase of 23,000 U/L and a serum creatinine of 1.9 mg/dl.

Which ONE of the following treatments would be associated with a decreased risk of ARF in this patient?

A. Intravenous isotonic saline at a rate of 2–3 ml/kg/hr before hospital arrival
B. Intravenous mannitol infusion at a rate of 2–3 ml/kg/hr
C. Intravenous dopamine infusion at a dose not to exceed 2μg/kg/min
D. Intravenous furosemide plus half-saline at 2–3 ml/kg/hr
E. Oral N-acetylcystein plus half-isotonic saline at 2–3 ml/kg/hr

The correct answer is A. Several strategies have been proposed to prevent or attenuate the development of ARF in rhabdomyolysis. The most important is aggressive volume replacement. In patients with traumatic rhabdomyolysis, fluid restriction should be initiated in the field, even before the crushed extremity is released. Urinary alkalinization has been advocated as means to increase the solubility of heme proteins within the tubule. It has also been suggested that alkalinization may decrease the cycling of myoglobin, thereby reducing the generation of reactive oxygen species. The use of mannitol has also been advocated; however, it has not been shown to have greater efficacy than volume expansion with saline alone. No benefit has been demonstrated for dopamine, furosemide, or N-acetylcystein in this setting.

Reference

Abassi ZA, Hoffman A, Better OS (1998) Acute renal failure complicating crush injury. Semin Nephrol 18:558–565

CASE 13

An 18-year old man with a history of congenital AIDS is admitted with a four-day history of progressive fatigue, weakness, confusion, myalgia, and oliguria. Medications before hospital admissions included indinavir, didanosine, stavudine, tenofovir, zidovudine, trimetoprine-sulfamethoxazole, and atoravastatin. Upon admission, his BP was 90/50 mmHg and he was in acute respiratory distress. On review of arterial blood gases, his pH was 6.93 with a $HCO3^-$ of 5 mEq/l. His BUN was 78 mg/dl, serum creatinine 7.6 mg/dl, and creatinine kinase 124 U/l. Urine microscopy revealed no crystalluria. His plasma lactate level was 5.4 mmol/L, rising to 16.7 mmol/l on the third hospital day despite therapy with continuous venovenous hemofiltration using bicarbonate buffered fluids. Blood and urine cultures, bronchoscopy, and abdominal and pelvic CT scans were all negative.

Which ONE of the following medications is the most likely cause of his ARF?

A. Indinavir
B. Tenofovir
C. Zidovudine
D. Trimethoprin-sulfamethozazole
E. Atorvastatin

The correct answer is B. Several recent case reports have described acute tubular necrosis (ATN) in association with severe lactic acidosis in patients treated with tenofovir. The other four drugs listed have also been associated with ARF; however, their patterns of renal failure are not consistent with this patient's presentation. Indinavir causes ARF through deposition of insoluble drug crystals in the kidneys or obstructive uropathy from indiavir stones. The absence of crystalluria makes indinavir toxicity unlikely. In addition, indinavir toxicity is not associated with lactic acidosis. Zidovudine has been associated with lactic acidosis; however, zidovudine-associated ARF is due to rhabdomyolysis, which can be excluded by the normal serum creatinine kinase. Atorvastatin is also associated with rhabdomyolysis and myoglobinuric ARF—not present in this patient. Trimethoprin-sulfamethoxazole may cause acute interstitial nephritis but is not associated with the severe lactic acidosis seen in this patient.

References

Peraxella MA (2000) Acute renal failure in HIV-infected patients: A brief review of common causes. AM J Med Sci 319:385–391

Schaaf B, Aries SP, Kramme E, et al. (2003) Acute renal failure associated with tenofovir treatment in a patient with acquired immunodeficiency syndrome. Clin Inf Dis 37: e41–43

CASE 14

A 16-year old male with end-stage liver disease, secondary to chronic hepatitis C infection, undergoes an orthotropic liver transplant. Preoperatively, his serum creatinine is 1.1 mg/dl and his bilirubin is 28 mg/dl. His intraoperative course is unremarkable, with a lowest recorded BP of 95/60 mmHg. On the third post-operative day he is noted to have tense ascites, and his bilirubin, which had fallen to 11 mg/dl, is 21 mg/dl. His BP is 110/72 mmHg on no vasopressors. His central venous pressure is 16 mmHg and pulmonary capillary occlusion pressure is 19 mmHg. His urine output is 130 ml over 24 hours. After irrigating his Foley catheter, his intravesical pressure is reported as 37 cm H_2O. His serum creatinine is 2.6 mg/dl. His urine sodium is less than 10 mEq/L. Urine microscopy demonstrates occasional bile-stained casts. A tacrolimus level is reported as 8 ng/dl.

Which ONE of the following options would be the MOST appropriate next step for management of his ARF?

A. Infusion of 1500 ml of normal saline
B. Infusion of 1500 ml of iso-oncotic human serum albumin
C. Initiation of terlipressin infusion
D. Abdominal decompression by paracentesis
E. Initiation of continuous venovenous hemofiltration

The correct answer is D. The abdominal compartment syndrome is characterized by increased intra-abdominal pressure resulting in decreased renal perfusion. It is most commonly seen in trauma patients who have received massive volume resuscitation, but may be seen in a variety of other settings, including tight abdominal surgical closure or as a result of scarring after burn injuries—both of which result in mechanical limitation of the abdominal wall—and in association with bowel obstruction and pancreatitis in which intra-abdominal fluid sequestration leads to increased intra-abdominal pressure. A recent report has described this syndrome after liver transplantation. The diagnosis of abdominal compartment syndrome should be considered in patients developing ARF in the setting of tense distention of the abdomen. The diagnosis is commonly made by measurement of intravesical pressure, which correlates with intra-abdominal pressure. This diagnosis can be excluded when the intravesical pressure is <10 mm Hg (<14 cm H2O), and is virtually always present if the pressure is greater than 25 mmHg (34 cm H2O), as in this case. The treatment consists of abdominal decompression, which may be achieved acutely by paracentesis, although the majority of patients ultimately require surgical decompression. Renal function usually recovers promptly following normalization of intra-abdominal pressure. Volume resuscitation with either crystalloid or colloid is not indicated because volume-responsive prerenal azotemia is unlikely given the elevated central venous and pulmonary artery pressures. Terlipressin has been suggested as potentially beneficial for the treatment of hepatorenal syndrome (HRS). Although this diagnosis is also associated with a low urine sodium

concentration, a diagnosis of HRS must be deferred until all other etiologies of ARF are excluded. This patient has no clinical parameters suggesting an urgent need for renal replacement therapy. Because his renal function may recover following abdominal decompression, initiation of continuous renal replacement therapy is not appropriate.

References

Baily J, Shapiro MJ (2000) Abdominal compartment syndrome. Crit Care 4:23–29
Biancofiore G, Bindi ML, Romanelli AM, et al. (2003) Intra-abdominal pressure monitoring in liver transplant recipients: a prospective study. Intensive Care Med 29:30–36

CASE 15

A 10-year old male is admitted to the hospital with nausea, vomiting, and confusion. On examination, he is jaundiced and volume-overloaded with pulmonary rales and peripheral edema. Laboratory data reveal a serum creatinine of 5.7 mg/dl, an alanine aminotransferase of 851 U/L, an aspirate aminotransferase level of 262 U/L, and a bilirubin of 3.8 mg/dl. His family reports that a *traditional* healer for complaints of rheumatism recently treated him.

Which ONE of the following compounds is most likely responsible for these syndromes?

A. Ephedra
B. Cyprinol
C. Aristocholic acid
D. Glycyrrhetic acid
E. Chromium picolinate

The correct answer is B. The patient presents with ichthyotoxism resulting from the ingestion of fish gallbladders or rib. The manifestations of ichthyotoxism include nephrotoxic ATN and acute hepatitis, with elevations of alanine aminoteransferase level out of proportion to the aspirate aminotransferase level. Ephedra (Ma-Huang) may cause renal failure in the setting of exercise-induced rhabdomyolysis. Aristocholic acid is the toxin associated with Chinese herb nephropathy and is associated with chronic interstitial fibrosis. Glycyrrhetic acid is a constituent of licorice root that inhibits the enzyme 11-ÿ-hydroxysteroid dehydrogenase, producing a syndrome-mimicking mineralocorticoid excess. ARF has been described as a result of hypokalemia-induced rhabdomyolysis. Chromium picolinate may be found in some over-the counter supplements used for weight loss, lipid-lowering, and glycemic control and has been associated with case reports of chronic interstitial nephritis.

Reference

Xuan BHN, Thi TX, Nguyen ST, et al. (2003) AEF after fish gallbladder ingestion: a large case series from Vietnam. Am J Kidney Dis 41:220–224

CASE 16

Which ONE of the following statements regarding the use of low-dose (≤2 mcg/kg/min) of dopamine in the treatment of ARF is correct?

A. It may cause systemic vasoconstriction
B. It decreases the duration of oliguria in ARF
C. It stimulates proximal tubular sodium reabsorption
D. It decreases the need for renal replacement therapy
E. It decreases mortality risk

The correct answer is A. Renal dose dopamine (≤2 mcg/kg/min) has been widely utilized in the management of ARF. At low doses, dopamine increases renal plasma flow (augmenting GFR in models of renal ischemia) and inhibits proximal sodium reabsorption) resulting in natriruresis and increased urine flow). Although these low doses of dopamine primarily result in activation of vasodilatory dopaminergic receptors, systemic vasoconstriction may be seen as the result of the adrenergic receptor stimulation. The low dose of dopamine does not decrease the duration of oliguria, the need for renal replacement therapy, or mortality.

Reference

Bellomo R, Chapman M, Finfer S (2000) Low-dose dopamine in patients with early renal dysfunction: a placebo-controlled randomized trial. Australian and New Zealand Intensive Care Society Clinical Trials Group. Lancet 356:2139–2143

CASE 18

A nine-year old Hispanic girl develops sepsis and acute renal failure secondary to chronic pancreatitis. She requires mechanical ventilation for respiratory failure, but does not require RRT. Her hemoglobin is noted to progressively fall from 11.5 g/dl to 8.5 g/dl on her daily laboratory evaluation.

Which ONE of the following statements regarding anemia management in this setting is correct?

A. The use of recombinant human erythropoietin in critically ill patients is associated with decreased transfusion requirements.

B. The use of recombinant human erythropoietin to keep the hemoglobin between 11 g/dl and 12 g/dl is associated with a reduction in mortality risk.
C. A strategy of red blood cell transfusion to keep the hemoglobin above 10 g/dl is associated with a reduction in mortality risk.
D. A restrictive red blood cell transfusion strategy—providing transfusion only when hemoglobin is less than 7 g/dl—is associated with increased mortality in patients with underlying cardiovascular disease.
E. None of the above

The correct answer is A. Recumbent human erythropoietin (rHuEpo) has been demonstrated to decrease transfusion requirements in critically ill patients, but has no effect on patient survival. The use of a restrictive transfusion strategy (threshold hemoglobin of 7 g/dl) is associated with lower hospital mortality rates as compared to a liberal strategy designed to maintain the hemoglobin concentration above 10 g/dl. There are no increased risks observed when the restrictive transfusion strategy is used in patients with underlying cardiovascular disease.

Reference

Corwin HL, Gettinger A, Pearl RG, et al. (2002) Efficacy of recombinant human erythropoietin in critically ill patients: a randomized controlled trial. JAMA 288:2827–2835

CASE 19

An 11-year old boy develops ARF following operative repair of a 5.6 cm bowel perforation. He is oliguric, with urine output averaging 5 ml/hour, and volume-overloaded, with a central venous pressure of 26 mmHg. His BP is 110/65 mmHg, his heart rate is 102 beats per minute, and he has a transcutaneous oxygen saturation of 88% on a fractional inspired oxygen of 0.80 on volume-cycled mechanical ventilation. His preoperative serum creatinine was 0.6 mg/dl and has increased to 2.2 mg/dl on the first post-operative day. Following intravenous administration of 80 mg of furosemide, his urine output increases to 10 ml/hr for four hours.

Which ONE of the following therapeutic interventions is most appropriate at this time?

A. Begin a continuous infusion of furosemide at 5 mg/hour.
B. Administer 500 mg intravenous chlorothiazide followed by 5 mg bumetanide.
C. Begin a continuous infusion of dopamine at 1.5 mcg/kg/min.
D. Begin a continuous infusion of dobutamine at 5 mcg/kg/min.
E. Initiate renal replacement therapy.

The correct answer is E. The case describes a patient with oliguric renal failure due to ischemic acute tubular necrosis, complicated by severe volume overload with respiratory compromise. He has not responded to a bolus infusion of high dose furosemide. The most appropriate intervention at this time would be the initiation of RRT for management of volume overload. Clinical studies do not support the use of further diuretic therapy after an initial failure to respond. There is no role for the use of low-dose dopamine in the management of oliguric ARF. Dobutamine is an inotrope with vasodilatory properties. Although potentially beneficial in the management of prerenal azotemia due to heart failure, it has no role in the management of ischemic ATN.

Reference

Mehta RL, Pascual MT, Soroko S. et al. (2002) Diuretics, mortality, and no recovery of renal function in acute renal failure. JAMA 288:2547–2553

CASE 20

Which ONE of the following is NOT a risk factor for the development of contrast nephropathy.

A. History of diabetes
B. Decompensated congestive heart failure
C. Peripheral vascular disease
D. Lisinopril
E. Celecoxib

The correct answer is D. Multiple risk factors for the development of radiocontrast nephropathy (RCN) have been identified, including renal insufficiency, diabetes mellitus, cardiovascular disease, and peripheral vascular disease. Inhibitors of cyclo-oxygenase (celecoxib) have been demonstrated to increase the risk of RCN in experimental models. Although it is commonly assumed that angiotensin-converting enzyme inhibitors also increase the risk of RCN, data suggest that this is not the case and that they may actually be protective. In a recent randomized clinical trail, captopril administration decreased the risk of RCN in high-risk patients.

References

Gupta RK, Kappor A, Tewari S, et al. (1999) Captopril for prevention of contrast-induced nephropathy in diabetic patients: a randomized study. Indian Heart J 51:521–526

Hansi K, Gunnala V, Mascarenhas M, et al. (2003) Angiotensin converting enzyme inhibitor may be protective in contrast induced nephropathy. J Am Soc Nephrol 14:282A–2283A

CASE 21

Which ONE of the statements regarding modality selection for RRT in ARF is most correct?

A. Continuous renal replacement therapy (CRRT) is associated with improved survival as compared to intermittent hemodialysis after adjusting for comorbidity and acuity of illness.
B. Intermittent hemodialysis is associated with increased recovery of renal function as compared to CRRT.
C. Sustained low-efficiency dialysis is associated with decreased mortality as compared to intermittent hemodialysis.
D. Peritoneal dialysis is associated with decreased survival as compared to CRRT.
E. There is no relationship between dose of therapy and outcome in either intermittent hemodialysis or CRRT.

The correct answer is D. In contrast to peritoneal dialysis, CRRT is associated with improved survival. After adjusting for comorbidities and acuity of illness, however, no survival benefit has been consistently observed when CRRT is compared to intermittent hemodialysis, although there is some suggestion that CRRT may be associated with a higher rate of recovery of renal function. No studies comparing outcomes with sustained low-efficiency dialysis or other forms of *slow* hemodialysis and conventional intermittent hemodialysis have been reported. There is clear data that there is a relationship between increased doses of therapy and survival in ARF.

Reference

Phu NH, Hien TT, Mai NTH, et al. (2002) Hemofiltration and peritoneal dialysis in infection-associated acute renal failure in Vietnam. N Engl J Med 347:895–902

CASE 22

Which ONE of the following strategies will provide the greatest benefit in preventing acute contrast nephropathy in a diabetic patient with a serum creatinine of 2.2 mg/dl?

A. Volume expansion with 0.9% saline (1 ml/kg/h for 4 h pr and 6 h post procedure), and pretreatment with fenoldopam.
B. Volume expansion with 0.9% saline (1 ml/kg/h for 12 h pr and 12 h post procedure), and pretreatment with N-acetylcysteine.
C. Volume expansion with 0.45% saline (1 ml/kg/h for 4 h pr and 6 h post procedure), and pretreatment with N-acetylcysteamine.
D. Volume expansion with isotonic sodium bicarbonate (1 ml/kg/h for 4 hours prior and 6 hours post-procedure).

E. Volume expansion with isotonic sodium bicarbonate (1 ml/kg/h for 4 hours prior and 6 hours post-procedure) and hemodialysis within 2 hours of completion of contrast study.

The correct answer is B. Volume expansion with saline is the mainstay of prevention of radiocontract nephropathy (RCN). The optimal rate of infusion is 1 ml/kg/h for 12 hours prior and 12 hours following radiocontrast administration. The data regarding the use of N-acetylcysteamine are conflicting. Until a well-designed large randomized controlled trial of N-acetylcystein is conducted, the use of this agent in clinical practice is considered to be appropriate.

Reference

Kshirsagar AV, Poole C, Mottl A, et al. (2004) N-acetylcysteamine for the prevention of radiocontrast induced nephropathy: A meta-analysis of prospective controlled trials. J Am Soc Nephrol 15:761–769

CASE 23

A six-year old girl is admitted with increasing ascites. Her serum creatinine on admission is 1.4 mg/dl. Following a large volume paracentesis, her urine output precipitously decreases to less than 100 ml/d, and her serum creatinine increases to 2.7 mg/dl. Ascitic fluid culture is sterile. Her urine sodium is 8 mEq/l. Following infusion of 1500 ml of 0.9% saline, she has no increase in her urine output.

Which ONE of the following medications will most likely provide the best balance between improved renal function and adverse effects?

A. Octreotide
B. Dopamine
C. Terlipressin
D. Ornipressin
E. Spironolactone

The correct answer is C. This patient has hepatorenal syndrome (HRS). The only effective pharmacologic therapy currently available for the management of HRS is the administration of vasoconstrictors. Two classes of drugs have been used—vasopressin analogues and α-adrenergic agonists—with most given in combination with intravenous albumin to further treat arterial under-filling. The best success has been observed with the vasopressin v_1-receptor agonist terlipressin. Ischemia from arterial vasoconstriction is the major complication associated with terlipressin therapy, with ischemic side effects necessitating discontinuation of therapy in 5 to 10% of patients. Ornipressin is another vasopressin v_1-receptor agonist. The incidence of ischemic complication in patients treated with ornipressin is 30-40%. Octreotide is

a somatostatin analogue that causes splanchnic vasoconstriction. It is not effective at improving renal function in HRD when used as a single agent, but has some benefit in combination with midodrine. Dopamine is not effective in the treatment of HRS. Spironolactone—an aldosterone receptor antagonist—is a highly effective diuretic in patients with advanced liver disease, but has no impact on renal function in patients with HRS.

Reference

Gines P, Guevara A, Arroyo V, et al. (2003) Hepatorenal syndrome. Lancet 362:1819–1827

CASE 24

Which ONE of the following statements regarding the use of low-dose dopamine (< 2 μg/kg/min) in the treatment of ischemic ATN is correct?

A. It reduces in-hospital mortality
B. It increases the risk of postoperative arterial fibrillation
C. It decreases the duration of dialysis-dependence
D. It precipitates hyperthyroid storm
E. It improves responsiveness to loop diuretics

The correct answer is B. Two clinical studies in cardiac surgery patients have associated low-dose dopamine therapy with increased incidence of arterial arrhythmias, presumably mediated by β-adrenergic stimulation, which is present even at putative dopaminergic doses. Low-dose dopamine has not been found to have any of the above benefits in adequate prospective, comparative studies. Dopamine has been reported to cause hypothyroidism, not hyperthyroidism.

References

Argalious M, Motta P, Khandwala F, et al. (2005) "Renal dose" dopamine is associated with the risk of new-onset arterial fibrollation after cardiac surgery. Crit Care Med 33:1327–1332
Chiolero R, Borgeat A, Fisher A (1991) Postoperative arrhythmias and risk factors after open heart surgery. Thoracic Cardiovasc Surg 39:81–84

CASE 25

A 17-year old, HIV-positive female begins a highly active antiretroviral therapy (HAART) regimen, including efavirenz, tenofpvir, and lamivudine. She takes trimetoprim-sulfamethoxazole for pneumocystis prophylaxis. Renal function and urinalysis are normal before commencing therapy. Six weeks later, she presents for follow-up with the following laboratory studies: sodium 140 mEq/l, potassium

4.8 mEq/l, chloride 115 mEq/l, bicarbonate 15 mEq/l, BUN 60 mg/dl, and phosphorous 1.9 mg/dl. Urinalysis shows specific gravity 1.015, pH 5, trace protein, 2+ glucose, otherwise negative dipstick, microscopy with few muddy brown granular casts and renal tubular cells per high power field, and no other cells, casts, or crystals.

Which ONE of the following is the MOST likely cause of acute kidney failure in this patient?

A. Efavirenz nephrotoxicity
B. HIV nephropathy
C. Allergic interstitial nephritis caused by trimethoprim-sulphamethoxazole
D. Lamivudine toxicity (mitochondrial toxicity)
E. Tenofovir nephrotoxicity

The correct answer is E. The combination of Fanconi syndrome and acute kidney injury with acute tubular necrosis is most suggestive of tenofovir toxicity in this patient. Collapsing HIV nephropathy with rapid progression is unlikely in the absence of significant proteinuria. The diagnosis of acute kidney injury caused by the mitochondrial toxicity of the nucleoside reverse transcriptase inhibitor is not supported by the normal anion gap and the absence of myoglobinuria (heme-negative urine dipstick). Urine microscopy is not suggestive of allergic interstitial nephritis. Efavirens is a nonnucleoside reverse transcriptase inhibitor without reported nephrotoxicity.

Reference

Daugas E, Rougier JP, Hill G (2005) HAART-related nephropathies in HIV-infected patients. Kidney Int 67:393–403

CASE 26

A 12-month old boy sustains a cerebral hemorrhage with subsequent hydrocephalus requiring ventriculostomy after catheter-directed thrombosis of a sinus thrombosis. He is maintained on mechanical ventilation. Atracuronium is administered for neuromuscular blockade, and protocol and fentanyld are administered for sedation and pain control. Hypertonic saline and mannitol are administered to reduce cerebral edema. A phenylephrine infusion is initiated to increase the mean arterial BP to maintain adequate cerebral perfusion pressure. His baseline serum creatinine was 0.3 mg/dl, rising to 1.2 mg/dl on Hospital Day 3 and 2.5 mg/dl on Hospital Day 5. On Day 5, his creatinine phosphokinase is 8,750 U/l. His troponin is 20 ng/ml, and electrocardiogram shows a right bundle branch block with diffuse ST and T-wave changes.

Which of the following medications was MOST likely to be responsible for his ARF?

A. Atracuronium
B. Fentanyle
C. Mannitol
D. Phenylephrine
E. Propofol

The correct answer is E. The patient described in this case has the manifestations of the propofol infusion syndrome, characterized by cardiac dysfunction, metabolic acidosis, and rhabdomyolysis with acute kidney injury. Risk factors for this complication of sedation include prolonged therapy with high doses of propofol, and concomitant administration of catecholamines and/or corticosteroids in the setting of acute neurologic injury or acute inflammatory disease complicated by severe infection or sepsis. None of the other listed drugs are associated with this presentation.

Reference

Casserly B, O'Mahony E, Timm EG, et al. (2004) Propofol infusion syndrome: an unusual cause of renal failure. Am J Kidney Dis 44:e98–101

CASE 27

A 15-year old boy with a history of hypertension, Type 2 diabetes mellitus, known cardiovascular disease, and chronic kidney disease, with a serum creatinine of 2.5 mg/dl, on chronic therapy with metoprolol, lisinopril, furosemide, and insulin undergoes a cardiac angiogram procedure.

Which ONE of the following is NOT a risk factor for the development RCN?

A. Stage of chronic kidney disease
B. Angiotensin-converting enzyme inhibitor use
C. History of diabetes mellitus
D. Use of intra-aortic balloon pump
E. Administration of >300 ml of iodinated contrast

The correct answer is B. Risk factors for the development of RCN include the presence of Stage 3, 4 or 5 (GFR <60 ml/min/1.73 m2), a history of diabetes mellitus, use of an intra-aortic ballon pump, and administration of large volumes of radiocontrast media. Angiotensin-converting enzyme inhibitor use has not been identified as a risk, and may actually convey a protective benefit.

Reference

Marenzi G, Lauri G, Assanelli E (2004) Contrast-induced nephropathy in patients undergoing primary angioplasty fooor acute myocardial infarction. J Am Coll Cardiol 44:1780–1785

CASE 28

A 10-year old boy with nephrotic syndrome on steroid therapy is brought to the ER by paramedics. The patient reports that he fell while getting out of the shower two days previous and had been unable to get up. He denies any past history of kidney disease. Upon physical examination, he has diffuse ecchymoses of his back and lower extremities, and his left hip is laterally rotated.

Which ONE of the following initial laboratory values, obtained upon presentation to the emergency room, will MOST reliably predict his risk for developing acute kidney injury and the need for RRT?

A. Serum creatinine of 1.8 mg/dl
B. Serum potassium of 5.6 mEq/l
C. Serum bicarbonate of 17 mEq/l
D. Creatine phosphokinase of 9650 U/l
E. Urine pH of 5.5

The correct answer is A. The initial serum creatinine value $\geq$ 1.7 mg/dl was found to be the most reliable predictor of the development of acute kidney injury or need for RRT in a series of 97 consecutive patients with rhabdomyolysis in an urban emergency room over a four-year period. The initial creatinine phosphokinase (CPK) levels, initial serum potassium concentration, and urine pH and specific gravity did not differentiate between patients who did and did not develop acute kidney injury.

Reference

Fernandez WG, Hung O, Bruno GR (2005) Factors predictive of acute renal failure and need for hemodialysis among emergency department patients with rhabdomyolysis. Am J Emerg Med 23:1–7

CASE 29

An eight-year old boy undergoes aortic valve replacement surgery. His past medical history includes congestive heart failure and chronic renal insufficiency (baseline creatinine 1.9 mg/dl). He receives prophylactic furosemide (3 mg/hr) and dopamine (2 μg/kg/min) intraoperatively, and maintains a urine output of >2 ml/kg/hr. On return to the intensive care unit (ICU), he has good gas exchange but labile BP,

requiring an increase in dopamine dose to 10 μg/kg/min. His pulse is 110 beats/min and regular, BP 80/60 mmHg, and central venous pressure is 4 mmHg. His physical examination is otherwise unremarkable. His urine output has decreased to 0.3 ml/kg/hr over the past three hours and his serum creatinine has increased to 2.5 mg/dl. Serum sodium is 138 mEq/l, potassium 3.2 mEq/l, chloride 110 mEq/l, bicarbonate 28 mEq/l, BUN 60 mg/dl, glucose 90 mg/dl, and hemoglobin 8 g/dl. Urinalysis is unremarkable, apart from 2+ proteinuria. Urine chemistries include a fractional excretion of sodium 3%, and a fractional excretion of urea 20%. You are consulted to initiate RRT.

Which ONE of the following therapeutic plans in MOST appropriate at this point?

A. Continue furosemide infusion, transfuse two units packed red blood cells, and wean dopamine to 2 μg/kg/min
B. Discontinue furosemide infusion
C. Initiate continuous RRT
D. Discontinue furosemide infusion, bolus with normal saline to achieve a CVP of 8 to 12 mmHg
E. Wean dopamine, start vasopressin 0.04 U/min

The correct answer is D. The most appropriate therapeutic plan in this patient is to discontinue diuretic therapy and administer saline to correct hypovolemia and prerenal azotemia. The diagnosis of furosemide-induced prerenal azotemia is supported by the hemodynamic parameters and urine chemistries on this patient. Studies have shown that prophylactic administration of furosemide, by infusion or bolus, adversely effects renal function following cardiac surgery, probably by causing prerenal azotemia. There is no indication for RRT or any of the other proposed regimens.

References

Lombardi R, Ferrerio A, Servetto C (2003) Renal function after cardiac surgery: adverse effect of furosemide. Ren. Fail 25:775–786

Lassnigg A, Donner E, Grubhofer G, et al. (2000) Lack of renoprotective effects of dopamine and furosemide during cardiac surgery. J Am Soc Nephrol 11:97–104

CASE 30

A two-year old male develops oliguric acute renal failure in the setting of multiple organ failure after a motor vehicle accident. He is mechanically ventilated and requires pressor therapy with 0.15 μg/kg/min of norepinephrine to maintain a mean arterial BP of 60 mmHg.

Which ONE of the following statements regarding RRT in this setting is evidenced-based?

A. Intermittent hemodialysis is associated with increased mortality as compared to continuous RRT.
B. Intermittent hemodialysis should be prescribed to deliver a single-pool Kt/V of 1.2 on a three times per week schedule.
C. Continuous renal replacement therapy (CRRT) should be prescribed to deliver an effluent flow rate of 25 ml/kg/hr.
D. CRRT will provide greater volume removal with less hemodynamic instability than intermittent hemodialysis.
E. Survival with sustained low-efficiency hemodialysis is comparable to survival with CRRT.

The correct answer is D. It has been shown that CRRT is able to provide greater net volume removal than intermittent hemodialysis, despite producing less hemodynamic instability. Despite this benefit, CRRT has not been demonstrated to provide a survival benefit as compared to intermittent hemodialysis (choice A is incorrect). Choice B is incorrect because the optimal dose of intermittent hemodialysis when delivered on a three times per week basis in patients with acute renal injury is not known. There have been no studies comparing outcomes with sustained low-efficiency hemodialysis to outcomes with either conventional intermittent hemodialysis or any of the continuous therapies (choice E is incorrect). Large, single-center, randomized, controlled trials have demonstrated improved survivial in continuos venovenous hemofiltration (CVVH) when prescribed to deliver ultrafiltration rates of 35 ml/kg/hr and 45 ml/kg/hr as compared to 20 ml/kg/hr. (choice C is incorrect).

References

Augustine JJ, Sandy D, Seifert TH (2004) A randomized controlled trial comparing intermittent with continuous dialysis in patients with acute renal failure. Am J Kidney Dis 44:1000–1007

Tolwani A (2005) Renal replacement therapies for acute renal failure: does dose matter? Am J Kidney Dis 45:1139–1143

CASE 31

A four-year old girl undergoes cardiac surgery for congenital heart disease with pulmonary hypertension and severe right heart failure, which is associated with chronic renal insufficiency (baseline serum creatinine 1.5 mg/dl). After four hours of cardiopulmonary bypass, it is difficult to wean her from bypass. She returns to the ICU intubated and anuric on furosemide 15 mg/hr. Her BP is 70/30 mmHg on vasopressin, dopamine, and norepinephrine infusions. She is mechanically ventilated and has oxygen saturation of 90% on an inspired oxygen of 1.0 liter with 15 cm H_20 positive end-expiratory pressure (PEEP) and inhaled nitric oxide therapy.

Central venous pressure is 35 mmHg and venous oxygen saturation is 50%. Her weight is increased 2.5 kg from postoperatively, and the sternal wound has not been closed because of massive edema. Her chest x-ray demonstrates bilateral pulmonary edema. Her serum creatinine is 2.8 mg/dl, sodium 135 mEq/l, potassium 4.5 mEq/l, chloride 100 mEq/l, bicarbonate 12 mEq/l, BUN 70 mg/dl, and glucose 80 mg/dl. Urinalysis is not available. The surgical team plans to transfuse five units of fresh frozen plasma in preparation for a return to the operating room for placement of a right ventricular assist device and sternal closure. You are asked to initiate emergent RRT.

Which ONE of the following interventions is MOST appropriate in this setting?

A. Give intravenous boluses of 100 mg furosemide with 300 mg chlorothiazide and increase furosemide infusion to 30 mg/hr
B. Start a nesiritide infusion
C. Initiate slow continuous ultrafiltration (SCUF)
D. Give a Mannitol bolus and infusion
E. Initiate continuos venovenous hemofiltration (CVVH)

The correct answer is E. Initiation of RRT with CVVH is the most appropriate therapy for this hemodynamically unstable patient with renal insufficiency, diuretic refractory oliguria, and severe volume overload. Volume overload is contributing to pulmonary dysfunction, inability to achieve sternal wound closure, and possibly even to right-sided cardiac dysfunction and shock. Even with maximal response, it is highly unlikely that diuresis can correct volume overload in a timely fashion, particularly in someone refractory to furosemide infusion of 5–15 mg/hr. SCUF will not correct metabolic acidosis, or provide therapy for evolving azotemia. Mannitol and nesiritide are of no proven benefit in this scenario, and have the potential for harm by causing pulmonary edema or hypotension, respectively. Although serum creatinine has not yet increased significantly to reflect evolving acute-on-chronic renal failure in this patient, there is a strong rationale to initiate RRT at this time. Cardiac surgery patients commonly develop oliguria, acidosis, or azotemia in the perioperative period, and many investigators claim superior outcomes with aggressive use of RRT in this setting. There are no adequate controlled trials to guide the timing of renal replacement therapy initiation in patients with acute kidney injury following cardiac surgery, which remains a matter of clinical judgment.

References

Bent P, Tan HK, Bellomo R, et al. (2001) Early and intensive continuous hemofiltration for severe renal failure after cardiac surgery. Ann Thorac Surg 71:832–837

Demirkilic U, Kuralay E, Yenicesu M, et al. (2004) Timing of replacement therapy for acute renal failure after cardiac surgery. J Card Surg 19:17–20

CASE 32

A 17-year old male with a history of liver disease secondary to hepatitis C viral infection is admitted to the hospital with increasing abdominal girth. He has a history of a prior episode of gastrointestinal bleeding from esophageal varices and has been treated with endoscopic variceal banding. He has had poor intake of food and fluids for the past three days, but denies any episodes of vomiting or hematemasis. Upon physical examination, his BP is 105/64 mmHg with a heart rate of 69 beats/min, and a temperature of 37 °C. His skin is grossly jaundiced. His neck veins are not visible when his head is elevated at 30 °. He has decreased breath sounds at the lung bases bilaterally, without rales. His abdomen is grossly distended and there is trace peripheral edema. His BUN is 26 mg/dl, serum creatinine 2.6 mg/dl, sodium 128 mEq/l, and bilirubin 8.4 mg/dl. His urine sodium concentration is <10 mEq/l. Urinalysis reveals many bile-stained epithelial cells and casts with no proteinuria. A diagnostic paracentesis reveals 110 white blood cells/ml with 45% neutrophils.

Which ONE of the following interventions is MOST appropriate at this time?

A. Administration of at least 1.5 liters of isotonic saline
B. Administration of 75 g of hyperoncotic (25%) albumin
C. Initiation of octreotide
D. Initiation of octreotide and midodrine
E. Emergent placement of a transjugular intrahepatic portosystemic shunt (TIPS)

The correct answer is A. The differential diagnosis of acute kidney injury in a patient with advanced liver disease includes prerenal azotemia, acute tubular necrosis, hepatorenal syndrome, and glomerular disease. In this patient, the primary differentiation is between prerenal azotemia and hepatorenal syndrome. Glomerular disease is unlikely given the absence of proteinuria and hematuria. Acute tubular necrosis is unlikely given the very low urine sodium concentration. Hepatorenal syndrome is differentiated from a prerenal state based on assessment of effective intravascular volume and/or the response to a volume challenge. The appropriate intervention should therefore be intravascular volume expansion as both a diagnostic and therapeutic trial. There is no evidence to support the administration of hypertonic albumin or other colloid solutions in the routine management of renal dysfunction in patients with advanced liver disease (choice B is incorrect). The combination of octreotide and midodrine is of potential benefit in patients with hepatorenal syndrome—however, this diagnosis has not yet been established in this patient (choice D is incorrect). Placement of a TIPS may be of benefit in some patients with hepatorenal syndrome, particularly if they have responded to vasoconstrictor therapy, but should not be used prior to establishment of the diagnosis, and should probably be withheld until after a trail of vasoconstrictors (choice E is incorrect).

Reference

Gines P, Guevara M, Arroyo V et al. (2003) Hepatorenal syndrome. Lancet 362:1819–1827

CASE 33

A five-year old boy with a history of congenital heart disease, congestive heart failure, and chronic kidney disease undergoes cardiopulmonary bypass surgery. He receives furosemide at 5 mg/hr and dopamine at 3 μg/kg/min perioperatively. He is uneventfully extubated postoperatively, but then develops arterial fibrillation with a rate of 140 beats/min, fails therapy with adenosine, becomes hypotensive, and is reintubated. He is now oliguric, with an irregular heart rate of 120 beats/min, BP of 60/50 mmHg, and central venous pressure of 4 mmHg. The dopamine infusion is increased to 6 μg/kg/min for treatment of hypotension. His serum creatinine is now 2.5 mg/dl, sodium 135 mEq/l, potassium 3.4 mEq/l, chloride 105 mEq/l, bicarbonate 20 mEq/l, BUN 70 mg/dl, glucose 110 mg/dl. His urinalysis is unremarkable.

In addition to potassium repletion and discontinuation of his furosemide infusion, which ONE of the following interventions is MOST appropriate?

A. Add a parenteral β-blocker to achieve rate control
B. Give vasopressin and rapidly wean off dopamine
C. Give a bolus of normal saline and rapidly wean off dopamine
D. Switch dopamine to phenylphrine
E. Switch dopamine to Dobutamine

The correct answer is C. This patient has acute-on-chronic renal failure with prerenal azotemia caused by furosemide-induced hypovolemia, masked by the use of dopamine, and aggravated by development of uncontrolled atrial fibrillation. In addition to dopaminergic receptors, dopamine stimulates β-adrenergic and α-adrenergic arterial receptors, which may be pro-arrhythmic (β-adrenergic effect) and mask hypovolemia (by α-adrenergic arterial and venous constriction, and β-adrenergic inotropic effect). Potassium repletion, discontinuation of furosemide infusion, and active volume expansion are required for this patient. Saline boluses to raise CVP to 8–12 mmHg should permit rapid weaning off of pro-arrhythmic dopamine, and correction of hypovolemia will also remove a 2nd mechanism of cathecholamine-driven tachycardia. If rate control is still inadequate and perfusion-impaired, rate control with a β-blocker, and (if necessary) use of a pressor or cardioversion could be considered. If a pressor is required for this patient, phenylephrine would be preferred to norepinephrine to avoid β-adrenergic stimulation; Dobutamine should be avoided for the same reason.

Reference

Murray PT (2003) Use of dopaminergic agents for renoprotection in the ICU. Yearbook of Intensive Care and Emergency Medicine, Springer-Verlag, pp. 637–648

CASE 34

A six-year old girl with congenital cyanotic heart disease undergoes cardiac surgery. She remains intubated, mechanically ventilated, and is sedated with continuous infusions of propofol and fentanyle. Initially, she has a low cardiac index and requires hemodynamics support with an intraaortic balloon pump and a continuous infusion of epinephrine, but by the third postoperative day she is hemodynamically stable with a mean arterial BP of 60 mmHg on no pressor support. Her urine output on the first postoperative day is 600 ml and falls to <100 ml/24 hr on the second and third postoperative days despite net positive fluid balance of 5.2 liters. Her pulmonary artery occlusion pressure is 16 mmHg. Her transcutaneous capillary oxygen saturation is 98% on fractional inspired oxygen of 0.4. Laboratory tests reveal a creatinine of 2.7 mg/dl (preoperative value 0.9 mg/dl), BUN 46 mg/dl, sodium 134 mEq/l, potassium 4.7 mEq/l, and bicarbonate 22 mEq/l. Her arterial blood pH is 7.31.

Which ONE of the following statements regarding initiation of renal replacement therapy in this clinical setting is evidence-based?

A. Delaying initiation of RRT until her BUN is >60 mg/dl will increase her mortality risk by 70%.
B. RRT should have been initiated within the first 24 hours after onset of oliguria to minimize her mortality risk
C. Initiation of RRT to correct her metabolic acidosis will decrease her mortality risk by approximately 45%.
D. RRT should be delayed until her BUN is >80 mg/dl to allow her to become more hemodynamically stable.
E. There is insufficient data from prospective clinical trials to guide the optimal timing of RRT in this setting.

The correct answer is E. Several retrospective analyses have suggested that earlier initiation of renal replacement therapy in critically ill patients is associated with improved survival, however this was not shown in the single prospective randomized trial attempting to evaluate this question. This study was insufficiently powered and evaluated patients with a lesser severity of illness than commonly seen in critical care units. None of the other four statements is based on clinical data.

References

Palevsky PM (2005) Renal replacement therapy I: Indications and timing. Crit Care Clin 21:347–356
Towani A (2005) renal replacement therapies for acute renal failure:does dose matter? Am J Kidney Dis 45:1139–1143

CASE 35

An 18-year old female with advanced liver disease secondary to sclerosing cholangitis is admitted with increasing ascites. Her serum creatinine one month ago was 1.2 mg/dl. Upon admission, her serum creatinine is 1.7 mg/dl. Her physical examination is remarkable for a BP of 110/70 mmHg, massive ascites, and minimal peripheral edema. A paracentesis is performed with drainage of 9.2 liters of fluid, accompanied by the administration of 75 g of hyperoncotic (25%) albumin. Two days later, her serum creatinine is 2.6 mg/dl, rising to 3.2 mg/dl despite the administration of 1.5 liters of isotonic saline.

Which ONE of the following interventions is MOST appropriate at this time?

A. Administration of octreotide
B. Administration of octreotide and dopamine
C. Administration of octreotide and midodrine
D. Emergent splenorenal shunt
E. Removal from liver transplant waiting list

The correct answer is C. The patient described here has acute kidney injury due to the hepatorenal syndrome. Pre-renal azotemia has been effectively excluded based on the failure to respond to administration of isotonic saline. In case series, pharmacologic therapy with vasoconstrictors such as the vasopressin analogue terlipressin, or the somatostatin analogue octreotide in combination with the α-adrenergic midodrine, has been associated with sustained improvement in renal function. The use of octreotide alone is not effective (choice A is incorrect) and the combination of octreotide and dopamine has not been evaluated (choice B is incorrect). There is no indication for emergent splenorenal shunt—this surgery is performed to decompress the portal circulation in patients with intractable gastrointestinal bleeding from portal hypertension, and is not associated with improvement in renal function (choice D is incorrect). The development of hepatorenal syndrome does not contraindicate liver transplantation. Patients who respond to vasoconstrictor therapy have similar outcomes as patients who do not have hepatorenal syndrome (choice E is incorrect).

References

Gines P, Guevara M, Arroyo V, et al. (2003) Hepatorenal syndrome. Lancet 362:1819–1827
Gines P, Cardenas A, Arroyo V, et al. (2004) Management of cirrhosis and ascites. N Engl J Med 350:1646–1654

Kalambokis G, Economou M, Fotopoulos A, et al. (2005) The effects of chronic treatment with octreotide versus octreotide plus midodrine on systemic hemodynamics and renal hemodynamics and function in nonazotemic cirrhotic patients with ascites. Am J Gastroenterol 100:879–885

Kiser TH, Fish DN, Obritsch MD, et al. (2005) Vassopressin, not octreotide, may be beneficial in the treatment of hepatorenal syndrome: a retrospective study. Nephrol Dial Transplant 20:1813–1820

CASE 36

A 12-year old girl with a poorly differentiated non-Hodgkin's lymphoma is started on chemotherapy with cyclophosphamide, daunorubicin, vincristine, and prednisone. Despite aggressive intravenous volume expansion with isotonic saline, she develops oliguria and a rising serum creatinine on the day after chemotherapy is initiated.

Which ONE of the following findings has the HIGHEST specificity for the correct diagnosis of the cause of this patient's acute kidney injury?

A. Serum uric acid> 20 mg/dl
B. Urine uric acid>20 mg/dl
C. Urine uric acid to urine urea nitrogen ration>0.1
D. Urine uric acid to creatinine ratio>1.0
E. Uric acid crystals on urine microscopy

The correct answer is D. The patient in this clinical vignette has acute renal injury due to tumor lysis syndrome with acute uric acid nephropathy. The most specific diagnostic test for the diagnosis of uric acid nephropathy is the urine uric acid-to-creatinine ratio. A value of >1 is highly specific for this syndrome with values of less than 0.6–0.75 in other etiologies of acute renal injury. Although urine uric acid crystals are often observed in acute urate nephropathy, they are not always present and may be seen in many other clinical settings (choice E is incorrect). The absolute values of serum or urine uric acid concentrations and the urine uric acid-to-urine urea nitrogen ratio are not diagnostic for uric acid nephropathy (choice A, B, and C are incorrect).

Reference

Kelton J, Kelly WN, Holmes EW (1978) A rapid method for the diagnosis of acute uric acid nephropathy. Arch Intern Med 138:612–615

CASE 37

A 14-year old girl is admitted with severe community-acquired pneumonia and sepsis. Upon admission to the ICU, she becomes acutely confused and hypoxic, and she is intubated after a respiratory arrest. After intubation, her BP decreases from 130/70 mmHg to 100/55 mmHg on a dopamine infusion of 8 μg/kg/min, with a central venous pressure of 8 mmHg. Ventilation settings are tidal volume 6 ml/kg, respiratory rate 35/min, positive end-expiratory pressure (PEEP) 15 cm H_2O, and oxygen saturation 90% on 70% inspired oxygen. Plateau pressure (static airway pressure measured during an inspiratory pause) is 35 cm H_2O. Her chest x-ray shows bilateral pulmonary infiltrates with good central venous catheter and endotracheal tube placement. Her arterial gases are pH 7.19, pCO_2 65 mmHg, pO_2 60 mmHg, and bicarbonate 24 mEq/l. Central venous oxygen saturation is 51%. Urine output is 10 ml/hr and serum creatinine has increased from 0.8 mg/dl upon admission to 1.5 mg/dl. Her hemoglobin is 7 g/dl.

Which ONE of the following is the BEST management plan for her acute kidney injury?

A. Increase the PEEP to 20 cm H2O
B. Transfuse 1 to 2 units of packed red blood cells
C. Start a furosemide infusion
D. Begin a norepinephrine infusion and wean the dopamine infusion
E. Increase the respiratory rate

The correct answer is B. This patient should receive early goal-directed therapy for septic shock. Ventral venous pressure is within the 8–12 mmHg range recommended for early goal-directed therapy of septic shock, but central venous oxygen saturation is low. Transfusion of packed red blood cells to achieve a hemoglobin of 10 g/dl is recommended to increase central venous oxygen saturation to $\geq$ 70%. Dobutamine would be added to normalize central venous oxygen saturation if transfusion to a hemoglobin of 10 g/dl failed to achieve this goal. Furosemide infusion (choice C is incorrect) or increased PEEP (choice A) would exacerbate hypovolemis (the impact of positive pressure ventilation with decreased venous return has caused hypovolemia in this patient, masked in part by positive intrathoracic pressure elevating the central venous pressure, and by dopamine-induced venoconstriction) and norepinephrine would continue to mask it (choice D is incorrect). Although increasing respiratory rate would improve hypercapnia and pH (choice E), any improvement in renal blood flow by this mechanism would be less substantial than the effects of volume expansion, and would risk significantly increasing auto PEEP *air trapping*. Finally, raising central venous oxygen saturation will also improve arterial oxygenation, and might permit use of a lower fraction of inspired oxygen and perhaps less PEEP, further improving management. This is the best approach to improving systemic and renal perfusion in this patient.

References

Kuiper JW, Groeneveld AB, Slutsky AS, et al. (2005) Mechanical ventilation and acute renal failure. Cri Care Med 33:1460–1461

Rivers E, Nguyen B, Havstad S, et al. (2001) Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 345:1368–1377

CASE 38

A seven-year old girl with no history of kidney disease undergoes aortic valve replacement bypass surgery. In the initial postoperative period, she has a low cardiac index and requires hemodynamic support with an intra-aortic balloon pump and a continuous infusion of epinephrine. By the third postoperative day, however, she is hemodynamically stable with a mean arterial BP of 54 mmHg of off-pressor support. She remains intubated, mechanically ventilated, and is sedated with continuous infusions of propofol and fentanyl. Despite net positive fluid balance, she has developed progressive oliguria, her BUN is 84 mg/dl, and her serum creatinine is 4.3 mg/dl. You are consulted by the cardiothoracic surgeons to initiate RRT.

Which ONE of the following statements regarding modality of RRT in this clinical setting is evidence-based?

A. Continuous RRT would be associated with a greater probability of survival in comparison to intermittent hemodialysis.
B. Intermittent hemodialysis would be associated with an increased risk of the combined outcome of death or nonrecovery of renal function.
C. Sustained, low-efficiency dialysis (SLED) would provide more rapid correction of metabolic acidosis than CRRT.
D. CRRT would be associated with greater probability of achieving negative net fluid balance without exacerbating hemodynamic instability than SLED.
E. SLED would require lower levels of anticoagulation than intermittent hemodialysis.

The correct answer is C. There are no data establishing better survival or recovery of renal function with CRRT, intermittent hemodialysis, or SLED (choices A and B are not correct). CRRT has been demonstrated to be associated with a greater probability of achieving negative fluid balance without exacerbating hemodynamic instability, in comparison to intermittent hemodialysis—however, hemodynamic stability during SLED is similar to that observed during CRRT (choice D is incorrect). Similarly, SLED requires a lower total anticoagulant dose than CRRT due to the shorter duration of treatment (choice E is incorrect). SLED has, however, been shown to provide more rapid correction of metabolic acidosis than CRRT (choice C is correct).

Reference

Augustine JJ, Sandy D, Seifert TH, et al. (2004) A randomized controlled trial comparing intermittent with continuous dialysis in patients with ARF. Am J Kidney Dis 44:1000–1007

CASE 39

A seven-year old girl is to begin chemotherapy for a poorly differentiated non-Hodgkin's lymphoma.

Which ONE of the following is NOT effective at reducing her risk of developing acute kidney injury as a result of induction chemotherapy?

A. Furosemide
B. Rasburicase
C. Allopurinol
D. Isotonic sodium chloride
E. Sodium bicarbonate

The correct answer is A. The major risk for acute kidney injury (AKI) in this patient is tumor lysis syndrome. A variety of therapies may be of benefit in preventing AKI in tumor lysis syndrome, including volume expansion with isotonic saline, inhibiting uric acid generation using the xanthine oxidase inhibitor, Allopurinol, and using rasburicase (recombinant uricase) to convert uric acid to allantoin. Urinary alkalinization using sodium bicarbonate has also been recommended as a prophylactic measure to increase the urinary solubility of uric acid—however, urinary alkalinization may increase the risk of calcium phosphate precipitation in patients with with concomittent hyperphosphatemis. There is however, no role for loop-acting diuretics such as furosemide for the prevention of AKI in the tumor lysis syndrome.

Reference

Humphreys BD, Soiffer RJ, Mage CC (2005) Renal failure associated with cancer and its treatment: an update. J Am Soc Nephrol 16:151–161

CASE 40

A two-year old patient presents with septic shock, a BP of 80/50 mmHg, a central venous pressure of 4 mmHg, oliguria (urine output 10 ml/hr), a central venous oxygen saturation of 60%, a transcutaneous pulse oximeter saturation of 98% on room air, a respiratory rate of 18/min, bilateral interstitial edema on chest x-ray, a serum creatinine concentration of 2 g/dl, and a hemoglobin concentration of 9 g/dl.

Which ONE of the following options is the BEST choice for treatment of this patient?

A. Infuse 50 ml of 25% albumin intravenously, then reevaluate central venous oxygen saturation
B. Transfuse 1 unit packed red blood cells
C. Administer 80 mg furosemide intravenously
D. Infuse boluses of isotonic saline until the central venous pressure is 8 to 12 mmHg, then recheck central venous oxygen saturation
E. Transfuse 1 unit packed red blood cells and administer 80 mg furosemide intravenously

The correct answer is D. This patient has septic shock complicated by respiratory and renal failure, and should receive early goal-directed therapy. Saline boluses to achieve the target central venous pressure range of 8–12 mmHg is the best approach (choice D). There is no proven advantage of albumin or other colloids in this setting (choice A), even with hypoalbuminemia and acute lung injury with early pulmonary edema. There is no indication for blood transfusion at this point (choices B and E), but this would be indicated if central venous oxygen saturation remained below 70% with a hemoglobin below 10 grams/dl when the target central venous pressure of 8–12 mmHg is achieved. Diuresis alone (choice C) is contraindicated at this point in the resuscitation of this patient.

References

Finfer S, Bellomo R, Boyce N, et al. (2004) SAFE Study Invetigators. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. N Engl J Med 350:2247–2256

Rivers E, Nguyen B, Havstad S, etal (2001) Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 345:1368–1377

CASE 41

You are asked to see a 13-year old boy—trauma victim—who sustained closed head trauma resulting in cerebral edema. He is intubated and mechanically ventilated. His BP is 90/60 mmHg on no pressor agent, and his urine output is 40 ml/hr. Laboratory testing reveals serum creatinine 8 mg/dl, potassium 5.9 mEq/l, bicarbonate 12 mEq/l, and serum creatinine phosphokinase 100,000 U/l. Bilateral infiltrates are present on his chest x-ray.

Which ONE of the following interventions is MOST appropriate at this time?

A. Begin infusions of mannitol, bicarbonate, and saline
B. Administer intravenous calcium
C. Initiate continuous venovenous hemofiltration

D. Initiate daily intermittent hemodialysis
E. Administer 200 mg of intravenous furosemide

The correct answer is C. This patient has severe acute renal failure in association with acute brain injury, cerebral edema, and elevated intracranial pressure. He also has significant rhabdomyolysis, with hperphisphatemia and hypocalcemia. Mannitol or any intravenous fluids will exacerbate pulmonary edema, and diuretic therapy will not improve renal function or control hyperphosphatemia/ hypocalcemia in this setting (choices A and E are incorrect). Bicarbonate therapy (choice C) might also precipitate tetany by lowering systemic ionized calcium. Calcium infusion is contraindicated in this severely hyperphosphatemic patient (choice B is incorrect). CVVH will provide better control of hyperphosphatemis and hypocalcemia, and correct azotemia and acidosis without raising intracranial pressure (a proven adverse effect of intermittent dialysis in the presence of cerebral edema) (choice D is incorrect).

Reference

Davenport A (2001) Renal replacement therapy in the patient with acute brain injury. Am J Kid Dis 37:457–466

Chapter 7
Hereditary Nephritis and Genetic Disorders

CASE 1

Deafness is least likely to be associated with which ONE of the following genetic disorders affecting the kidney?

A. Branchiootorenal syndrome
B. Alport syndrome
C. Alstrome syndrome
D. Fechtner syndrome
E. Nail-patella syndrome

The correct answer is E. The Nail-Patella Syndrome, which is caused by mutations in a gene encoding for a transcription factor (LMX1B) expressed in the podocytes, is not associated with deafness. In the other hand, deafness is a major feature of the branchiootorenal (BOR), Alport, Alstrome, and Fechtner syndromes. Deafness in BOR syndrome is due to the absence or underdevelopment of the cochlea. A cochlear defect is also responsible for the hearing loss associated with Alport and Fechtner syndromes. COL4A3, AOL4A4, and COL4A5—the proteins mutated in Alport syndrome—are strongly expressed in the matrix that connects the tension fibroblast to the basilar membrane in the lateral aspect of the spiral ligament at the basal turn of the cochlea. MYHIIA—the protein mutated in Fechtner syndrome—is a nonmuscle myosin that is predominantly expressed in these tension fibroblasts. The structural integrity and function of the tension fibroblasts and matrix are essential to increase the tension of the basilar membrane to the degree needed for high-frequency sound reception. The pathogenesis of deafness in Alstrome syndrome is not understood.

Reference

Richardson D, Shires M, Davidson AM (2001) Renal diagnosis without renal biopsy. Nephritis and sensorineural deafness. Nephrol Dial Transplant 16:1291–1294

F. Assadi, *Clinical Decisions in Pediatric Nephrology.*

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CASE 2

Which ONE of the following is NOT associated with hyperglycemia?

A. Seven-year old, overweight boy with pigmented retinopathy and mental retardation
B. 12-year old girl with nerve deafness and retinitis pigmentosa
C. 18-year old girl with small kidneys containing a peripheral rim of cortical cysts, renal insufficiency, and a septate vagina
D. 14-year old boy with deafness, proteinuria, and a renal biopsy showing focal segmental glomerulosclerosis and podocytes containing many dysmorphic mitochondria
E. 19-year old female with polycystic kidneys, cleft tongue, and history of surgical repair of digital abnormalities in early childhood

The correct answer is E. The clinical presentations of these patients suggest differential diagnoses that include conditions associated with diabetes mellitus in all but choice E. The association of polycystic kidneys, and orofacial and digital malformations in a female patient is pathognomonic of oro-facial-digital (OFD) syndrome Type 1. This is a rare, x-linked dominant disorder with prenatal lethality in males. The presence of hyperglycemia or noninsulin-dependent diabetes mellitus in the patients described in choices A and B suggests a possible diagnosis of Alstrome syndrome. This is an autosomal recessive disease characterized by obesity, Type 2 diabetes mellitus, retinitis pigmentosa, nerve deafness, and frequently a slowing progressive chronic tubulointerstitial nephropathy. The association of diabetes mellitus in the patient described in choice A would favor a diagnosis of Alstrome syndrome rather than the more common autosomal recessive Bardet Biedl syndrome, which is not associated with diabetes mellitus. Similarly, the association of diabetes mellitus in the patient described in choice B would favor the diagnosis of Alstrome syndrome, rather than Usher syndrome, which is a more common cause of coexisting nerve deafness and retinitis pigmentosa. The association in choice C of imaging findings consistent with glomerulocystic kidney disease, genital abnormalities, and Type 2 diabetes mellitus points to a diagnosis of maturity-onset diabetes of the young Type 5 (MODY5). MODY5, caused by mutations in the gene encoding hepatocyte nuclear factor (HNF)-1β, is characterized by the association of diabetes mellitus, abnormal renal development, and genital tract malformations. The renal phenotype is variable and includes renal agenesis, multicystic renal dysplasia, hypoplastic glomerulocystic kidneys with abnormal calyces and papillae, and oligomeganephronia. The genital tract malformations may include absence of fallopian tubes or uterus, vaginal atresia, fusion abnormalities such as bicornuate uterus or biseptate vagina, and (rarely) male genital tract abnormalities such as hypospadias. Finally, the presence of dysmorphic mitochondria in the podocytes in choice D suggests a *A3243 G* mutation in the mitochondrial *tRNA* gene, which has been associated with FSGS, diabetes mellitus and hearing loss.

References

Bingham C, Ellard S, Cole TR, et al. (2002) Solitary kidney and diverse genital tract malformations associated with hepatocytes nuclear factor-1b mutations. Kidney Int 61: 1243–1251

Collin GB, Marshall PM, Ikeda A, et al. (2002) Mutations in *ALMS1* cause obesity, Type 2 diabetes and neurosensory degeneration in Alstrom syndrome. Nat Genet 31:74–78

Romio L, Wright V, Price K, et al. (2003) OFD1, the gene mutated in oral-facial-digital syndrome Type 1, is expressed in the metanephros and in human embryonic renal mesenchymal cells. J Am Soc Nephrol 14: 680–689

Hotta O, Inoue CN, Miyabayashi S, et al. (2001) Clinical and pathologic features of focal segmental glomerulosclerosis with mitochondrial tRNA Leu (UUR) gene mutation. Kidney Int 59:1236–1243

CASE 3

A 13-year old boy develops right upper-quadrant pain and fever with shaking chills. An abdominal ultrasound reveals hyperechoic liver parenchyma, dilatation of several intrahepatic bile ducts, and a few bilateral renal cysts.

The defect responsible for this condition is MOST likely to be a mutation(s) in:

A. *PKHD1*
B. *PKHD1*
C. *PKD2*
D. *TSC2*
E. *OFD1*

The correct answer is A. The clinical presentation and imaging studies in this patient are consistent with Caroli's disease (congenital hepatic fibrosis, and mild autosomal recessive polycystic kidney disease presenting with ascending cholangitis). Mutations in the recently identified *PKHD1* gene have been found in cases of congenital hepatic fibrosis and Caroli's disease with minimal or mild renal involvement, as well as in patients with more typical presentations of severe autosomal recessive polycystic kidney disease (ARPKD). Congenital hepatic fibrosis and dilatation of the intrahepatic bile ducts are much more rarely associated with autosomal dominant polycystic kidney disease (ADPKD) caused by *PKD1* or *PKD2* mutations. Mutations in *TSC2* (causing tuberous sclerosis complex) or in *PRKCSH* (causing autosomal dominant polycystic liver disease) would not be consistent with the presentation or findings in this patient.

References

Bergmann C, Senderek J, Sedlacek B, et al. (2003) Spectrum of mutations in the genes for autosomal recessive polycystic kidney disease (*ARPKD*/*PKHD1*). J Am Soc Nephrol 14:76–89

Rossetti S, Torra R, Coto E, et al. (2003) A complete mutation screen of *PKHD1* in autosomal recessive polycystic kidney disease pedigrees. Kidney Int 64:391–403

CASE 4

A nine-year old girl with sensorineural hearing loss has progressive renal insufficiency. Her father and a paternal aunt also had renal failure, and the father's renal biopsy showed features consistent with Alport syndrome.

Which ONE of the following statements is correct?

A. If mutation analysis were to be performed, it is likely that a mutation would be found in either the *COL4A3* gene or the *COL2A4* gene.
B. The risk of post-transplant anti-glomerular basement membrane disease is significant and should preclude transplantation.
C. The likelihood that the children of this patient would develop evidence of Alport syndrome is 50% for both male and female offspring.
D. A search for diffuse leiomyomatosis should be initiated.
E. Her children are at risk for the development of thin basement membrane nephropathy.

The correct answer is C. The pattern of inheritance described in this case is consistent with x-linked dominant or autosomal dominant disease—the former being more likely because autosomal dominant Alport syndrome is very rare. Although x-linked Alport syndrome is usually mild in female heterozygotes, severe disease can occur due to skewed inactivation of the x-chromosome. X-linked Alport syndrome is caused by mutations in *COL4A3* or *COL4A4*; therefore, answer A is wrong. Answer B is not correct because less than 3% of Alport patients develop anti-GBM disease following renal transplantation and this small risk does not preclude renal transplantation. The Alport syndrome-diffuse leiomyomatosis contiguous gene syndrome is very rare and, although it needs to be kept in mind, specific investigations for its detection (answer D) are not indicated in the absence of suggestive symptoms such as dysphagia, dyspnea, vulvovaginal leiomyomas, or juvenile cataracts. At least some cases of thin-basement membrane disease are heterozygote carriers of autosomal recessive Alport syndrome with *COL4A3* or *COL4A4* mutations. X-linked Alport syndrome is dominant, and patients with *COL4A5* mutations have Alport syndrome, not thin-basement membrane disease; therefore, answer E is wrong.

References

Badenas C, Praga M, Tazon B, et al. (2002) Mutations in the *COL4A4* and *COL4A3* gene cause familial benign hematuria. J Am Soc Nephrol 13:1248–1254

Byrne MC, Budisavljevic MN, Fan Z, et al. (2002) Renal transplant in patients with Alport syndrome. Am J Kidney Dis 39:769–775

Mothes H, Heidet L, Arrondel C, et al. (2002) Alport syndrome associated with diffuse leiomyomatosis: *COL4A5-COL4A6* deletion associated with a mild form of Alport nephropathy. Nephrol Dial Transplant 17:70–74

CASE 5

The father of a patient is being evaluated as a potential kidney donor for his four-year old son, who has end-stage renal disease secondary to focal segmental glomerulosclerosis. The potential donor undergoes a CT examination of the kidneys with contrast enhancement. The CT examination reveals two cysts measuring 4 mm in diameter.

Which ONE of the following would be the best course of action?

A. Stop further evaluation as a potential donor because he meets imaging criteria for a diagnosis of ADPKD.
B. Proceed with the evaluation because a diagnosis of ADPKD can be excluded by the results of the CT examination.
C. Tell the patient that he probably does have ADPKD and that genetic testing on him, the recipient, and other available family members will be necessary to confirm this diagnosis.
D. Tell the patient that he probably does not have autosomal dominant polycystic kidney disease (ADPKD) and that genetic testing on him, the recipient, and other available family members will be necessary to confirm this diagnosis.
E. Proceed with magnetic resonance examination of the abdomen.

The correct answer is D. The imaging criteria or the diagnosis of ADPKD in first-degree relatives of affected individuals have been based on ultrasonography. Current imaging techniques, particularly CT and MR, have a much higher resolution, and therefore the sonographic criteria developed over a decade ago cannot be indiscriminately applied. Furthermore, while these sonographic criteria have a very high sensitivity for the diagnosis of PKD1 disease, their sensitivity for the diagnosis of PKD2 disease in individuals less than 30 years old is low. The presence of two cysts detected by ultrasound in a 10-year old individual at 50% risk of ADPKD would have met the criteria for a positive diagnosis. This is not the case using CT examinations. Therefore, answer A is wrong. Answer B is also wrong, because the diagnosis of ADPKD (particularly PKD2) cannot be reliably excluded. Answers C and D could be correct, but answer D seem more likely, in view of the severity of the disease in the father. Although MRI is the most sensitive technique for detecting renal cysts, it seems unlikely that many cysts detectable by MR would have been missed by the contrast enhanced CT.

References

Nicolau C, Torra R, Badenas C et al. (1999) Autosomal dominant polycystic kidney disease Types 1 and 2: assessment of US sensitivity for diagnosis. Radiology 213:273–276

Rossetti S, Chauveau D, Walker D, et al. (2002) A complete mutation screen of the ADPKD genes by DHPLC. Kidney Int 61:1588–1599

Zand MS, Stang J Dumalo M, et al. (2001) Screening a living donor kidney for polycystic kidney disease using heavily T2-weighted MRI. Am J Kidney Dis 38:612–619

CASE 6

For which ONE of the following diseases is genetic testing most helpful?

A. von Hipple-Lindau disease (VHL)
B. Autosomal dominant polycystic kidney disease
C. Tuberous sclerosis complex (TSC)
D. Alport syndrome
E. Congenital hepatic fibrosis

The correct answer is A. The availability of genetic testing for VHL has, in most cases, eliminated the need for lifelong follow-up of *at risk* unaffected individuals for the early detection of the life-threatening complications of this disease. On the other hand, genetic testing for ADPKD, TSC, Alport syndrome, and congenital hepatic fibrosis is much more rarely performed because existing clinical criteria are usually adequate for the clinical management of these patients. The lack of effective therapies limits the benefits of early diagnosis, and the yield of mutations analysis is significantly less than 100%. At present, the main indication for genetic testing for ADPKD is evaluation of living related donors for renal transplantation when the imaging studies are inconclusive.

References

Bergmann C, Senderek J, Selacek B, et al. (2003) Spectrum of mutations in the gene for autosomal recessive polycystic kidney disease (ARPKD/*PKHD1*). J Am Soc Nephrol 14:76–89

Maranchie JK, Linehan WM (2003) Genetic disorders and renal cell carcinoma. Urol Clin North Am 30:133–141

Rossetti S, Torra R, Coto E, et al. (2003) A complete mutation screen of *PKHD1*in autosomal recessive polycystic disease (ARPKD) pedigrees. Kidney Int 64:391–403

CASE 7

A 12-year old Caucasian girl is found to have a solid mass upon ultrasound evaluation of the abdomen for malignant hypertension.

Which ONE of the following findings on physical examination would be most helpful in establishing the diagnosis of von Hipple-Lindau disease?

A. Fibrofolliculomas and trichdiscomas
B. Facial angiofibromas and subungual fibromas
C. Cutaneous leimyomas
D. Retinal hemangioblastoma
E. Normal skin examination

The correct answer is D. Retinal hemangioblastomas are seen in up to 60% of the patients with von Hipple-Lindau disease, and in about half of the cases are mutifocal and bilateral. Fibrofolliculomas and trichodiscomas are characteristic of Birt-Hogg-Dube disease—an autosomal dominant syndrome associated with chromophobe and conventional renal cell carcinomas, and with oncocytomas. These skin lesions typically appear as multiple, small, dome-shaped, yellowish or skin-colored papules, scattered over the face, neck, scalp, and upper trunk. Facial angiofibromas or forehead plaques and periungual or subungual fibromas, along with hypomelanotic macules and shagreen patches, are major features of tuberous sclerosis complex. Cutaneous and uterine leiomyomas, uterine leiomyosarcomas, and papillary renal cell, bladder, and breast carcinomas are part of a recently recognized syndrome caused by mutations in the gene encoding fumarate hydrate—an enzyme of tricarboxylic acid cycle.

Reference

Singh AD, Shields CL, Shields JA (2001) von Hipple-Lindau disease. Survey of ophthalmology 46:117–142

CASE 8

A 14-year old girl with nephritic syndrome has had no improvement despite a course of therapy with steroids.

Genetic testing of patients with steroid-resistant idiopathic nephrotic syndrome may be helpful because:

A. It will determine whether further therapy is indicated
B. It will rule out recurrent disease after transplantation if a mutation is found
C. It may be important for genetic counseling
D. All of the above
E. None of the above

The correct answer is C. The nephritic syndrome associated with nephron or podocin mutations has been thought to be resistant to steroid therapy and not at risk for recurrence after transplantation. Cases of familial focal segmental glomerulosclerosis (FSGS) have responded to immunosuppressive regimens—particularly methylprednisolone pulses and cyclosporine—and recurrence of nephritic syndrome after renal transplantation can occur in patients with nephrin or with podocin mutations. Therefore, answer A and B are probably wrong. On the other hand, detection of mutations in podocyte genes that control glomerular protein per selectivity may assist in the detection of affected family members or in the evaluation of living related kidney donors. Therefore, answer C is correct.

References

Bertili R, Ginevri G, Dagnino M et al. (2003) Recurrence of focal segmental glomerulosclerosis after renal transplantation in patients with mutations of podocin. Am J Kidney Dis 41: 1314–1321

Carraro M, Csridi G, Bruschi M et al. (2002). Serum glomerular permeability activity in patients with podocin mutations (NPHS2) and steroid-resistant nephritic syndrome. J Am Soc Nephrol 13:1946–1952

CASE 9

A 10-year old Caucasian sister of a patient with Fabry's disease is found to have low-grade proteinuria.

Which ONE of the following tests would be most helpful in determining whether she has Fabry's disease?

A. Determination of alfa-galactosidase activity in plasma
B. Determination of alfa-galactosidase in peripheral leukocytes
C. Determination of alfa-galactosidase in urine cell pellets
D. Genetic testing
E. Urine protein electrophoresis

The correct answer is D. The diagnosis of Fabry disease in male patients can be easily made through an enzymatic assay in plasma, leukocytes, or cultures fibroblasts, but it is very difficult to determine the carrier status in females. Because of x-chromosome inactivation, even obligate heterozygous females can show normal alfa-galactosidase-A enzyme activity. The only method of detecting a female carrier is through molecular analysis. Although alpha-galactosidase A activity may be abnormal in urine cell pellets of Fabry patients, the sensitivity of this test is not known.

Reference

Guffon N (2003) Clinical manifestation in female patients with Fabry disease. J Med Genet 40: e38

CASE 10

A 14-year old boy has recurrent calcium oxalate stones and excretes excessive amounts of oxalate. There is family history of kidney stones. Glomerular filtration rate is normal, and there is no evidence of systemic oxalosis. Testing for primary hyperoxaluria reveals excessive urinary 1-glyceric acid, and genetic testing confirms a mutation in the *DGDH*gene.

Which ONE of the following statements regarding this patient is MOST correct?

A. The patient has primary hyperoxaluria Type 1 (PH1) and will probably need liver and kidney transplantation.
B. The patient has benign dietary hyperoxaliuria.
C. The patient is likely to benefit from pyridoxine therapy.
D. The patient has primary hyperoxaluria Type 2 (PH2) and is unlikely to develop renal failure or systemic oxalosis.
E. The patient's children are at risk for systemic oxalosis.

The correct answer is D. Excessive urinary excretion of L-glyceric acid indicates the diagnosis of primary hyperoxaluria Type 2, and this is confirmed by mutations in *DGDH*. Patients with PH2 suffer from kidney stones but, in contrast to PH1, do not have systemic oxalosis, and transplantation is unnecessary. Urinary L-glyceric acid excretion is not elevated in dietary hyperoxaluria. Pyridoxine therapy is useful in some patients with PH1, but its value in PH2 has not been reported. Because the patient does not have PH1, his children will not be at risk for systemic oxalosis.

Reference

Miliner DS, Wilson DM, Smith LH (2001). Phenotypic expression of primary hyperoxaluria:Comparative features of Types I and II Kidney Int 59:31–36

CASE 11

An 11-year old Caucasian boy has renal Fanconi syndrome, nephrocalcinosis, and a reduced glomerular filtration rate.

Which ONE of the following findings would make you doubt the diagnosis of Dent's disease?

A. Hypercalciuria
B. A similar syndrome in the father
C. Proteinuria
D. Rickets
E. The absence of a family history

The correct answer is B. Dent's disease is inherited in an x-linked fashion, and *CLCN5* is located on chromosome x. Father-to-son inheritance is inconsistent with x-linkage. Proteinuria is a hallmark of Dent's disease, and hypercalciuria is present in virtually all patients until renal function begins to decline. Rickets, although present in a minority of patients, is a well-recognized feature of the disease.

Although this is clearly a genetic disease, a family history of affected relatives may be absent, either because of incomplete information on family members or as a consequence of the highly variable severity of phenotype even within families.

Reference

Scheinman SJ (1998) X-linked hypercalciuric nephrolithiasis: Clinical syndromes and chloride channel mutations. Kidney Int 53:3–17

CASE 12

A nine-year old boy is found to have cystine kidney stones.

Which ONE of the following statements regarding therapy is MOST correct?

A. Molecular genetic testing would be important in guiding therapy.
B. If he is able to maintain a high fluid intake, particularly at night, chelating therapy might not be needed.
C. He should be treated with penicillamine or tropronin.
D. Restriction of dietary sources of cosine is a critical component of successful therapy.
E. Medical therapy can prevent stone growth but cannot itself lead to reduction in stone size.

The correct answer is B. Maintaining dilute urine is a critical goal of therapy in patients with cystinuria. In patients with mildly or moderately excessive cosine excretion, maintenance of a consistently high fluid intake may be sufficient to make chelating therapy unnecessary. Therapy with a sulfhydryl agent (penicillamine or tiopronin) is often necessary in patients in whom stones recur despite a high fluid intake and urinary alkalinization, but will not be needed in all patients. Restriction of dietary sources of cosine is not useful. Results of molecular genetic testing do not alter therapy. Successful adherence to a strict medical regimen including high fluid intake, urinary alkalinization, and often chelating therapy, can lead to reduction in stone size over time.

Reference

Barbey F, Joly D, Rieu O et al. (2000) Medical management of cystinuria: critical reappraisal of long-term results. J Urol 163:1419–1423

CASE 13

A 6-year old boy is being evaluated for polyuria. He is found to have nephrocalcinosis and hyperurecimia, and his physician suspects that he may have a hereditary syndrome associated with mutations in paracellin-1.

Which ONE of the following, if observed, would be most suggestive of this diagnosis?

A. Hypokalemic metabolic alkalosis
B. Salt-wasting
C. Hypocalciuria
D. Hypomagnesemia
E. High serum levels of renin and aldosterone

The correct answer is D. Familial hypomagnesemia with hypercalciuria and nephrocalcinosis (FHHNC) is associated with mutations in paracellin-1, inherited in an autosomal recessive fashion. The combination of polyuria, nephrocalcinosis, and hyperurecemia in the setting of clinically significant hypomagnesemia would be strongly suggestive of this diagnosis. Unlike the Bartter or Gitelman's syndromes, salt-wasting, hypokalemia, and metabolic alkalosis are not features of FHHNC. Urinary calcium excretion is excessive in FHHNC, presumably reflecting the defect in paracellular reabsorption of divalent cations in the Loop of Henle. Serum levels of renin and aldosterone are high in Bartter syndrome, but normal in FHHNC.

References

Blanchard A, Jeunemaitre X, Coudol P et al. (2001) Paracellin-1 is critical for magnesium and calcium reabsorption in the human thick ascending limb of Henle. Kidney Int 59:2206–2215

Knrad M, Weber S (2003) Recent advances in molecular genetics of hereditary magnesium-losing disorders J Am Soc Nephrol 14:249–260

Praga M, Vara J, Gonzalez-Parra E, et al. (1995) Familial hypomagnesemia with hypercalciuria and nephrocalcinosis. Kidney Int 47:1419–425

CASE 14

Several members of a family have hypokalemic metabolic alkalosis.

Which of the following, if present in all of the affected patients, would strongly favor the diagnosis of Gitleman syndrome?

A. Hypercaciuria
B. Hypomagnesemia
C. Hyperuricosuria
D. Presentation in early childhood
E. Presence of severe muscle weakness

The correct answer is B. Hypomagnesemia is a characteristic feature of Gitelman syndrome, although it is not yet understood why mutations that inactivate the NaCl cotransporter cause significant hypomagnesemia. As when this cotransporter is inhibited by thiazide diuretics, patients with Gitleman's syndrome have hypocalciuria, and the contrast with hypercalciuria typically seen in Bartter syndrome is

useful diagnostically in distinguishing the two syndromes. Hyperuricosuria is not a feature of Gitleman syndrome. While Bartter syndrome often presents in the postnatal period, or in early childhood, Gitleman syndrome more often presents in adolescence or young adult years, and the clinical symptoms such as muscle weakness are relatively mild.

References

Cruz DN, Shaer AJ, Bia MJ (2001) Gitleman's syndrome revisited: an evaluation of symptoms and health-related quality of life. Kidney Int 59:710–717

Peters M, Jeck N, Reinalter S, et al. (2002) Clinical presentations of genetically defined patients with hypokalemic salt-losing tubulopathies. Am J Med 15:183–190

CASE 15

You are asked to see a four-year old Caucasian girl who recently developed a severe nephrotic syndrome. She has two siblings who developed similar problems in childhood. A renal biopsy reveals focal and segmental glomerulosclerosis.

Which ONE of the following statements is MOST likely to be correct?

A. Nephrotic syndrome will not recur after renal transplantation.
B. She will likely have a mutation in the gene encoding podocin.
C. She should be evaluated for a mitochondrila gene mutation.
D. She will likely have a mutation in the gene encoding alpha-actinin-4.
E. She is likely to respond to glucocorticoid treatment.

The correct answer is B. The history suggests a familial FSGS, probably autosomal recessive. Podocin mutations have been detected in approximately one-half of these patients. The nephritic syndrome recurs in up to one third of patients with familial FSGS following renal transplantation. In the absence of clues suggesting a mitochondrial disease, such as diabetes mellitus, hearing loss, neurological manifestations, or cardiomyopathy, evaluation for a mitochondrial gene disease is not indicated. Alpha actinin-4 mutations have been associated with a later onset, autosomal-dominant FSGS that is not consistent with the clinical presentation of this patient. Although some patients with familial FSGS can respond to combination regimens, such as methylprednisolone boluses and cyclosporine, responsiveness to glucocorticoid treatment alone is unlikely.

References

Bertelli R, Ginevri F, Caridi G, et al. (2003) Recurrence of focal segmental glomerulosclerosis after renal transplantation in patients with mutations of podocin. Am J Kidney Dis 41: 1314–321

Carraro M, Caridi G, Bruschi M, et al. (2002) Serum glomerular permeability activity in patients with podocin mutations (NPHS2) and steroid-resistant nephritic syndrome. J Am Soc Nephrol 13:1946–1952

Karle SM, Uetz B, Ronner V, et al. (2002) Novel mutations in *NPHS2* detected in both familial and sporadic steroid-resistant nephritic syndrome. I Am Soc Nephrol 13:388–393

Tsukaguchi H, Sudhakar A, and Le TC, et al. (2002) *NPHS2* mutations in late-onset focal segmental glomerulosclerosis: R229Q is a common disease-associated allele. J Clin Invest 110: 1659–1666

Yorgin PD, Belson A, Higgins J, et al. (2001) Pulse methylprednisolone, cyclosporine, and ACE-inhibitor therapy decreases proteinuria in two siblings with familial focal segmental glomerulosclerosis. Am J Kidney Dis 37:e44

CASE 16

A neonate has salt-wasting with volume-depletion, hyperkalemia, and metabolic acidosis in the setting of respiratory distress.

Which ONE of the following choices provides the MOST likely diagnosis?

A. Liddle's syndrome
B. Autosomal recessive pseudohypoaldosteronism Type I
C. Autosomal dominant pseudohypoaldosteronism Type I
D. Pseudohypoaldosteronism Type II (Gordon syndrome)
E. Glucocorticoid-remediable aldosteronism (primary hyperaldosteronism)

The correct answer is B. In a neonate, the combination of hyperkalemia, volume-depletion, and metabolic acidosis suggests the presence of a syndrome of pseudohypoaldosteronism. The autosomal recessive form of pseudohypoaldosteronism Type I has severe clinical manifestations, including respiratory distress, that reflect deficiency of function of the epithelial sodium channel expressed in respiratory epithelium. The autosomal dominant for pseudohypoaldosteronism Type I has a milder phenotype that often improves with age and is not associated with respiratory symptoms. In pseudohypoaldosteronis Type II, hypertension is an important feature, and in this respect this syndrome really does not resemble an aldosterone-deficient state, and it may be more appropriately called *familial hyperkalemic hypertension*, also known as *Gordon syndrome*. In glucocorticoid-remediable aldosteronism, the clinical features reflect aldosterone excess and not deficiency, and include hypertension, hypokalemia, and metabolic alkalosis. Liddle syndrome is associated with hypertension, hypokalemia, and metabolic alkalosis, resembling an aldosterone excess state, although the defect is excessive activation of the epithelial sodium channel.

Reference

Strautnieks SS, Thompson RJ, Gardiner RM, et al. (1996) Anovel splice-site mutation in the gamma subunit of the epithelial sodium channel gene in three pseudohypoaldosteronism Type 1 families. Nat Genet 13:248–450

CASE 17

An eight-year old hypertensive boy is referred for evaluation of hyperkalemia and metabolic acidosis and is found to have hypercalciuria and a normal serum magnesium level.

Which ONE of the following drugs is MOST likely to benefit this child?

A. Spironolactone
B. Amiloride
C. Hydralazine
D. Hydrochlorothiazide
E. Furosemide

The correct answer is D. The presence of metabolic acidosis and hyperkalemia in a child with hypertension point to a diagnosis of Gordon's syndrome (familial hyperkalemic hypertension), because other familial syndromes of childhood hypertension (such as Liddle's syndrome and glucocorticoid-remediable aldosteronism) are associated with hypokalemia and metabolic alkalosis. Hypercalciuria and normal serum magnesium levels are also consistent with Gordon's syndrome, which in many respects represents a mirror image of Gitleman's syndrome. Gordon's syndrome is associated with mutations in the kinases *WNK1* and *WNL4* that lead to enhanced expression or function of the sodium-chloride contransport, NCCT. Thus, therapy with thiazide diuretics corrects all of the abnormalities in Gordon's syndrome. Diuretics that complete with aldosterone for binding to receptor (spironolactone), or inhibit the epithelial sodium channel (amiloride), or the NKCC2 transporter (furosemide), have not been shown to be of benefit—nor has the vasodilator hydralazine.

Reference

Mayan H, Vered I, Mouallem M, et al. (2002) Pseudohypoaldosteronism Type II: marked sensitivity to thiazides, hypercalciuria, normomagnesemia, and low bone mineral density. J Clin Endocrinol Metab 87:3248–3254

CASE 18

A child is found to have mild hyperkalemia, metabolic acidosis, and renal salt-wasting. Improvement of these abnormalities is noted as the child gets older.

Which of the following syndromes is most consistent with such a course?

A. Liddle's syndrome
B. Autosomal dominant pseudohypoaldosteronism Type 1

C. Autosomal recessive pseudohypoaldosteronism Type 1
D. Pseudohypoaldosteronism Type II (Gordon's syndrome)
E. Glucocorticoid-remedible aldosteronism

The correct answer is B. The clinical features described in this child resemble an adlosterone-deficient state rather then Liddle's syndrome or glucocorticoid-remedible aldosteronism, in which one finds hypokalemia, metabolic alkalosis, and hypertension. Hyperkalemia, metabolic acidosis, and salt-wasting can improve with age in autosomal dominant pseudohypoaldosteronism Type 1, which is typically mild. The autosomal recessive pseudohypoaldosteronism Type 1 is much more severe and does not improve with age. Gordon's syndrome features hypertension and also does not improve with age. Mutations in *WNK1* and *WNK4* are found in patients with Gordon's syndrome.

Reference

Geller DS, Rodriquez-Soriano J, Vallo Boado A, et al. (1998) Mutations in the mineralocorticoid receptor gene cause autosomal dominant pseudohypoaldosteronism Type 1. Nat Genet 19:279–281

CASE 19

Mutations in the *UMOD* gene encoding the Tamm-Horsfall protein has been found in patients with which ONE of the following pairs of overlapping syndromes?

A. Bartter and Gitleman syndrome
B. Lowe syndrome and Dent's disease
C. Familial juvenile hyperuricemic nephropathy and medullary cystic kidney disease Type 2
D. Liddle syndrome and glucocorticoid-remediable aldosteronism
E. Autosomal dominant and autosomal recessive distal renal tubular acidosis

The correct answer is C. Familial juvenile hyperuricemic nephropathy and medullary cystic kidney disease Type 2 is associated with mutations in the *UMOD* gene. It is not known why the gene encoding the Tamm-Horsfall protein should be associated with hyperuricemia, but it may be worth noting that both the Tamm-Horsfall protein and paracellin-1 are expressed in the thick ascending limb of the Loop of Henle, and mutations in both are associated with hyperuricemia. The four genes mutated in Bartter syndrome are different from the *NCCT* gene that is mutated in Gitelman's syndrome, and the same is true for Low's syndrome and Dent's disease, Liddle's syndrome and glucocorticoid-remediable aldosteronism, and both the autosomal recessive and dominant forms of distal renal tubular acidosis.

Reference

Hart TC, Gorry MC, Hart PS, et al. (2002) Mutations of the UMOD gene are responsible for medullary cystic kidney disease Type 2 and familial juvenile hyperuricemic nephropathy. J Med Genet 39:882–892

CASE 20

During evaluation for growth retardation, a five-year old girl is found to have hyperchloremic metabolic acidosis, hypokalemia, hypercalciuria, and evidence of rickets.

Which ONE of the following statements regarding inherited distal renal tubular acidosis (RTA) is correct?

A. It is associated with mutations in the sodium-bicarbonate transporter *NBC1*.
B. Patients with distal RTA and mutations in the basolateral anion exchanger *AE1* usually also have hereditary spherocytosis.
C. Mutations in the basolateral anion exchanger AE1 occur in both the dominant and recessive forms of distal RTA.
D. It goes away as the child gets older.
E. It is associated with ocular abnormalities.

The correct answer is C. The basolateral anion exchange AE1 transports bicarbonate to exit the basolateral surface of the Type A intercalated cells of the collecting duct, and is essential to producing acidic urine. Mutations in AE1 occur in both dominant and recessive forms of distal RTA. This same gene is expressed in the erythrocyte, but the mutations associated with distal RTA are different from those associated with hereditary spherocytosis, and patients with RTA invariably do not have spherocytosis. Inherited distal RTA is not associated with ocular abnormalities, although when it occurs in association with mutations in the B1 subunit of the V-type proton ATPase, it may be associated with sensorineural deafness. The sodium-bicarbonate transporter NBC1 is expressed in the proximal tubular cell and in the eye, and mutations in this gene are associated with inherited proximal RTA and ocular abnormalities. Inherited distal RTA does not typically improve with age.

Reference

Karet FE (2002) Inherited distal renal tubular acidosis (2002) J Am Soc Nephrol 13:2178–2184

CASE 21

Several children in a family have impaired growth and chronic metabolic acidosis.

Which ONE of the following choices would most strongly suggest proximal rather than distal renal tubular acidosis?

A. Uric acid nephrolithiasis
B. Requirement for large doses of bicarbonate to assure adequate growth
C. Hypokalemia
D. Bone disease
E. Nephrocalcinosis

The correct answer is B. When metabolic acidosis results from failure to regenerate bicarbonate in the proximal renal tubule, large doses of bicarbonate replacement are often required to assure adequate growth. Hypokalemia is associated with both proximal and distal RTA. Bone demineralization and nephrocalcinosis are typical features of distal RTA, although rickets can accompany proximal RTA as well, and nephrocalcinosis can occur in some settings of proximal RTA (renal Fanconi syndrome). Uric acid nephrolithiasis occurs in patients with a persistently acid urine, which is not a feature of renal tubular acidosis.

References

Alper SL (2002) Genetic diseases of acid-base transporters. Annu Rev Physiol 64:899–923
Karet FE (2002) Inherited distal renal tubular acidosis. J Am Soc Nephrol 13:2178–2184

CASE 22

A 12-year old boy is being evaluated for progressive renal insufficiency. He has had evidence of the renal Fanconi syndrome with aminoaciduria and low molecular weight proteinuria for the past several years. There is evidence for hypophosphatemic rickets, and he has hyperchloremic metabolic acidosis. Family history includes a maternal uncle and maternal grandfather who both reached end-stage renal disease with evidence of similar features. He has mental retardation and was born with cataracts.

Which ONE of the following choices is the MOST likely diagnosis?

A. Cystinosis
B. Lowe syndrome
C. Dent's disease
D. Autosomal dominant distal renal tubular acidosis
E. Primary hyperoxaluria

The correct answer is B. This boy has features of a generalized Fanconi syndrome, hypophosphatemic rickets, renal failure, and a family history consistent with x-linked inheritance. These features alone would be consistent with either Lowe

syndrome or Dent's disease, but several observations are valuable in distinguishing these two entities. Hyperchloremic metabolic acidosis is a common feature in Lowe syndrome but not Dent's disease. Renal failure commonly occurs at an earlier age in Low's syndrome than in Dent's disease, most often not developing until the third or fourth decade in Dent's disease. Mental retardation and congenital cataracts are typical features of the oculocerebrorenal syndrome of Lowe but not of Dent's disease.

Cystinosis can also be associated with the Fanconi syndrome, metabolic acidosis, renal failure, and ocular and neurologic abnormalities. The eye findings in cystinosis, however, involve the retina (or, in the juvenile form, the cornea) rather than the lenses. Furthermore, cystinosis is an autosomal disease, and in this family there is strong evidence of x-linked inheritance. Distal RTA and primary hyperoxaluria are also autosomal diseases, and neither would explain the full range of clinical abnormalities in this boy.

Reference

Charnas LR, Bernardini I, Rader D, et al. (1991) Clinical and laboratory findings in the oculocerebrorenal syndrome of Low, with special reference to growth and renal function. N Engl J Med 324:1318–1325

CASE 23

The mother of a 16-year old Caucasian boy seeks your advice regarding prognosis and future treatment of her son who has recently been diagnosed as having Alport syndrome. Her husband is healthy, but her grandfather died of chronic kidney failure. Her son currently has mild sensorineural hearing impairment, lenticonus, and well-controlled hypertension (BP 130/82 mmHg) on an ACE inhibitor. His serum creatinine is 1.4 mg/dl, and his protein excretion is 1.0 g/day. One year ago, he underwent genetic testing as a part of a research study and was found to have deletion mutation of the *COL4A5* gene of the X-chromosome.

Which ONE of the following choices best describes the clinical course that this patient is most likely to follow?

A. His renal failure is not likely to progress, and renal transplantation will not be needed.
B. His renal failure is likely to progress, and renal transplantation can be considered to be associated with a low risk (<5%) of post transplant glomerulonephritis.
C. His renal failure is likely to progress, and renal transplantation would be associated with a moderate risk (15% or more) of post-transplant glomerulonephritis.
D. His renal failure is likely to progress, but his hearing impairment is not likely to progress.

E. His renal failure is likely to progress, and renal transplantation would be associated with a high probability of recurrent disease.

The correct answer is C. This patient has the classic form of Alport syndrome due to a mutation (large deletion) of the *COLA4A5* gene on the x-chromosome (xq22). Large deletion mutations of this gene have been associated with progressive renal disease and a substantially higher risk of the development of anti-glomerular basement membrane (GBM) autoantibody-induced glomerulonephritis in the renal allograft. In patients with this type of mutation, the risk of anti-GBM nephritis in the allograft may be as high as 15%. Nearly all such post-transplant glomerulonephritis occurs in patients with the large deletion type of mutation.

Reference

Jais JP, Knebelman B, Giatras I, et al. (2000) X-linked Alport syndrome: Natural history in 195 families and genotype-phenotype correlations in males. J Am Soc Nephrol 11: 649–657

CASE 24

A 61-year old woman with ADPKD has recently begun treatment with hemodialysis and seeks your advice regarding evaluation of her 19-year old grandson, who is asymptomatic but anticipating marriage. He has recently undergone a renal ultrasound examination that disclosed no abnormalities.

What advice would you give to the grandson?

A. No further evaluation is needed because he is almost certainly unaffected.
B. Further evaluation with magnetic resonance imaging of the kidneys is needed to determine if he is affected.
C. Further evaluation with genetic testing for mutations on chromosome 16 is needed to determine if he is affected.
D. Further evaluation with genetic testing for mutations on chromosome 4 is needed to determine if he is affected.
E. No further testing is needed because the results are likely to be inconclusive.

The correct answer is A. Autosomal dominant polycystic kidney disease (ADPKD) is due to mutations in at least three separate genetic loci. ADPKD Type 1 is due to mutations of the polycystin-1 gene located on chromosome 16 (16p13.3). It is the most common form, accounting for about 85% of the cases. ADPKD Type 2 is due to mutations of the polycystin-2 gene located on chromosome 4 (4q21–23). It accounts for about 15% of cases. A third locus has been identified, but the gene has not yet been cloned.

This patient almost certainly has ADPKD Type 2 due to a mutation of the polycystine gene on chromosome 4. Patients with ADPKD Type 2 are usually much older at the time of discovery and have a slower progression of disease. Screening of offspring after age 30 (with ultrasound or CT) is highly effective in detecting affected individuals. Further testing with CT or MRI is likely to confirm the findings by ultrasound, but this issue has not been well studied in ADPKD Type 2. Screening individuals with a family history of ADPKD using genetic testing for gene mutations is the gold standard to identify those with the disease.

Reference

Torra R, Badenas C, Perez-Oller L, et al. (2000) Increased prevalence of polycystic kidney disease Type 2 among elderly polycystic patients 36 :728–734

CASE 25

A 12-year old girl presents with hematuria. Her previous medical history is unremarkable. The family history is notable for the neonatal death of a young brother due to respiratory insufficiency and renal cystic disease. An abdominal sonography revealed an enlarged liver with dilated intrahepatic bile ducts, splenomegaly, evidence of portal hypertension, and enlarged echogenic kidneys.

Which ONE of the following disorders is MOST likely present in this patient?

A. Autosomal recessive polycystic kidney disease (ARPKD)
B. Isolated congenital hepatic fibrosis
C. Nephronophthisis due to mutations in *NPHP1*
D. Autosomal dominant polycystic kidney disease due to mutations in *PKD1*
E. Isolated autosomal dominant polycystic liver disease

The correct answer is A. In ARPKD, affected children typically present *in utero* with enlarged echogenic kidneys, as well as oligohydramnios secondary to poor urine output. Approximately 30% of the affected neonates die shortly after birth as a result of severe pulmonary hypoplasia and secondary respiratory insufficiency. Among the survivors, the clinical phenotype variably includes systemic hypertension, renal insufficiency, and portal hypertension due to portal tract fibrosis. Marked interfamilial variation has been described in ARPKD and likely reflects the influence of modifier genes. Therefore, ARPKD (choice A) most likely fits the clinical scenario described. Isolated congenital hepatic fibrosis is by definition confined to the biliary tract. The other incorrect choices represent renal cystic diseases not typically associated with symptomatic congenital hepatic fibrosis.

Reference

Kaplan BS, Kaplan P, de Chadarevian JP et al. (1988) Variable expression of autosomal recessive polycystic kidney disease and congenital hepatic fibrosis within a family. Am J Med Gent 29:639–647

CASE 26

An 18-year old man is referred for evaluation of elevated serum creatinine (1.9 mg/dl). His maternal grandfather died of kidney failure and his mother started on dialysis when she was 48-years old. Physical examination is unremarkable except for a BP of 134/80 mmHg. Laboratory evaluation reveals a serum creatinine of 2.0 mg/dl, uric acid 7.5 mg/dl, BUN 36 mg/dl, and bicarbonate 22 mEq/l. A 24-hour urine volume is 3600 ml and total protein excretion is 150 mg. Urine sediment is normal. Ultrasonography reveals normal-sized kidneys with increased echogenicity and a single 2-cm cyst in the right kidney. Gadolinium-enhanced MRI showed multiple small cysts ranging from 3 mm to 2 cm in diameter in the corticomedullary region.

Which ONE of the following is the MOST likely diagnosis?

A. Nephronophthisis
B. Medullary cystic kidney disease
C. Herediatary nephritis
D. Autosomal dominant polycystic kidney disease
E. Autosomal recessive polycystic kidney disease

The correct answer is B. The family history of kidney failure with an autosomal dominant pattern of inheritance, and the imaging studies support a diagnosis of medullary cystic kidney disease as the cause of renal insufficiency. The diagnosis of nephronophthisis can be excluded because this is an autosomal recessive disorder that leads to end-stage renal failure in childhood or adolescence. The absence of microhematuria and proteinuria are not consistent with a diagnosis of hereditary nephritis as the cause of renal insufficiency. The development of renal insufficiency in ADPKD is always associated with marked renal enlargement. The autosomal dominant pattern of inheritance and the absence of findings consistent with congenital hepatic fibrosis rule out the diagnosis of autosomal recessive polycystic kidney disease.

References

Betz R, Rensing C, Otto E, et al. (2000) Children with nephronophthisis. J Pediatr 136:828–831
Hildebrandt F, Jungers P, Robino C et al. (2001) Nephronophthisis and medullary cystic kidney disease and medullary sponge kidney disease, In: Diseases of Kidney, 7th, edited by Schrier R, Philadelphia, Lippincott, Williams and Wilkins, pp 521–528

CASE 27

Fetal renal enlargement and increased echogenicity are noted during a routine antenatal sonogram in a 27-year old woman with a 30-week gestation. Hexadactyly is also noted. The bladder and amniotic fluid are normal. There is no history of consanguinity or inherited diseases in the family.

Which ONE of the following choices is the MOST correct diagnosis?

A. Autosomal dominant polycystic kidney disease
B. Autosomal recessive polycystic kidney disease
C. Nephronophthisis
D. Joubert syndrome
E. Bardet-Biedle syndrome

The correct answer is E. The presence of hexadactyly makes the diagnosis of Bardet-Biedle syndrome likely. Hexadactyly is not a feature of autosomal dominant polycystic kidney disease, autosomal recessive polycystic kidney disease, nephronophthisis, or Joubert syndrome.

Reference

Cossart M, Eurin D, Didier F et al. (2004) Antenatal renal sonographic anomalies and postnatal follow-up of renal involvement in Bardet-Biedle syndrome. Ultrasound Obstet Gynecol 24:51–54

CASE 28

A 16-year old boy presents with a three-year history of radiographic kidney stones. His serum calcium is 12.4 mg/dl and intact PTH is 365 pg/ml. A computed tomography of the abdomen reveals a few small renal cysts and bilateral kidney stones. A sestamibi scan reveals an enlarged parathyroid gland. His father had polycystic kidneys and died years ago from metastatic parathyroid carcinoma. No one else in the family is known to have autosomal dominant polycystic kidney disease.

Which ONE of the following choices is the MOST likely diagnosis?

A. Autosomal dominant polycystic kidney disease
B. Multiple endocrine neoplasia Type 1
C. Multiple endocrine neoplasia Type 2
D. Hyperparathyroidism-Jaw Tumor syndrome
E. Von Hippel-Lindau disease

The correct answer is D. The association of familial hyperparathyroidism, renal cysts, and the history of parathyroid carcinoma should raise the possibility of Hyperparathyroidism-Jaw Tumor syndrome in the differential diagnosis. Multiple endocrine neoplasia Types 1 and Type 2 are not associated with renal cystic disease. Autosomal dominant polycystic kidney disease and primary hyperparathyroidism are not included in the family history of hyperparathyroidism. Hyperparathyroidism is not a feature of Von Hipple-Lindau disease.

Reference

Cavaco BM, Guerra L, Bradley KJ (2004) Hyperparathyroidism-jaw tumor syndrome in Roma families from Portugal is due to a founder mutation of the *HRPT2* gene. J Clin Endocrinol Metab 89:1747–1752

CASE 29

A 10-year old boy presents with acute renal failure. Hemoglobin 7 g/dl. Platelet count 15,000/ml, and LDH 5510 U/l. There are numerous schistocytes on the blood smear. The chest x-ray shows small bilateral pleural effusions. Echocardiography reveals a reduced left-ventricular ejection fraction. He has a history of recurrent hemolytic anemia and thrombocytopenia since age three. He was treated with steroids and had splenctomy when he was five-years old. vWF-cleaving protease (vWF-CP) activity was found to be 0% (normal >40%). vWF-CP auto-antibodies were negative.

Which ONE of the following statements regarding this patient is FALSE?

A. His parents have low vWF-CP activities.
B. He has homozygous or compound heterozygous *ADAMTS13* gene mutations.
C. Treatment should include plasma exchange with fresh frozen plasma.
D. Infusions of fresh frozen plasma every two weeks to maintain vWF-CP activity >3% is sufficient to prevent relapses of thrombotic thrombocytopenic purpura.
E. None of the above

The correct answer is C. The history of recurrent episodes of microangiopathic hemolytic anemia with undetectable vWF-cleaving protease activity and absence of vWF-CP autoantibodies strongly suggest the diagnosis of inherited thrombotic thrombocytopenic purpura (TTP). Inherited TTP is a recessive disorder caused by homozygous *ADAMTS13* mutations. Carriers of *ADAMTS13* gene mutations can have partially reduced vWF-CP activities. Transfusions of *ADAMTS13* (fresh frozen plasma or cryosupernatant) to maintain the vWF-CP activity over 3% is sufficient to prevent relapses. The only false statement is C. In the absence of *ADAMTS13* autoantibodies, plasma exchange is not necessary.

Reference

Koo B, Oh D, Chung SY (2002) Deficiency of von Willebrand factor-cleaving protease activity in the plasma of malignant patients. Thrombosis Re 105:471–476

CASE 30

A five-year old female presents with anasarca. Her BP is 92/60 mmHg. The laboratory tests show serum creatinine 0.7 mg/dl, albumin 1.6 g/dl, and cholesterol 482 mg/dl. Urine protein 6.1 g/24 hours. Oval fat bodies are found in the urine sediment.

Which ONE of the following statements regarding the evaluation of idiopathic nephritic syndrome in childhood is TRUE?

A. Children with idiopathic nephritic syndrome benefit from genetic testing for *NPHS2* (podocin) mutations because the results will be helpful in determining whether treatment with steroid is indicated.
B. Children with steroid-resistant idiopathic nephritic syndrome benefit from genetic testing for *NPHS2* (podocin) mutations because the results will be helpful in planning for renal transplantation.
C. The majority of children with steroid-resistant idiopathic nephritic syndrome have *NPHS2* (podocin) mutations.
D. Age of onset and severity of steroid-resistant nephritic syndrome are unrelated to the type of *NPHS2* mutations.
E. *NPHS2* mutation is a good marker for the disease but is unrelated to the cause of the syndrome.

The correct answer is B. Patients with *NPHS2* mutations are less likely to have a recurrence of FSGS in the renal transplant than those without. In addition, because of the possibility that heterozygous *NPHS2* mutations could make the recipient and the donor more susceptible to the development of proteinuria and FSGS, caution has been recommended before considering transplantation from a living donor carrying a *NPHS2* mutation. Minimal change disease responsive to administration of steroids is the most common cause of childhood nephratic syndrome. Treatment with steroids is indicated without need of renal biopsy or genetic testing for *NPHS2*. Choice A is therefore incorrect. *NPHS2* mutations are found in up to 30% of children with steroid-resistant idiopathic nephritic syndrome. Therefore, choice C is wrong. Choice D is also wrong because patients with mutations leading to retention of podocin in the endoplasmic reticulum have an earlier onset of the disease and more severe phenotype than those with homozygous mutations expressed on the plasma membrane. Choice E is incorrect because disease-causing podocin mutations cause nephritic syndrome by failing to recruit nephron into rafts either because of retention in the endoplasmic reticulum or failure to associate with raft in the plasma membrane.

Reference

Ruf RG, Lichtenberger A, Karle SM, et al. (2004) Patients with mutations in *NPHS2* (podocin) do not respond to standard steroid treatment of nephritic syndrome. J AM Soc Nephrol 15: 722–732

CASE 31

A 19-year old female is found to have microscopic hematuria without proteinuria during a routine medical examination. She has been in excellent health and the remainder of her examination, including BP and general chemistries are normal. She has a normal excretory urogram and cystoscopy. The question of hereditary nephritis is raised because her mother also has microscopic hematuria. She is concerned about being a carrier for x-linked Alport syndrome, because she is planning to raise a family.

Which ONE of the following options would be BEST to evaluate the patient for carrier status of x-linked Alport syndrome?

A. Hearing test and eye examination
B. Skin biopsy
C. Kidney biopsy
D. *COL4A5* mutation analysis
E. Slit lamp testing

The correct answer is B. The immunohistochemical study of a skin biopsy is diagnostic in approximately 80% of patients with x-linked Alport syndrome, and avoids the need of a more invasive renal biopsy. Confocal microscopy of the skin with three-dimensional reconstruction of the epidermal basal membrane increases the sensitivity of the test. *COL4A5* is usually absent from epidermal and glomerular basal membranes in male patients and has a segmental distribution in female patients. Testing for *COL4A5* mutation using sequence analyses identifies more than 60% of mutations in individuals with x-linked Alport syndrome and could be considered as an alternative, but at present it is probably less sensitive than a skin biopsy. Sensorineural deafness, anterior lenticonus, pigmentary changes in the perimacular region, and corneal dystrophy (rare) or alterations in the corneal epithelial basement membrane are features of Alport syndrome. Their occurrence in females is too low to be used for diagnosis.

References

Kashtan CE (2004) Familial hematuria due to Type IV collagen mutations: Alport syndrome and thin-basement membrane nephropathy. Curr Opin Pediatr 16:177–181

Muda AO, Massella L, Giannakakis K, et al. (2003) Confocal microscopy of the skin biopsy in the diagnosis of X-linked Alport syndrome. J Invest Dermatol 121:208–211

CASE 32

A 10-month old boy presents with failure to thrive. Evaluation reveals metabolic acidosis in the context of Fanconi syndrome. His neurocognitive status is appropriate for his age and there is no family history of a similar disorder.

Which ONE of the following genetic disorders is MOST likely present in this boy?

A. Cystinosis due to *CTNS* mutations
B. Lowe syndrome due to *OCRL* mutations
C. Dent's disease due to *CLCN5* mutations
D. Dent's disease due to *ORCL* mutations
E. Lowe syndrome due to *CLCN5* mutations

The correct answer is A. Cystinosis is an autosomal recessive lysosomal storage disease. It is the most common inherited cause of the renal Fanconi syndrome, as well as a multi-system disorder that affects the eyes, muscles, central nervous system, lungs, and various endocrine organs. These patients, however, typically do not have neurocognitive impairment. In contrast, both Lowe syndrome and Dent disease are x-linked disorders. In Lowe syndrome, full expression of the Fanconi syndrome typically does not occur in infancy, whereas in Dent disease metabolic acidosis due to the proximal tubular dysfunction is rarely seen.

Reference

Gahl W, Thoene J, Schneider J (2002) Cystinosis. N Engl J Med 347:111–121

CASE 33

A five-year old girl presents with polyuria and failure to thrive. Diagnostic evaluation reveals that she has hypomegnesemia and hyperuricemia.

Which ONE of the following associated clinical features would MOST strongly suggest that she has defects in paracellin-1 function (*CLDN16* mutations)?

A. Autosomal recessive inheritance
B. Association of hypomagnesemia and nephrocalcinosis
C. Association of hypomagnesemia and mild hypokalemic metabolic alkalosis
D. History of neonatal seizures in a maternal cousin
E. Normal renal function

The correct answer is B. Familial hypomagnezemia with hypercalciuria and nephrocalcinosis is an autosomal recessive disorder caused by defects in

paracellin-1 function. This disorder is distinguished from other magnesium-losing tubular disorders by clinical presentation during early childhood with recurrent urinary tract infections, polyuria/polydipsia, isosthenuria, and renal stones. Affected children typically have bilateral nephrocalcinosis, and develop progressive renal failure. Some seek medical attention due to associated failure to thrive, vomiting, abdominal pain, titanic episodes, or generalized seizures. Besides hypomagnesemia, biochemical abnormalities include hypermagnesiuria and hypercalciuria, and impaired GFR is often detected at the time of diagnosis. A substantial percentage of patients have an incomplete distal renal tubular acidosis, hypocitraturia, and hyperuricemia.

Reference

Konard M, Weber S (2003) Recent advances in molecular genetics of hereditary magnesium-losing disorders. J Am Soc Nephrol 14:249–260

CASE 34

A four-year old girl presents with metabolic acidosis and failure to thrive. Diagnostic evaluation reveals an isolated proximal renal tubular acidosis without associated features of renal Fanconi syndrome. She does have ocular abnormalities, including cataracts.

Which ONE of the following disorders is the MOST likely cause of her syndrome?

A. Cystinosis due to *CTNS* mutations
B. Lowe syndrome due to *OCRL* mutations
C. Lowe syndrome due to *CLCN5* mutations
D. Isolated proximal RTA due to *SLC4A4* mutations
E. Carbonic anhydrase II deficiency

The correct answer is D. RTA results from defective bicarbonate reabsorption and is commonly associated with a generalized defect in proximal tubular function, e.g., cystinosis or Lowe syndrome. However, isolated proximal renal tubular acidosis can occur in association with ocular abnormalities, including glaucoma, band keratopathy, and cataracts. This autosomal recessive disorder results from loss-of-function mutations in *SLC4A4*, the gene encoding the electrogenic Na^+-bicarbonate exchanger, NBCe1. The clinical presentation in this patient is most consistent with isolated proximal RTA due to *SLC4A4* mutations.

Reference

Igarashi T, Sekine T, Inatomi J et al. (2002) Unraveling the molecular pathogenesis of isolated proximal renal tubular acidosis. J Am Soc Nephrol 13:2171–2177

CASE 35

A seven-year old male presents with headache and severe hypertension. Diagnostic evaluation is notable for hypokalemic metabolic alkalosis, and there is no evidence for renal artery stenosis or coarctation of the aorta. His urinary 18-hydroxycortisol is within the normal range. His family history is notable for early-onset hypertension in his mother and several maternal cousins. While his hypertension is refractory to therapy with ACE inhibitors, angiotensin-receptor blockers, and calcium channel antagonists, he responds well to amiloride therapy.

Which ONE of the following disorders is MOST likely to provide the diagnosis?

A. Liddle syndrome (β or γ subunits of epithelial sodium channels) (ENaCl)
B. Glucocorticoid-remediable aldosteronism
C. Gordon syndrome (mutations involving *WNK1*)
D. Gordon syndrome (mutations involving *WNK4*)
E. Autosomal dominant pseudohypoaldosteronism Type 1

The correct answer is A. The constellation of clinical findings and laboratory data are most consistent with the diagnosis of Liddle syndrome. Glucocorticoid-remediable aldosteronism is typically associated with high urinary 18-hydroxycortisol excretion, which was not observed in this patient. Hypokalemic metabolic alkalosis is inconsistent with Gordon syndrome, which is typically associated with hyperkalemic metabolic acidosis.

Reference

Warnock DG (2001) Liddle syndrome: genetics and mechanisms of Na^+ channel defects. Am J Med Sci 322:302–307

CASE 36

A 12-year old boy is noted to be hypertensive during a routine medical examination. He is otherwise in excellent physical condition. Further evaluation reveals mild hyperkalemic hyperchloremic metabolic acidosis and hypercalciuria.

Which ONE of the following disorders is the MOST likely cause of this patient's syndrome?

A. Liddle syndrome
B. Gordon syndrome
C. Glucocorticoid-remediable aldosteronism
D. Autosomal dominant distal renal tubular acidosis
E. Activating mutation in the mineralocorticoid receptor

The correct answer is B. Among the single-gene disorders causing low-renin hypertension, Gordon syndrome is distinguished by the associated hyperkalemia and metabolic acidosis. In contrast, Liddle syndrome, glucocorticoid-remediable aldosteronism, and an activating mutation in the dominant distal RTA, are not typically associated with hypertension.

Reference

O'Shaughnessy KM, Karet FE (2004) Salt handling and hypertension. J Clin Invest 113: 1075–1081

CASE 37

An 11-year old girl presented with short stature and was found to have chronic renal failure. The parents are cousins, but there was no family history of renal disease. There was a history of polydipsia, polyuria, and salt craving. Her growth parameters were below the third percentile. BP was normal. Neurological examination was normal. There were no other abnormal findings. Urinalysis was negative for protein, glucose, and blood. The pH was 7.0, and specific gravity was 1.008. GFR was 12 ml/min. Hemoglobin is 7.0 g/dl, WBC 11,500/mm^3 platelet 269,000/mm^3. Serum sodium was 130 mEq/l, potassium 4.0 mEq/l, chloride 111 mEq/l, bicarbonate 7 mEq/l, BUN 80 mg/dl, creatinine 6.7 mg/dl, calcium 8.0 mg/dl, and phosphorous 6.9 mg/dl. Renal ultrasound showed bilateral small kidneys with increased echogenicity. A contrast cystogram was normal. A slit lamp examination was normal and an audiometry revealed no sensineural loss.

What is the most likely diagnosis?

A. Cystic nephroblastoma
B. Medullary sponge kidney
C. Familial juvenile nephronophthisis
D. Polycystic kidney disease
E. Tuberosclerosis

The correct answer is C. Familial juvenile nephronophthisis (JNPH) and medullary cystic kidney disease (MCKD) are similar diseases that develop in children and adults, respectively. NPH is an autosomal recessive disorder that is linked to mutations of genes located at at least four chromosome sites. NPH may be associated with cerebro-retinal degeneration and hepatic fibrosis. Familial INPH-1 has been mapped to chromosome 2 (2q12–13). The gene *NPH-1* is responsible for the synthesis of nephrocystin. These patients develop ESRD in a median age of 13 years. Familial adolescent *NPH-3* has been mapped to chromosome 3 (3q21–22). Patients with *NPH-3* mutations develop ESRD at a median age of 19 years. *NPH-2* is the autosomal recessive form, having an infantile, perinatal or prenatal onset. It is

linked to chromosome 9q22–31. A fourth gene locus, *NPH-4*, has been postulated, accounting for rare cases. Molecular genetic diagnosis is possible.

The clinical features of failure to thrive, polyuria, polydipsis, anemia, and ESRD in the presence of normal BP and normal urinalysis are most likely consistent with NPH.

Reference

Hildebrandt F, Jungers P, Robino C, et al. (2001) Nephronophthisis and medullary cystic kidney disease and medullary sponge kidney disease, In: Diseases of Kidney, 7th ed, edited by Schrier R, Philadelphia, Lippincott, Williams and Wilkins, pp 521–528

CASE 38

A three-week old boy developed nephrotic syndrome. His mother had previously had a miscarriage at 12 weeks gestation. His birth weight was 3.3 kg following an uneventful pregnancy, labor, and delivery. The placenta was large, but not weighed. His parents had no Finnish ancestry. Urine showed 4+ protein, 10–20 red blood cells, and 2–5 granular casts. BP was 110/49 mmHg. Serum albumin was 1.2 g/dl and 24-hour urine contained 1.2 g protein. Serum creatinine was 4.1 mg/dl, and GFR 11 ml/min. He died of pneumonia in the 6th week of life.

What is the most likely diagnosis?

A. Congenital syphilis
B. Diffuse mesangeal glomerulosclserosis
C. Wilms tumor
D. Congenital CMV infection
E. All of the above

The correct answer is E. Nephrotic syndrome that is present at birth or develops in the first few weeks of life may be due to several disorders including intrauterine infections (congenital syphilis, congenital cyromegalovirus disease, congenital rubella, congenital toxoplasmosis), focal and segmental glomerulosclerosis, diffuse glomerulosclerosis, and Wilms tumor, in addition to the classic Finnish type of congenital nephritic syndrome. The Finnish type of congenital nephritic syndrome is due to mutations of the *NPHS-1* gene located on chromosome 19 (19q13.1). This gene determines the synthesis of nephrin, which is a major constituent, or the slit pore diaphragm of the visceral glomerular epithelial cells. These mutations give rise to a nearly total deficiency of nephrin, absence of the slit foot processes, and a marked increase in glomerular permeability to proteins. Most patients develop renal failure and die of infections or thrombosis before five years of age unless vigorously supported by anticoagulants, diuretics, albumin infusions, and antibiotics, as needed. Angiotensin inhibitors, NSAIDs, or glucocorticoids do not reduce

proteinuria or prolong life. Renal transplantation may be life-saving, but a new disease may develop in the graft due to the formation and deposition of antinephrin antibodies.

Reference

Hamed RMA, Shomaf M (2001) Congenital nephritic syndrome: a clinico-pathological study of thirty children. J Nephrol 14:104–109

CASE 39

A 14-month old girl was admitted to the hospital because of respiratory distress and puffy eyes. She was one of three normal siblings. The 23-year old mother had had three spontaneous abortions during the 6^{th}-8^{th} months of pregnancy. A fetal karyotype was reported as normal. The patient did not experience any neonatal complications. She began failing to thrive at five months of age. Her food intake diminished and she experienced breathlessness during sleep. Medical care was not sought because of a lack of health care insurance. Physical examination revealed a protruding forehead, absent nasal bridge and a macrocephalic head. She had a disproportional short-limbed short stature.

BP was 130/90 mmHg. Eye examination was normal. Echocardiography demonstrated right ventricular hypertrophy. Urinalysis was unremarkable except for 1+ proteinuria. Hyperchloremic metabolic acidosis (pH 7.24, bicarbonate 16 mEq/l, chloride 124 mEq/L), hyperkalemia (5.5 mEq/l), and hyperphosphatemia (6.5 mg/dl) were wounds in association with renal insufficiency (BUN 35 mg/dl, serum creatinine1.8 mg/dl, GFR 40 ml/min/1.73 m^2). Skeletal x-ray revealed long, narrow bell-shaped thorax with short horizontal ribs, short limbs and distal phalanges. Renal sonogram showed hyperechoic cortical zones, compressed pyramids, and a mild dilatation of both peeves. A head ultrasound demonstrated hydrocephalus. A ventriculostomy was performed to treat the hydrocephalus. She subsequently developed end-stage renal disease and underwent a successful cadaveric renal transplantation at three years of age.

What disorder associated with chronic renal failure can be diagnosed on the basis of the abnormalities presented in this patient?

A. Ellis-van Creveld syndrome
B. Ivemark syndrome (renal-hepatic-pancreatic dysplasia)
C. Barnes syndrome (thoracolaryngopelvic dysplasia)
D. Jeune syndrome (asphyxiating thoracic deformity)
E. Thoracopelvic dystosis

The correct answer is D. Asphyxiating thoracic dysplasia (Jeune syndrome) is a group of autosomal recessive osteochondrodysplasias that may involve the kidneys.

Patients with Jeune syndrome typically present at birth with a small bell-shaped thoracic cage. Many experience asphyxia, with or without pulmonary infection, within the first few weeks of life. Progressive renal failure usually occurs in those who survive childhood. Histology of the kidney shows manifestations of nephronophthisis.

The nature and degree of renal involvement is variable. Tubular dilatation and atrophy; interstitial fibrosis, glomerular sclerosis, cortical cysts, cystic dysplasia and diffuse cystic disease have been described. Early renal manifestations include proteinuria, proximal tubular dysfunction, polyuria, and hypertension. A link between Jeune syndrome and familial juvenile nephronophthisis and Laurence-Moon-Biedl syndromes has been suggested. Prenatal diagnosis of Jeune syndrome is possible. Present knowledge suggests that the locus of the gene associated with Jeune syndrome may be situated at 12p11.2p12.2.

Because of the absence of polydactyly, nail, tooth and heart defects, differentiation from other kinds of bone dysplasia such as Ellis-van-Creveld syndrome is easy. Ivemark syndrome can be excluded because of the absence of billiary dysgenesis and pancreatic fibrosis. Barnes syndrome and thoracopelvic dysplasia are excluded because they have an autosomal dominant mode of inheritance.

Radiologic manifestations of Jeune syndrome are variable and include a small thoracic cage with short ribs, and irregular costochondral junctions. The pelvis exhibits hypoplastic iliac wings and a horizontal angle of the acetabular roof. The long bone is often short and wide.

References

Donaldson MCD, Warner AA, Trompeter RS, et al. (1985) Familial juvenile nephronophthisis, Jeune's syndrome and associated disorders. Arch Dis Child 60:426–434

Gruskin AB, Baluarte HJ, Cote ML, et al. (1974) The renal disease of thoracic asphyxiate dystrophy. Birth Defects 10:44–50

Nagai T, Nishimura G, Kato R, et al. (1995) Del (12) (p11.21p12.2) associated with an asphyxiating thoracic dystrophy or chondroectodermal dysplasia-like syndrome. Am J Med Genet 55: 8–16

CASE 41

A 22-month old girl was admitted for failure to thrive and abnormal movements for the past few weeks. She was the 1900g product of a 36-week twin pregnancy (the twin weighed 2500g and did well). She had multiple upper respiratory tract infections, a history of recurrent cyanotic episodes, with upward gaze deviation and generalized floppiness. Her feeding was poor with episodes of coughing and tussive emesis for the week preceding admission. She had moderate developmental delay. The family history was unremarkable for hereditary disorders, seizures, or renal abnormalities. Physical examination revealed an alert infant with a weight of 4.1 kg and height of 53 cm on the 25^{th} percentile. Her BP was elevated at 129/64 mmHg,

and her respiratory rate was 44/min. The heart rate was regular with a grade of 2/6 systolic ejection murmur at the left sternal border. There was no organomegaly on palpation of the abdomen. There was no cyanosis or peripheral edema. Cutaneous examination revealed a hypopigmented macula on the left abdomen, measuring $1.7 \times 2.4\,\mathrm{cm}$ in diameter, and multiple similar lesions on the chest and lower extremities. No focal neurological signs were present.

Laboratory data revealed a serum creatinine of 0.4 mg/dl, BUN of 18 mg/dl, and normal electrolytes. The hemoglobin was 12 g/dl with normal indices. Serum aldosterone and renin were normal. Urinalysis revealed a pH of 5.0, specific gravity of 1.008, and normal microscopic examination. A renal ultrasound examination revealed markedly enlarged kidneys (both kidneys measured 9.9 cm in length) with multiple noncommunicating cysts.

What is the most likely diagnosis?

A. Autosomal recessive polycystic kidney disease
B. Nephronophthisis
C. Multicystic kidney disease
D. Tuberous sclerosis
E. Medullary sponge kidney

The correct answer is D. The neurocutaneous syndrome—tuberous sclerosis—is inherited as a dominant trait, but 50% of cases appear to be new mutations. The most common skin abnormality is the hypopigmented macula, usually oval or leaf-shaped and present at birth in 80%–90% of patients. Other cutaneous lesions include adenoma sebaceous and shagreen patches. Central nervous system disease is common and presents as convulsions in most patients. Mental retardation is frequent. Sclerotic patches (tubers) are scattered throughout the cortical gray matter. The CT scan of the skull is often diagnostic and reveals intracerebral calcification. Cardiac rhabdomyomas are found in at least 50% of patients and may lead to arrhythmias.

The classic renal lesion of tuberous sclerosis is angiomyolipomas, which occur in 50%–80% of patients and often are bilateral and multiple. Renal cysts are the second most common renal lesions, and can be present with the angiomyolipomas. Large kidney cysts can be present at birth. The radiological appearance of the kidneys is often similar to that of adult-type polycystic kidney disease. The cysts are anechoic lesions varying in size from 2 mm to 2 cm, with thin uniform walls. Most children are asymptomatic—rarely are pain or hematuria the presenting symptoms. Proteinuria can develop. The incidence of renal carcinoma is less than 5%—surgical intervention is then indicated.

Infantile polycystic kidney disease, nephronophthisis, multicystic kidney disease, and medullary sponge kidneys are easily excluded in the absence of hypopigmented skin lesion and intracranial calcification.

References

Stapleton FB, Johnson D, Kaplan GW, et al. (1980) The cystic renal lesion in tuberous sclerosis. J Pediatr 97:574–579

Stillwell TJ, Gomez MR, Kelias PP (1987) Renal lesions in tuberous sclerosis. J Urol 138:477–481

CASE 42

An 18-month old boy was hospitalized because of seizures. At birth, he was found to have male pseudohermaphrodism with hypolastic phallus, penoscrotal hypospadias, urogenital sinus, and bilateral cryptorchidism. Karyotype was XY. On admission, BP was 130/90 mmHg. The child had generalized edema. The child was severely oliguric. Hemoglobin was 9.5 g/dl, white blood cells 14400/mm^3, platelet 565,000/mm^3, serum creatinine 4.8 mg/dl, BUN 53 mg/dl, serum sodium 138 mEq/l, potassium 6.5 mEq/l, calcium 8.3 mg/dl, phosphorus 6.8 mg/dl, total protein 5.6 g/dl, and albumin 1.6 g/dl. Urinalysis revealed proteinuria 4+ and microscopic hematuria. Renal ultrasound revealed a mass in the right kidney.

What was the cause of renal failure?

A. Drash syndrome
B. Congenital Thorch complex
C. Hereditary nephritic syndrome
D. Minimal change nephritic syndrome
E. Idiopathic focal and segmental glomerulosclerosis

The correct answer is A. The mass present in the right kidney was a Wilms' tumor and renal failure was due to diffuse mesangial sclerosis (DMS). The child had all the features diagnostic of what is now well-known as Drash syndrome. This is a case of congenital nephritic syndrome with a nephritic urinary sediment and severe renal insufficiency associated with ambiguous genitalia and Wilm's tumor. Most case of congenital nephritic syndrome is of the Finnish variety (FCNS). The major histological difference between diffuse mesangial and FCNS is the presence of global and segmental sclerosing glomerular lesions and crescents in DMS. Both types show cystic dilatation of the proximal tubules with fetal or immature glomeruli. Progression to end-stage renal disease occurs early in DMS. It is a late or absent feature of surviving infants with DMS.

References

Drash A, Sherman F, Hartmann WH, et al. (1970) A syndrome of psudo-hermaphroidism, wilm's tumor, hypertension, and degenerative renal disease. J Pediatr 76:585–593

Hamed RMA, Shomaf M (2001) Congenital nephritic syndrome: a clinico-pathological study of thirty children. J Nephrol 14:104–109

Schneller M, Braga SE, Moser H (1983) Congenital nephritic syndrome: clinico-pathological heterogeneity and prenatal diagnosis. Clin Nephrol 19:243–249

CASE 43

A three-week old male infant was referred with vomiting and renal failure. He was born following a normal pregnancy with normal antenatal ultrasound examinations. He was delivered by emergency C-section for breech presentation associated with fetal distress at 42 weeks. Birth weight was 3.4 kg, and Apgar scores were 9 and 10 at 1 and 5 minutes, respectively. Upon examination, there was there was edema of hands and feet, and he was dysmorphic with simple cup-shaped ears, short fingers with distal tapering, and flexed flexion deformity of two fingers of his hands. There was no organomegaly and genitalia were normal.

At three days he began vomiting and began to loose weight. Both parents are healthy unrelated Caucasians. The initial investigation revealed sodium 128 mEq/l, potassium 6.3 mEq/l, BUN 65 mg/dl, creatinine 4.5 mg/dl, bicarbonate 12 mEq/l, and uric acid 16.5 mg/dl. The full blood count was normal. Cultures of blood and urine were sterile. Pyloric ultrasound examination was normal. Renal ultrasound examination demonstrated bright kidneys, both 5 cm in length. He was treated with fluids, sodium bicarbonate, and broad spectrum antibiotics while awaiting the results of blood and urine cultures. He was discharged at 20 days, but because of persistent vomiting he was readmitted at age 23 days. He was mildly dehydrated. BP was 95/65 mmHg. Hemoglobin was 13.3 g/dl, white blood cell count 8,900/ml, platelet 250,000/ml, sodium 131 mEq/l, potassium 4.4 mEq/l, BUN 42 mg/dl, creatinine 3.1 mg/dl, calcium 8.3 mg/dl, phosphate 7.3 mg/dl, alkaline phosphatase 420 IU/l, albumin 2.9 g/dl, uric acid 14.5 mg/dl, aspatate aminotransferase 55 IU/l, pH 7.23, and bicarbonate 13 mEq/l. Urinalysis revealed pH 6.0, specific gravity 1.010, sodium 44 mEq/l, and potassium 8 mEq/l. A renal ultrasound demonstrated bilateral marked echogenicity with prominent medullary pyramid. Each kidney measured 5 cm in length. A 99m DTPA scan demonstrated perfusion but no function. A voiding cystoureterogram revealed bilateral grade 4 vesico-ureteric reflux. The karyotype was 46 XY. Nasogastric tube feeding was uninitiated and treatment with sodium bicarbonate and calcium carbonate supplements was commenced.

What is the most likely diagnosis?

A. Acute tubular necrosis
B. Lesch-Nyhan syndrome
C. Congenital cystic dysplastic kidneys
D. Nephronophthisis

The correct answer is B. The striking ultrasonic appearance of the kidneys and the clinical recognition of gout and the very high plasma uric acid level that was disproportionately raised relative to the high serum creatinine was an early clue to the presence of uric acid nephropathy, and led to the appropriate diagnostic study of measuring hypoxanthine guanine phosphoribosyl-transferase (HGPRT). Complete HGRPT deficiency is associated with presentation in infancy as Lesch-Nyhan syndrome. Uric acid overproduction is associated with developmental delay,

choreo-athetosis, and spasticity between 1 and 16 years. Gouty arthritis and tophi are seldom seen before puberty. Death usually occurs in the 2nd and 3rd decade due to renal failure or recurrent infections. Patients with a partial HGPRT deficiency often develop uric acid nephropathy and uric acid stones, but they do not develop the characteristic self-mutilation. HGPRT activity in lysed red cells is undetectable in both forms of clinical expression, but patients with partial deficiency demonstrate detectable activity in intact erythrocytes. HGPRT deficiency is x-linked, and thus both clinical syndromes occur only in males. Enzyme kinetic studies on fibroblasts of the mother were normal, implying a mutation in the case of our patient.

Although treatment with allopurinol, combined with alkalinization of the urine, may prevent the renal consequences of excess uric acid production, such therapy appears to have no effect on the distressing neurological manifestations of Lesch-Nyhan syndrome.

Reference

Holland PC, Dillon JM, Pincott J, et al. (1983) hypoxanthine guanine phosphoribosyl-transferase deficiency presenting with gout and renal failure in infancy. Arch Dis Child 58:831–833

Chapter 8
Glomerular, Vascular, and Tubulo-Interstitial Diseases

CASE 1

The mother of a three-year old Asian boy with steroid-sensitive idiopathic nephrotic syndrome seeks advice regarding future therapy for her son. He has had four relapses of the nephrotic syndrome in the last year, each time responding rapidly to oral prednisone. Relapses have occurred when prednisone was tapered to <20 mg every other day. He now has reduced stature for his age and developed a behavioral disorder believed to be due to excess glucocorticoids. Another physician has advised the mother that a 10-week course of oral cyclophosphamide is essential to control her son's disease and to prevent further relapses. The mother, however, is very fearful of the adverse side effects of cyclophosphamide.

Which ONE of the following statements is correct?

A. Alternate drugs, other than cyclophosphamide, are available to control the disease at an acceptable level of side effect.
B. Continuation of glucocorticoid therapy is the best option.
C. A course of cyclophosphamide is indicated and is preferable to all other options.
D. All therapy should be stopped while awaiting a spontaneous remission.
E. No treatment advice can be given unless a renal biopsy is performed.

The correct answer is A. This patient has a multiple relapsing, steroid-dependent form of idiopathic nephritic syndrome, almost certainly due to a minimal change lesion. Glucocorticoid complications have developed and alternative strategies of treatment are indicated. A renal biopsy is unlikely to contribute to therapeutic decision-making, even if a few focally sclerotic glomeruli were observed. Adjunctive therapy with cyclophosphamide, chlorambucil, cyclosporine, or levamisole would likely be associated with equivalent short-term results (remission of nephritic syndrome), but would have differing profiles of side effects. No treatment option is superior to another in terms of inducing a remission, and the decision on which to use is largely determined by the profile of adverse effects and the ability to produce a sustained remission without continuing treatment.

F. Assadi, *Clinical Decisions in Pediatric Nephrology.*

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References

Durkan AM, Hodson EM, Willis NS, et al. (2001) Immunosuppressive agents in childhood nephritic syndrome: a meta-analysis of randomized controlled trials. Kidney Int 59:1919–1927

Staderrmann MB, Lilien MR, van der Kar, et al. (2003) Is renal biopsy required prior to cyclophosphamide use in steroid sensitive nephritic syndrome? Clin Nephrol 60:315–317

CASE 2

A six-year old Caucasian boy presents with idiopathic nephrotic syndrome. Urine protein excretion is 6.2 g/d. A renal biopsy reveals diffuse mesangial proliferation and normal peripheral capillary walls. Mild lymphocytic infiltration is present in the interstitium. Immunofluorescence studies show extensive mesangial deposits of IgM and C3, but only traces of IgG and IgA. Electron microscopy shows mesangial proliferation, scattered small electron-dense deposits confined to the mesangium, foot-process effacement, and normal peripheral basement membranes.

Which ONE of the following features indicates a poor response to therapy and future prognosis?

A. Diffuse mesangial IgM deposition
B. Diffuse foot-process effacement
C. Male gender
D. Magnitude of proteinuria on initial examination
E. Absence of capillary wall electron-dense deposits

The correct answer is A. The findings are most typical of mesangial proliferative glomerulonephritis. The IgM deposits confer a worse prognosis and an increase in resistance to therapy with glucosteroids, and may signify a greater risk of evolution to focal segmental glomerulosclerosis. Male gender, the magnitude of proteinuria on initial examination, and findings by electron microscopy have little importance in guiding therapy.

Reference

Cohen AH, Adler SA (2001) Mesangial proliferative glomerulonephritis. In:Textbook of Nephrology, 4th ed., edited by Massry S and Glasscock RJ, Philadelphia, Lippincott, Williams and Wilkins, pp 717–719

CASE 3

A four-year old Africa-American boy develops idiopathic nephrotic syndrome associated with microscopic hematuria. His BP is 138/74 mmHg, and he has massive anasarca. His serum creatinine is 0.8 mg/dl, urine protein excretion is 12 g/day,

serum albumin is 1.8 g/dl, and the serum cholesterol is 480 mg/dl. Serum C3 and C4 concentrations are normal. Urinalysis reveals 10 to 15 erythrocytes per high-power field, numerous hyaline and granular and fatty acid casts, and oval fat bodies. The patient's mother refuses to permit a renal biopsy.

What would be the most appropriate initial therapy for the patient?

A. 40 mg/m^2 prednisone daily for two weeks, then 20 mg/m^2 every other day for an additional two weeks
B. 60 mg/m^2 prednisone daily for four weeks, then 40 mg/m^2 for an additional four weeks
C. 500 mg of intravenous methylprednisone daily for three doses; repeat monthly for six months
D. 5 mg/kg cyclosporin per day and 20 mg of prednisone every other day for four months
E. 2.5 mg/kg levamisole three times weekly for six months

The correct answer is B. This patient almost certainly has minimal change disease by clinical criteria. The initial treatment of choice is high dose daily prednisone for 4–6 weeks, followed by intermittent lower dose prednisone for an additional 4–6 weeks. IV methylprednisone will achieve equivalent short-term results but with a higher relapse rate. There is no need to consider alternative agents until a pattern of relapses has been determined during follow-up. Older male children with minimal change disease may require more intensive initial therapy. Low-dose, short-term prednisone treatment would likely be associated with a high-risk of relapse. A very low dose cyclosporine regimen could be used for older patients who refuse glucocorticoids or those who have contra-indications to steroid treatment.

Reference

Hiraoka M, Tsukara H, Haruke S, et al. (2000) Older boys benefit from higher initial prednisone therapy for nephrotic syndrome. Kidney Int 58: 1247–1252

CASE 4

A 16-year old African-American male is discovered to have idiopathic nephrotic syndrome and a reduced serum C3 level. His BP is 147/90 mmHg. Urine protein excretion is 5.3 g/day. Lupus, hepatitis B, and hepatitis C serologies are negative. Cryoglobulins are not found on repeated examinations. A renal biopsy shows the lesion of diffuse proliferative glomerulonephritis by light microscopy. Electron microscopy shows both subepithelial and subendothelial electron-dense deposits. The basement membrane is reduplicated, multilayered, and fenestrated.

In addition to control of BP with an ACE inhibitor, what would you recommend next?

A. 2.0 mg/kg cyclophosphamide per day and 20 mg of prednisone every other day for six months
B. 4.0 mg/kg cyclosporine per day and 20 mg of prednisone every other day for six months
C. 40 mg of prednisone every other day for 6 months, then 20 mg every other day for an additional six months
D. No additional therapy is advisable
E. 500 mg mycophenolate mofetile twice daily for six months

The correct answer is D. This patient with hypocomplementemia has the morphologic findings of membranoproliferative glomerulonephritis (MPGN), Type III. Recent retrospective studies of this subgroup of patients with MPGN indicate that glucocorticoid and/or immunosuppressive therapy is ineffective. Supportive therapy with renopreotecive agents (such as ACE inhibitor) should be employed.

Reference

Levin AM (1999) Management of membranoproliferative glomerulonephritis: Evidence based recommendations. Kidney Int 55:S41–S46

CASE 5

A seven-year old Hispanic boy with a rapidly progressive form of IgA nephropathy is placed on regular hemodialysis therapy for end-stage kidney disease. His brother (age 22) and an older adopted brother (age 24) both offer to donate a kidney. Both potential donors are healthy and have completely normal pretransplant medical evaluations. The older adopted brother is a 2-antigen mismatch, whereas the younger brother is also a 2-antigen mismatch (single haplotype match) with the patient.

Which ONE of the following choices would you recommend to the patient?

A. Renal transplantation is not appropriate because of the high risk of recurrence of IgA nephropathy and subsequent graft failure.
B. Renal transplantation from the adopted sibling is preferred because of a lower risk of recurrence of IgA nephropathy and a superior graft survival.
C. Renal transplantation from the adopted sibling is preferred because of a lower risk of recurrence of IgA nephropathy and equivalent graft survival.
D. Renal transplantation should be delayed until bilateral nephrectomy of the recipient is performed.
E. Renal transplantation from a cadaver donor is preferred; neither sibling should be used as a donor.

The correct answer is C. The anticipated survival of the graft from the living unrelated (adopted) brother and the single haplotype identical living related brother would be similar, but the likelihood of a recurrence of IgA nephropathy would be somewhat higher if the living related brother were used as the donor. However, because the recurrence of IgA nephropathy does not have a material effect on overall graft survival, renal transplantation is not contraindicated due to the risk of recurrence with either donor. The long-term results of renal transplantation with either living donor would be superior to that of a cadaver donor.

Reference

Ponticelli C, Traversi L, Felicianmi A, et al. (2001) Kidney transplantation in patients with IgA mesangial glomerulonephritis. Kidney Int 60:1948–1954

CASE 6

A six-year old Chinese girl develops gross hematuria and nonoliguric renal failure five days after the onset of a severe, purulent tonsillitis. She had received azithromycin due to a penicillin allergy. Her urinalysis revealed 4+ proteinuria, >100 dysmorphic erythrocytes, 10 to 15 leukocytes per high-power field, and several red blood cell casts. The serum creatinine was 4.6 mg/dl. A renal biopsy revealed 20 glomeruli, two of which showed segmental crescents, and one showed global gomerulosclerosis. The remainder showed mild mesangial hypercellularity. The interstitium revealed moderate focal inflammation and edema. Many tubular lumina were filled with erythrocytes, and the lining epithelial cells showed focal detachment and necrosis or apoptosis. The immunofluorescence study was positive for diffuse mesangial IgA and IgG deposits, along with C3 and focal deposits of fibrin/fibrinogen. Three days after the renal biopsy, her serum creatinine is 6.0 mg/dl.

What would you do next?

A. Start 1.0 g/day intravenous methylprednisolone for three days
B. Mycophenolate mofetil 2.0 g/day
C. Hemodialysis only as needed
D. Start 1 mg/kg oral prednisone per day and 1.0 g/m^2 intravenous cyclophosphamide
E. Start 1 mg/kg oral prednisone per day plus 1.5 mg/kg oral cyclophosphamide per day, plus daily plasma exchange

The correct answer is C. The patient has classic IgA nephropathy, in which an infection-related (pharyngitis) acute exacerbation with interstitial nephritis, acute tubular necrosis, and gross hematuria has developed. Spontaneous complete recovery, even if dialysis is required, is the rule in such cases, providing that crescentic

glomerular involvement is less than 25–30%. Aggressive treatment is not needed, unless conversion to more extensive (e.g.>50%) glomerular involvement occurs.

Reference

Declaux C, Jacquot C, Callard P, et al. (1993) Acute reversible renal failure with macroscopic hematuria in IgA nephropathy. Nephrol Dial Transpl 8:199–199

CASE 7

A 17-year old white male is referred for a second opinion regarding his diagnosis of focal and segmental glomerulosclerosis, documented by renal biopsy three months ago. The patient's proteinuria was first noted six months ago on a routine check-up. He is moderately obese. Physical examination shows a weight of 86 kg, height 160 cm, BMI 32 kg/m^2, BP 148/92 mmHg, and no edema present. He has 2.6 g of proteinuria daily, serum albumin is 4.2 g/dl, serum cholesterol is 232 mg/dl, BUN is 18 mg/dl, and creatinine is 1.2 mg/dl. Review of his renal biopsy shows ten glomeruli, of which two show segmental sclerosis. The other eight were markedly hypertrophied. There is 40% effacement of foot processes on electron microscopy, but no electron dense deposits or tubuloreticular inclusions are found.

Along with counseling about weight reduction, initial appropriate treatment for this patient would be which ONE of the following?

A. Use of an ACE inhibitor or an angiotensin II receptor antagonist
B. 4-6 mg/kb cyclosporine per day for four to six months
C. 2.0 g of mycophenolate mofetile daily for six months
D. IV cyclophosphamide at 1 g/m^2 monthly for six months
E. Prednisone 40 mg daily or every other day for a six-month course

The correct answer is A. This obese patient has focal and segmental glomerulosclerosis (FSGS) on renal biopsy. The picture is classic for obesity-related glomerulopathy with subnephrotic range proteinuria, normal albumin, glomerulomegaly, and only limited foot process effacement on electron microscopy. The pathogenesis of this form of secondary FSGS is felt to be related to hyperfiltration and/or glomerular capillary hypertension and not to an immunologic insult. Use of inhibitors of the renin-angiotensin system has been shown to decrease proteinuria and slow the progression of many glomerular diseases. Even in idiopathic FSGS, the evidence justifying the use of immunosuppressive agents to treat patients with subnephrotic range proteinuria is spare. This patient should not receive immunosuppressive agents.

Reference

Kambham N, Markowitz GB, Valeri AM, et al. (2001) Obesity-related glomerulopathy: an emerging epidemic. Kidney Int 2001; 59:1498–1509

CASE 8

A nine-year old African-American girl with idiopathic focal and segmental glomerulosclerosis (FSGS) and 5 g of proteinuria daily has been treated with an ACE inhibitor and prednisone for eight months without reduction in her proteinuria. Her serum creatinine is 1.4 mg/dl.

Which ONE of the following therapies should be offered to her at this point?

A. Continued prednisone in a tapering dose to complete a full year of treatment
B. 2 to 3 mg/kg oral cyclophosphamide per day for two to four months
C. 1.0 g of oral mycophenolate mofetile twice daily for six months
D. 4 to 6 mg/kg oral cyclosporine per day for six months
E. 1.0 g/m^2 intravenous cyclophosphamide monthly for six months

The correct answer is D. There are few controlled, randomized clinical trials of treatment of FSGS in both adults and children. Initial therapy is still considered to be at least a six-month course of glucosteroids. The use of ACE inhibitors and angiotensin II receptor antagonists will often decrease proteinuria and slow the progression of disease. If a patient has not responded to a six-month course of steroid treatment, there is little or no evidence that further steroid therapy is beneficial. Cyclophosphamide, although considered a second line drug of choice in the past, will give only a 15 to 20% complete and partial remission rate in steroid-resistant patients with FSGS. Cyclosporine has been shown, in a prospective randomized clinical trial, to lead to more remissions of the nephritic syndrome and less progression to renal failure. There is insufficient data at present on mycophenolate mofetile or IV cyclophosphamide to recommend them before proven therapies.

Reference

Matalon A, Valeri A, Appel GB (2000) Treatment of focal segmental glomerulosclerosis. Semin Nephrol 20:309–317

CASE 9

A 19-year old white female is found to have proteinuria on a urinalysis done for a college sports team physical examination. She is normotensive (BP is118/70 mmHg) and reports only mild pedal edema after eating Chinese food. Laboratory data show normal BUN and creatinine, urinalysis with 10 to 15 erythrocytes per high-power field, serum albumin of 3.2 g/dl, cholesterol of 272 mg/dl, and 24-hour urinary protein excretion of 4.2. Serologic tests including ANA, hepatitis B and C, and serum complement are all negative or normal. A renal biopsy reveals membranous nephropathy with well-defined spike formation and no mesangial deposits.

The best treatment for this patient includes which ONE of the following?

A. An ACE inhibitor, a low cholesterol diet, and the use of a *statin*
B. 2.0 g of oral mycophenolate mofetile daily for six months
C. 60 mg of prednisone daily in a tapering dose for at least six months
D. 3 to 4 mg/kg cyclosporine per day for four to six months
E. Intravenous methylprednisolone *pulse* of 1,000 mg daily for three days followed by oral steroids alliterating monthly with oral cyclophosphamide

The correct answer is A. The natural history of membranous glomerulonephritis has been quite varied with patients progressing to end-stage renal disease (ESRD) and others experiencing complete spontaneous remissions. Therapy should consider risk factors for progression to renal failure, and reserve vigorous treatment with immunosuppressive agents for patients likely to progress (i.e., patients with elevated serum creatinine, and patients with heavy proteinuria). This patient is in a low-risk category, and treatment with inhibitors of the renin-angiotensin system, statins, and symptomatic control of edema is adequate unless proteinuria increases over time.

Reference

Geddes CC, Cattran DC (2000) Treatment of idiopathic membranous nephropathy. Semin Nephrol 20:299–308

CASE 10

A 12-year-old African American girl with a 2-year history of well-documented systemic lupus erythematosus, but without known prior renal disease, develops fever, increased joint pain, and worsening facial rash. On physical examination, her BP is 130/90 mmHg and she has a molar rash and multiple erythematous lesions on her arms and torso, and pitting ankle edema. Her laboratory evaluation shows an elevated anti-double stranded DNA antibody titer, a low total hemolytic complement (CH50), and a low C3 level. The white blood cell count is 3600/mm^3, Hct is 22%, and platelet count is 95,000/mm^3. BUN is 23 mg/dl and creatinine is 1.6 mg/dl. The urinalysis shows 4+ proteinuria and many erythrocytes and red blood cell casts. A 24-hour urinary protein excretion is 4.5 g. A renal biopsy is performed and shows World Health Organization-class diffuse proliferative lupus nephritis.

What are the clinical and epidemiological features present that best predict a poor long-term renal outcome in this patient?

A. African-American race, anemia, and active serology (high anti-dsDNA antibody and low serum complement level)
B. African American race, anemia, heavy proteinuria, and elevated serum creatinine level

C. Heavy proteinuria, elevated serum creatinine level, and active serology
D. Low complement values and elevated anti-dsDNA antibody titer
E. Heavy proteinuria, hypertension, and elevated serum creatinine level

The correct answer is B. This patient has active severe lupus nephritis with positive serology, nephritis urinary sediment, renal dysfunction, and nephritic syndrome. Her biopsy, as expected, reveals diffuse proliferative disease. A number of clinical features have proven predictive value for a poor long-term prognosis in SLE nephritis. These predictive values include African-American race, persistent heavy proteinuria, elevated serum creatinine, anemia, hypocomplementemia, recurrent *nephritis flares*, and superimposed thrombotic microangiopathy. Lower socioeconomic status also predicts a poor outcome. Leukopenia and thrombocytopenia do not predict long-term outcome, unless the latter is associated with other manifestations and biopsy findings of a superimposed thrombotic microangiopathy.

Reference

Austin HA, Boumpas DT, Vaughan EM, et al. (1994) Predicting renal outcomes in severe lupus nephritis. Contributions of clinical and histological data. Kidney Int 43:544–550

CASE 11

A 14-year old girl with nephrotic syndrome is found to have 4.2 g/day of proteinuria, a serum creatinine of 1.2 mg/dl, an elevated anti-DNA antibody, and a low serum complement level. Her biopsy shows diffuse proliferative lupus nephritis (International Society of Nephrology/Renal Pathology Society Class IV).

Which ONE of the following treatment regimens has been shown to give the best long-term efficacy, with the fewest side effects, for the patient described above?

A. 750 to 1000 mg of mycophenolate mofetile twice daily for at least six months
B. 2 mg/kg oral cyclophosphamide per day combined with alternate-day prednisone with conversion of the cyclophosphamide to 2 mg/kg oral azathioprine per day for six months
C. 4 to 5 mg/kg cyclosporine per day and prednisone starting at 60 mg/fay and then tapering the dose for minimum treatment duration of six months
D. Monthly intravenous *pulse* cyclophosphamide for six months and followed by maintenance therapy with mycophenolate mofetile or azathioprine for one or two years
E. 2 mg/kg cyclosporine per day and prednisone starting at 60 mg/day and then tapering the dose for minimum treatment duration of six months

The correct answer is D. Although many immunosuppressive regimens have been used in patients with severe diffuse proliferative nephritis, current *standard* regimens use six monthly *pulses* of intravenous cyclophosphamide followed by maintenance therapy with either mycophenolate mofetile (MFF) or azathioprine. Maintenance therapy with every third month IV cyclophosphamide pulses is inferior to oral MFF or oral azathioprine in preventing the primary endpoint of death and chronic renal failure. The IV cyclophosphamide maintenance therapy is also associated with more infectious complications, more amenorrhea, and more hospitalization days than other groups. MMF and azathopeine are similar in complications and primary endpoint, but there are fewer relapses with the MMF group.

Reference

Illei GC, Austin HA, Crane M, et al. (2001) Combination therapy with pulse cyclophosphamide plus methylprednisolone improve long-term outcome without toxicity in patients with lupus nephritis. Ann Int Med 135 :248–257

CASE 12

A 10-year old white girl presents with recurrent episodes of gross hematuria in the previous one year. Her BP is 150/95 mmHg. No edema is present. A urinalysis reveals 50 to 100 erythrocytes per high-power fields (50% dysmorphic), several erythrocyte casts, and 4+ proteinuria. Six months ago, her serum creatinine was 0.9 mg/dl. Her serum creatinine is now 1.9 mg/dl, and a random urine protein/creatinine ratio is 2.0. A renal biopsy reveals that 30% of the glomeruli are involved with focal and segmental or circumferential cellular crescents. The remaining glomeruli show mesangial proliferation and focal and segmental glomerulosclerosis. The immunofluorescence study shows 3+ IgA, 2+ IgG, 1+ IgM, 3+ C3, negative C1q, and 3+ fibrin/fibrinogen.

In addition to BP control with an angiotensin converting enzyme (ACE) inhibitor, which ONE of the following therapies would you add to her regimen as initial therapy?

A. Omega-3 fatty acid (fish-oils), 6 g daily
B. Oral prednisone at 60 mg daily
C. Cyclosporine at 5 mg/kg daily
D. Oral prednisone at 60 mg daily; oral cyclophosphamide at 1.5 mg/kg daily
E. Oral prednisone at 60 mg daily; oral mycophenolate mofetil (Cellcept®) at 500 mg twice daily

The correct answer is D. This patient has IgA nephropathy with renal insufficiency, moderate proteinuria, and a proliferative and crescentic glomerulonephritis. An aggressive approach to treatment is indicated. At the present time, controlled studies

support the use of combinations of cyclophosphamide and prednisone as preferred initial therapy in patients with progressive IgA nephropathy. Oral prednisone alone may be ineffective in patients with already reduced renal function. Fish oils might be effective, but the presence of crescents points to the need for a more aggressive approach. Cyclosporine has been known to be effective in IgA nephropathy and may be harmful. Too few studies have been conducted using mycophenolate mofetile to recommend it as *first-line* therapy at the present time.

Reference

Ballardie FW, Roberts ISD (2002) Controlled prospective trial of prednisolone and cytotoxics in progressive IgA nephropathy. J Am Soc Nephrol 13:142–148

CASE 13

A 15-year old Hispanic male is found to have an antineutrophil cytoplasmic antibody (ANCA) associated microscopic polyangiitis with both renal and pulmonary involvement. He is treated with oral prednisone and cyclophosphamide. The prednisone is tapered and discontinued after four months, and azathioprine is substituted for cyclosphosphamide at six months. His initial serum creatinine was 2.1 mg/dl, and it decreased to a nadir of 1.7 mg/dl after six months of therapy. He is now seen for a follow-up examination one year after the initial diagnosis. He is asymotomatic. Therapy consists of 100 mg of azathioprine daily and 10 mg of enalepril daily. His BP is 130/80 mmHg. Physical examination is normal. Urinalysis reveals 1 to 2 erythrocytes and 1 white blood cell per high-power field, occasional granular casts, and 2+ proteinuria. The serum creatinine is now 1.8 mg/dl. The sedimentation rate is 20 mm/h. An ANCA test performed one week ago was positive in a titer of 1:128. Previous values have been intermittently positive at low titer.

What would you do next?

A. Reinstitute cyclophosphamide at 2.0 mg/kg/day; stop azathioprine
B. Reinstitute cyclophosphamide at 1.0 mg/kg/day; stop azathioprine
C. Continue azathioprine; observe carefully
D. Start prophylactic trimethoprin-sulfanethoxzole
E. Discontinue azathioprine; begin mycophenolate mofetil at 1.0 mg twice daily

The correct answer is C. This patient has ANCA-positive microscopic polyangiitis and is in a clinical remission, with residual proteinuria and renal impairment. The remission has been induced by sequential cyclophosphamide and azathioprine therapy and the only outward manifestation of possible continued *activity* of disease is a positive ANCA serology. While persistence of positive ANCA serology, despite clinical remissions, may herald a clinical relapse in some patients, many expectations to this findings have been described. Most experts agree that it is better

to carefully follow patients with clinically quiescent disease who are serologically positive, and to reinstitute therapy at the first sign of a clinical relapse, rather than to expose patients to unnecessary and potentially toxic therapy based solely on a serologic finding—which may represent a *false positive* with respect to *active* disease. Nevertheless, patients who are serologically *active* may be at increased risk of relapse, especially when they develop an intercurrent infection. Prophylactic trimethoprin-sulfamethoxazole may reduce the likelihood of a recrudescence of pulmonary angiitis, but seems to be less effective in preventing renal relapses. Mycophenolate mofetile may be effective as maintenance therapy in this situation, but prospective studies have not yet been conducted to test this point.

Reference

Levy J (2001) New aspects of management of ANCA-positive vasculitis. Nephrol Dial Transplant 16:1314–1317

CASE 14

A four-year old white girl is discovered to have microscopic hematuria during a routine examination. Her physical examination, including BP is normal. You see her for further investigation. History reveals that her younger sister, age six, also has persistent microscopic hematuria. There is no family history of deafness. The patient denies flank pain, fever, urinary tract symptoms, or episodes of gross hematuria. Laboratory values include a serum creatinine of 0.6 mg/dl, and the urine shows 10 to 15 dysmorphic erythrocytes and 1 to 2 leucocytes per high-power field. No casts are seen. A 24-hour urine reveals 18 mg of protein and a creatinine clearance of 210 ml/min. A random urine calcium-creatinine ratio is normal (<0.22). The random urine microalbumin-creatinine ratio is 35 mg/g cratinine.

Which ONE of the following tests is most likely to reveal the correct diagnosis?

A. A renal biopsy
B. An abdominal ultrasound
C. An audiogram
D. A computerized tomography (CT) scan of the abdomen with contrast
E. A cystoscopy

The correct answer is A. This patient has many clinical features that are strongly suggestive of thin basement membrane nephropathy (persistent microscopic hematuria, minimal proteinuria, normal renal function and BP, and absence of deafness). The dysmorphic erythrocytes points to a glomerular rather than a bladder or tubulointerstitial source for the hematuria. Cystic kidney disease, hydronephrosis or a renal seems unlikely, based on the history, physical examination, and urinalysis. IgA nephropathy ought to be differentiated from Thin basement membrane disease

(TBMD). Measurement of urinary microalbumin-creatinine ratio on a random urine specimen can differentiate IgA nephropathy from TBMD. In patients with TBMD, the urine microalbumin-creatinine ration is normal ($<30\,u$g/mg), whereas in IgA nephropathy, the ratio is consistently elevated above the normal level. A renal biopsy with electron microscopy and measurement of glomerular basement membrane width will establish the diagnosis.

References

Assadi F (2005) Value of urinary excretion of microalbuminuria in predicting glomerular lesions in children with isolated microscopic hematuria. Pediatr Nephrology 20:1131–1135
Monnens LAH (2001) Thin glomerular basement membrane disease. Kidney Int 60:799–800

CASE 15

What feature seen on a renal biopsy is most suggestive of a secondary form of membranous nephropathy?

A. Interstitial fibrosis
B. Focal sclerosis along with basement membrane thickening
C. Mesangial immune deposits along with epimembranous deposits
D. Electron-lucent epimembranous deposits with a moth-eaten appearance of the glomerular basement membrane (GBM)
E. Extensive spike formation surrounding the electron-dense deposits

The correct answer is C. Secondary forms of membranous nephropathy may be due to medications, systemic autoimmune diseases (such as SLE), infections, and neoplastic diseases. The finding of mesangial immune deposits, although present in up to 10% of biopsies of idiopathic membranous nephropathy, should suggest a secondary form of the disease. Focal sclerosis, interstitial fibrosis, spike formation, and lucent deposits with moth-eaten appearance of the GBM can be seen in both idiopathic and secondary forms.

Reference

Cattran DC (2001) Membranous nephropathy. In: Primer of kidney diseases National Kidney Foundation, edited by Greenberg AD, San Diego, Academic Press pp158–164

CASE 16

A 17-year old African-American male who is known to be HIV seropositive presents with generalized edema. He is found to have nephrotic syndrome with 12 g of proteinuria daily and a serum creatinine of 5.2 mg/d, and large echogenic kidneys are

seen by ultrasonography. Serum complement is normal and the ANA is negative. He has no active infections.

Which ONE of the following statements is most correct concerning a renal biopsy in this patient?

A. Renal biopsy would be of little value because he has classic HIV-associated nephropathy.
B. Renal biopsy is indicated to direct therapy.
C. Renal biopsy is contraindicated because of the risks of bleeding or infection.
D. Renal biopsy is not indicated because he has a severely elevated serum creatinine level.
E. Renal biopsy is indicated to document HIV-associated nephropathy because he has atypical features for the disease.

The correct answer is B. The patient has clinical features entirely consistent with HIV-associated nephropathy (HIVAN). She is African-American, has heavy proteinuria and renal dysfunction, and large echogenic kidneys are found on ultrasound examination. Standard therapy for this condition would be highly active anti-retroviral therapy (HAART) and the use of an ACE inhibitor or an angiotensin receptor antagonist to decrease proteinuria. Recently, the use of glucocorticoids for patients with severe renal dysfunction and HIVAN has been recommended. This patient, without opportunistic infections, would be an acceptable candidate for this therapeutic approach. Before starting steroids, it would be important to document that she does not have another associated glomerular disease. A number of glomerular diseases have been reported in HIV patients, including hepatitis B virus associated glomerulonephritis, IgA nephropathy, SLE, and thrombotic microangiopathies.

Using light microscopy, the classic pattern of HIV nephropathy is a collapsing form of FSGS (73%). There is both hypertrophy and true hyperplasia of the visceral epithelial cells. Tubulointerstitial disease is prominent with tubular degenerative and regenerative features, interstitial edema, fibrosis, and inflammation. Tubules are often dilated into microcysts. Collapsing FSGS is most commonly found in African-Americans. Other lesions include MPGN (10%), minimal change disease (6%), amyloid (3%), and lupus-like GN (2%). Focal segmental necrotizing GN, IgA nephropathy, immunotactoid GN, and thrombotic microangiopathy account for the remaining 6% of the cases.

Reference

Klotman PE (1999) HIV associated nephropathy. Kidney Int 56:1161–1176

CASE 17

A nine-year old white girl presents with chronic kidney disease (serum creatinine 3.1 mg/dl). She is asymptomatic. Her history is unremarkable except that she takes an over-the-counter nonsteroidal antiinflammatory agent (ibuprofen) for a few days each month for menstrual cramps and over-the-counter Chinese herbs for weight loss. Six months ago, during a routine examination, her serum creatinine was 1.1 mg/dl. Her current physical examination reveals a BP of 144/82 mmHg and obesity (weight 129 Kg; height 160 cm). No other abnormal findings are present. Urinalysis shows 8 to10 erythrocytes (all isomorphic), 4 to 6 leukocytes per high-power field, and trace proteinuria. Serum electrolytes, albumin, globulin, calcium, and phosphorous are normal. Serum cholesterol is 200 mg/dl. A renal ultrasound shows both kidneys at the lower limits of normal size and have increased echogenicity. One small cyst is seen in the cortex of the kidney. No dilatation of the ureters or renal pelvis is present.

A renal biopsy is likely to reveal which ONE of the following lesions?

A. Interstitial noncaseating granuloma
B. Hypocellular interstitial fibrosis and tubular atrophy
C. Lymphocytic interstitial inflammation and tubular atrophy
D. Small vessel vasculitis
E. Focal and segmental glomerulosclerosis

The correct answer is B. This obese woman very likely has developed a complication of the use of herbal medicine containing aristocholic acid. Such preparations are now recognized to produce a severe and progressive form of interstitial nephritis, characterized by a hypocellular interstitial fibrosis with tubular atrophy. Sarcoidosis, vasculitis, and glomerulosclerosis are unlikely because of the findings in the urine sediment and the minimal proteinuria and biochemical findings. Ibuprofen is a possible cause, but is less likely because of the infrequent use and the chronicity of the findings.

Reference

Vanherweghem JL (2000) Nephropathy and herbal medicine. Am J Kidney Dis 35:330–332

CASE 18

An eight-year old boy presents with the new onset of nephritic syndrome with 3.4 g proteimuria/day. He has been previously healthy, except for removal of a ruptured spleen at age two after a severe automobile accident. His BP is 150/90 mmHg, and his physical examination reveals 2+ peripheral edema. Laboratory studies reveal a serum creatinine of 1.6 mg/dl, albumin of 2.3 g/dl, cholesterol 310 mg/dl, C3 of

100 mg/dl, and C4 of 8 mg/dl. Antinuclear antibody is weakly positive. His urine reveals 4+ proteinuria, 3+ blood, and several hyaline, granular, and fatty casts.

A renal biopsy is most likely to reveal which ONE of the following histological diagnoses?

A. IgA nephropathy
B. Membranous glomerulonephritis
C. Membranoproliferative glomerulonephritis, Type I
D. Membranoproliferative glomerulonephritis, Type II
E. Fibrillary glomerulonephritis

The correct answer is C. This patient has features, which are strongly suggestive of chronic hepatitis C infection (acquired from a blood transfusion in connection with the accident and surgery) and membranoproliferative glomerulonephritis (MPGN), Type I. He has nephritic syndrome with a low C4 and a normal C3. The low C4 and normal C3 suggests the presence of cryoglobulinemia which is strongly associated with chronic hepatitis C infection and MPGN, Type I. The hepatitis C viral infection was probably acquired as a result of blood transfusions administered during his prior splenectomy. The clinical findings seen here are not usually observed in IgA nephropathy, membranous glomerulonephritis, or fibrillary glomerulonephritis.

Reference

Trejo O, Ramos-Casals M, Garcia-Carrasco J, et al. (2001) Cryoglobulinemia : study of etiologic factors, clinical and immunologic features in 443 patients from a single center. Medicine 80:252–262

CASE 19

A six-year-old boy is referred regarding his recent finding of proteinuria. He is asymptomatic. BP is 140/90 mmHg; urine protein excretion rate is 5.1 g/day; serum creatinine is 1.4 mg/dl; urine sediment shows microscopic hematuria. You perform a renal biopsy, which reveals diffuse mesangial proliferative glomerulonephritis with excessive IgM mesangial deposits. One of ten glomeruli shows segmental glomerulosclerosis.

Which ONE of the following statements is true regarding this patient?

A. He will likely respond with a complete remission following an 8-week course of prednisone
B. He has at least a 30% chance of progressing to ESRD
C. He should be evaluated for systemic lupus erythematous

D. He should be initially treated with a combination of prednisone and cyclophosphamide
E. He should be initially treated with mycophenlate mofetile

The correct Answer is B. The patient has clinical and renal characteristics strongly suggesting *IgM nephropathy*. This clinico-pathologic entity tends to be steroid resistant and in the face of persistent nephritic syndrome also shows a predilection to progress to ESRD. SLE is an unlikely cause of IgM deposition in the present clinical setting.

Reference

Myllymaki J, Saha H, Mustonen J et al. (2003) IgM nephropathy: Clinical picture and long-term prognosis. Am J Kidney Dis 41:343–350

CASE 20

A seven-year-old girl develops non-thrombocytopenic purpura of the lower extremities, abdominal pain, arthralgias, and gross hematuria. Urine protein excretion is mildly elevated at 300 mg/day, and serum creatinine is normal at 0.5 mg/dl. She recovers spontaneously after 10 days. The mother seeks your advice regarding her diagnosis and long-term prognosis. The urine is now normal, except for 4 to 6 erythrocytes/high power field. Protein excretion is now 90 mg/day.

Which ONE of the following statements is most correct regarding this patient?

A. She has a high likelihood of developing progressive chronic kidney disease
B. She should be evaluated for systemic lupus erythematous
C. She is at increased risk of developing pre-eclampsis with a pregnancy
D. A renal biopsy should be performed to estimate her prognosis
E. Serum IgG and IgA-fibronectin complex levels should be measured to estimate prognosis

The correct answer is C. Long-term follow-up of patients who developed Henoch-Schonlein purpura (HSP) in childhood has shown that such patients have an increased risk of pre-eclampsia. Overall, few patients with HSP in childhood progress to ESRD. With minimal proteinuria and a normal serum creatinine level little would be gained by performing a renal biopsy.

Reference

Ronkainen J, Nuutinen M, Koskimies O (2002) The adult kidney 24 years after childhood Henoch-Schonlein purpura: a retrospective study. Lancet 360:666–670

CASE 21

A five-year-old previously healthy girl presents with rapid deterioration of renal function, oliguria, and bilateral pulmonary infiltrates. These are no neurologic symptoms or fever. Serum creatinine is 5.4 mg/dl, and the urine shows 2+ proteinuria and moderate blood. Hematocrit is 28%, platelet count is 46,000/mm^3, and numerous schistocytes are seen in the peripheral blood smear. Complement levels are normal. Kidney size is normal by ultrasound.

Which ONE of the following laboratory tests would be most useful to identify the cause of her disease?

A. Anti-phospholipid antibodies
B. Direct and indirect Coombs test
C. C-reactive protein test
D. Anti-glomerular basement membrane antibody assay
E. Anti-neutrophil antibody assay

The correct answer is A. The constellation of findings in this patient (female gender, acute renal failure, microangiopathic hemolytic anemia, thrombocytopenia, and normal complement levels) is suggestive of the "catastrophic anti-phospholipid syndrome".

Reference

Nzerue CM, Hewan-Lowe K, Pierangeli S, et al. (2002) "Black swan in the kidney": Renal involvement in the anti-phospholipid syndrome. Kidney Int 62:733–744

CASE 22

A seven-year-old boy presents with the acute onset of renal failure. His serum creatinine is 8.2 mg/dl, and he requires treatment with hemodialysis. Serological studies reveal a higher titer of anti-neutrophil cytoplasmic autoantibodies (ANCA) of the anti-myeloperoxidase variety. His kidneys are of normal size by ultrasound. A renal biopsy reveals a necrotizing, crescentic glomerulonephritis with negative immunofluorescence. Approximately 5 of 20 glomeruli in the sample appear normal, and there is only mild to moderate interstitial fibrosis and tubular atrophy, but moderate periglomerular and interstitial inflammation is present.

On the basis of current evidence, which ONE of the following treatment regimens would most likely afford this patient the best renal survival?

A. Intravenous cyclophosphamide and intravenous methylprednisolone
B. Oral cyclophosphamide and oral prednisone

C. Intensive plasma exchange, oral cyclophosphamide, and oral prednisone
D. Oral methotrexate and oral prednisone
E. Oral mycophenolate mofetile and oral prednisone

The correct answer is C. Recent randomized controlled trials, involving a large cohort of patients (The MEPEX trial) have strongly suggested that the use of intensive plasma exchange as an adjunct to prednisone and short-term cyclophosphamide therapy (3 months) followed by long-term azathioprine therapy is useful in the management of patients with anti-neutrophil cytoplasmic antibody (ANCA) positive crescentic glomerulonephritis presenting with acute renal failure (often dialysis dependent). While long-term follow-up of patients treated in this manner are not yet available, short-term improvement (discontinuation of dialysis) occurs more frequently when intensive plasma exchange is added to the treatment regimen when compared to steroids and cyclophosphamide alone.

References

Gaskin G, Jayne DR (2002) The European Vasculitis Study Group: Adjunctive plasma exchange is superior to methylprednisolone in acute renal failure due to ANCA-associated vasculitis. J Am Soc Nephrol 13:S2A–S3A

Jayne D (2002) Conventional treatment and outcome of Eegener's granulomatosis. Cleveland Clinic J Med 69: S110–S115

CASE 23

Among patients presenting with pulmonary hemorrhage (hemoptysis) and rapidly progressive glomerulonephritis, which ONE of the following is the most common underlying finding?

A. Positive anti-glomerular basement membrane (GBM) autoantibodies
B. Positive circulating immune complexes
C. Depressed serum complement levels
D. Positive anti-neutrophil cytoplasmic autoantibodies
E. Positive cryoglobulin

The correct answer is D. ANCA-associated crescentic glomerulonephritis is the most common cause of pulmonary hemorrhage associated with rapidly progressive glomerulonephritis. Anti-GBM autoantibody associated disease (Goodpasture's disease) occurs much less frequently. Most patients with ANCA-associated crescentic glomerulonephritis have normal or elevated serum complement levels.

Reference

Gallagher H, Kwan JTC, Jayne DRW (2002) pulmonary-renal syndrome. A 4-yearr single center experience. Am J Kidney Dis 39:42–47

CASE 24

An eight-year-old girl is found to have proteinuria and hematuria. Urine protein excretion is 4.2 g/day. Serum creatinine is 1.5 mg/dl. BP is 135/85 mmHg. Arenal biopsy reveals IgA nephropathy. She is started on fish-oil therapy and an angiotensin-converting enzyme (ACE) inhibitor at maximum recommended dosage. Urine protein excretion decreases to 3.0 g/day, and serum creatinine increases to 1.6 mg/dl. Her BP is now 128/75 mmHg. She is adhering to low-salt diet.

Which ONE of the following therapeutic regimens should be offered next?

A. Add a dihydropyridine calcium channel blocker to reduce the BP to> 125/75 mmHg
B. Add dietary protein restriction (60 g/day) to her regimen
C. Add indomethacin 50 mg three times a day to her regimen
D. Initiate a course of oral and intravenous steroid for 6 months
E. Add an angiotensin receptor blocker to her regimen

The correct answer is E. The patient has partially responded to an ACE inhibitor with a 28% decline in protein excretion. However, she continues to excrete large amounts of protein in the urine (3.0 g/day) and has a persistent decline in estimated glomerular filtration rate. The COOPERATE trial, which included large numbers of patients with IgA nephropathy, demonstrated significant further reduction in proteinuria and improved renal outcome when an angiotensin receptor blocker (ARB) and an ACE inhibitor were used together, despite no further lowering BP. It is not likely that a non-steroidal anti-inflammatory agent would have much effect on proteinuria. A course of steroids could be tried, but only after failure of ACE inhibitor/ARB therapy. Dietary restriction of protein might also provide some benefit, but this is controversial. Further lowering of BP (<125/75 mmHg) would not likely have any additional anti-proteniuric or reno-protective effect.

Reference

Nakao N, Yoshimura A, Morita H, et al. (2003) Combination of angiotensin II receptor blocker and angiotensin converting enzyme inhibitor in non-diabetic renal disease (COOPERATE); A randomized clinical trial. Lancet 361:117–124

CASE 25

A 15-year-old male develops fever, cough, and blood-tinged sputum and is found to have multiple bilateral alveolar infiltrates with a suggestion of central cavitations. He also manifests hematuria, proteinuria, and a rising serum creatinine from 1.2 mg/dl to 2.2 mg/dl over the span of one week. His urine sediment contains many erythrocytes, 50% of which are normomorphic, and many leukocytes. His WBC is

16,000 mm^3. Platelets are normal in number. A urine culture is sterile. A sputum is negative for acid-fast bacilli and grows a mixed flora of Gram-positive and Gram-negative organisms. Urine protein excretion is 1.8 g/day. A sedimentation rate is 100 mm/h (Westergren method). Complement C3 is increased. An anti-neutrophil cytoplasmic autoantibodies (ANCA) test (by indirect immunofluorescence) is negative, and an anti-glomerular basement membrane (GBM) assay is also negative (by enzyme-linked immunosorbent method).

Which ONE of the following statements regarding this patient is correct?

A. Crescentic glomerulonephritis due to Wegener granulomatosis is excluded because of the result of the ANCA assay
B. Additional assays using antigen-specific tests (anti-myeloperoxidase and anti-proteinase 3) should be performed
C. The negative anti-GBM assay excludes a role for anti-GBM autoantibodies in his disease
D. The high percentage of normomorphic erythrocytes in the urine sediment is inconsistent with a diagnosis of crescentic glomerulonephritis
E. Bronchoscopy with biopsy should be performed

The correct answer is B: The sensitivity of an ANCA test for the diagnosis of Wegener's granulomatosis is increased by the use of combination of immunofluorescent and ELISA tests, the latter using a specific antigen (either myeloperoxidase or proteinase 3). False negative tests for anti-GBM antibodies occur with some assays. Bronchoscopic biopsies often reveal non-specific findings. In cresentic glomerulonephritis normomorphic erythrocytes are often >50% of the total erythrocytes in a urine specimen, but the total excretion of dysmorphic erythrocytes is always increased greatly above normal.

Reference

Van der Woude F (2002) Taking anti-neutrophil cytoplasmic antibody (ANCA) testing beyond the limits. Nephrol Dial Transplant 17:2081–2083

CASE 26

A 14-year-old girl develops pulmonary infiltrates, hilar adenopathy, fever, hematuria, proteinuria, and a rising serum creatinine level 3.6 mg/dl. Anti-neutrophil cytoplasmic autoantibodies (ANCA) tests reveal a high titer by indirect immunofluorescence and a high titer of anti-proteinase 3 (anti-PR3) antibodies. Anti-glomerular basement membrane (GBM) antibodies are negative. Her erythrocyte sedimentation rate is 110 mm/h (Westegren method). A renal biopsy reveals a necrotizing and crescentic glomerulonephritis with negative immunofluorescence. Sixty percent of glomeruli are involved with circumferential crescents. She is

treated with oral cyclophosphamide and oral prednisone and enters into a clinical remission. The pulmonary infiltrate resolve, serum creatinine returns to 1.0 mg/dl, but mild proteinuria (800 mg/day) persists. Her anti-PR3 antibody levels decrease to a titer of 1:8. She is given prophylactic trimethoprim-sulfamethoxazole. Six months later, her cyclophosphamide is reduced because of leucopenia. A follow-up titer of anti-PR3 antibody 1 month later is 1:256. She remains asymptomatic with persistent low grade proteinuria. Urine sediment shows 4–6 erythrocytes per high power field. Serum creatinine is 1.1 mg/dl.

AT this point, which ONE of the following options should be recommended?

A. Observe only, with monthly clinical examinations and ANCA tests
B. Add daily applications of nasal mupirocin ointment
C. Perform a repeat renal biopsy
D. Restart cyclophosphamide for 3 months, then convert to long-term azathioprine
E. Start mycophenolate mofetile

The correct answer is D. A four-fold increase in the titer of ANCA (1:8 to 1:256) often heralds a relapse of Wegener's granulomatosis. Such relapses can be prevented by "prophylactic" administration of an alkylating cytotoxic agent (e.g. cyclophosphamide). No trials have yet reported on the efficacy of mycophenolate mofetile as a "prophylactic" agent. The patient is already receiving Trimethoprim-sulfamethoxazole as a relapse prevention agent. Mupirocin could be helpful, by avoiding staphylococcus carriage, but this has not yet been conclusively shown in patients who are already on anti-microbial and who have four-fold rises in ANCA titer.

Reference

Han WK, Choi HK, Roth R, et al. (2003) Serila ANCA titers: Useful tool for prevention of relapses in ANCA-associated vasculitis. Kidney Int 63:1079–1085

CASE 27

You are asked to see a 10-year-old boy with chronic kidney disease (serum creatinine 2.6 mg/dl) for evaluation of chronic lead intoxication from environmental exposure?

Which ONE of the following noninvasive tests would be of greatest value?

A. Urine and serum uric acid levels
B. Blood lead measurement, before and after calcium disodium EDTA infusion
C. Quantitation of urinary coproporphyrin excretion

D. Measurement of erythrocyte aminolevulinate dehdydrase activity before and after treatment with dithiothreitol
E. Quantitation of erythrocyte basophilic stippling

The correct answer is D. Measurement of the urinary excretion of lead before and after an infusion of a chelating agent, such as calcium, disodium ethylene diamine tetra-acetic (EDTA) is considered the *gold-standard* for diagnosis of chronic lead intoxication. An alternative test, not involving an infusion of a chelating agent, has been suggested as having good precision in the diagnosis of chronic lead intoxication in patients with chronic kidney disease. The test involves the measurement of the activity of erythrocyte aminilevulinate dehdrase activity before and after treatment of the specimen with dithiothreitol.

Reference

Fontanellas A, Navarro S, Moran-Jiminez MJ, et al. (2002) Erythrocyte aminolevulinate dehydrase activity as lead marker in patients with chronic renal failure. Am J Kidney Dis 40:43–50

CASE 28

A 15-year-old girl with known systemic lupus erythematosus has had quiescent renal and extrarenal disease for the previous 5 years. She has recently developed periorbital edema and pedal edema in the absence of other signs or symptoms. BP is 138/79 mmHg. Laboratory evaluation revealed the following: BUN 23 mg/dl, serum creatinine 0.8 mg/dl, urinalysis: 4+ protein, trace blood, with 3–5 erythrocytes per high power field and no casts. A 24-hour urinary protein 18 g. Blood cholesterol level is 210 mg/dl. Anti-DNA antibody titer and seem complement values are normal. A renal biopsy is performed and appears normal by light microscopy, with immunofluorescence showing no immune deposition. Electron microscopic results will follow in several days.

In addition to diuretics and control of hypertension, hyperlipidemia, which ONE of the following choices provides the most appropriate therapy for this patient?

A. Monthly intravenous cyclophosphamide pulses for six months
B. Oral cyclosporine
C. Oral corticosteroids
D. Non-steroidal antiinfalmmatory agents daily
E. Oral corticosteroids plus cyclosporine

The correct answer is C. Recent reports document minimal change nephropathy in SLE patients. The absence of clinical findings, normal SLE serology, and renal

biopsy without immune deposits all point to this diagnosis. In adults up to four months of corticosteroids is the treatment of choice for minimal change disease.

Reference

Dube GK, Markowitz GS, Radhakrishnan J, et al. (2002) Minimal change disease in SLE. Clin Nephrol 120:126–126

CASE 29

A 16-year-old boy with renal biopsy-proven idiopathic membranous nephropathy comes to you for a second opinion. His records document 4 g of proteinuria daily and the excretion of a large amount of IgG and alfa-1 microglobulin. He is uncertain of the significance of the *globulinuria* and hopes that you will tell him.

Which ONE of the following statement is the MOST correct answer to this inquiry?

A. This globulinuria is of no significance because proteinuria is already in the nephritic range
B. Large amounts of globulinuria predicts the extent of tubulointerstitial damage on biopsy and also predicts a poor response to therapy
C. Large amounts of globulinuria predict the extent of tubulointrestitial damage on biopsy and also predict a poor response to therapy
D. Large amounts of globulinuria correlate with the extent of glomerulosclerosis
E. The excretion of globulinuria in this patient does not correlate with histologic findings but predicts a poor response to therapy

The correct answer is C. The excretion of large amounts of IgG and a microglobulin 1 has been correlated with tubulointerstitial damage on biopsy in membranous nephropathy as well as a poor response to treatment. This is independent of the extent of proteinuria.

References

Bazzi C, D'Amico G (2002) The urinary excretion of IgG and alpha-1 microglobulin predicts renal outcome and identifies patients deserving treatment in membranous nephropathy. Kidney Int 61:2276

Bazzi C, Petrini C, Rizza V, et al. (2001) Urinary excretion of IgG and alpha-1microglobulin predicts clinical course better than the extent of proteinuria in membranous nephropathy. Am J Kidney Dis 38:240–248

CASE 30

A 19-year-old female is referred for evaluation of her nephritic syndrome. Laboratory tests show the following: BUN 32 mg/dl, serum creatinine 3.5 mg/dl, 4+ proteinuria with 10–15 erythrocytes and 2–4 erythrocyte cats in the urinary sediment. Serum ant-nuclear antibodies, complements C3, C4 ANCA, anti-GBM antibodies HIV, hepatitis B virus surface antigen, hepatitis C virus antibody, serum and urine protein electrophoresis were all negative or normal. Her renal biopsy shows crescentic glomerulonephritis with active proliferative crescents in 8 of the 15 glomeruli. Immunofluroscence is positive for IgG, by electron microscopy, there are no deposits, but the glomerular basement membrane is filled with 20-nm non-branching fibrils.

Which ONE of the following choices would be BEST for the further evaluation of this patient?

A. Serum hepatitis C virus (HCV) antibody and HCV by reverse transcriptase polymerase chain reaction
B. Congo Red stains of biopsy
C. Serum and urine immunofixation, serum complement, and bone marrow biopsy
D. Anti-DNA antibody, extractable nuclear antigen (ENA), and anti-Sjogren syndrome A and B antibodies
E. HIV testing.

The correct answer is C. The patient has immunotactoid glomerulonephritis (ITGN) with 50 nm fibrils in a stacked pattern in the GBMs on EM of her biopsy. Although fibrillary GN is typically unassociated with other diseases, ITGN is associated with lymphoproliferative disorders, hypocomplementemia, and monoclonial plasma cell dyscrasias. Along with the initial laboratory tests a thorough physical and scanning evaluation for lymphoproliferative disease in indicated.

Reference

Schwartz MM, Korbet SM, Lewis EJ (2002) Immunotactoid glomerulopathy. J Am Soc Nephrol 13:1390–1397

CASE 32

Which ONE of the following choices would provide the best initial therapy for the patient described above?

A. No therapy
B. Corticosteroid plus oral or intravenous cyclophosphamide
C. Angiotensin-converting enzyme inhibitor

D. Colchicine
E. Stem cell transplantation

The correct answer is B. Although there is no proven therapy for fibrillary GN, many clinicians have been successful in treating the light microscopic pattern. There is evidence that crescentic fibrillary GN will respond to corticosteroids and cyclophosphamide. Although one might add ACE inhibitors or angiotensin II receptor blocker (ARB), they would not suffice as sole therapy here.

Reference

Blume C, Ivens K, May P et al.. Fibrillary glomerulonephritis associated with crescents as a therapeutic challenge. Am J Kidney Dis 2002; 40:420–425

CASE 33

Which ONE of the following sets of factor is associated with a more rapid progression to renal failure in focal and segmental glomerulosclerosis?

A. Greater proteinuria, the tip lesion, and advanced interstitial fibrosis
B. Greater proteinuria, the collapsing lesion, and michrohematuria
C. Greater proteinuria, elevated serum creatinine, and advanced interstitial fibrosis
D. Elevated serum creatinine, microhematuria
E. Elevated serum creatinine, the collapsing lesion, and microhematuria

The correct answer is C. Factors predictive of more rapid progression to renal failure in FSGS include heavier degrees of proteinuria, elevation of serum creatinine, in some studies Black race, and advanced interstitial fibrosis and the collapsing lesion on biopsy. The tip lesion has had a more benign prognosis in some.

Reference

Korbet S (2002) Treatment of primary focal and segmental glomerulosclerosis. Kidney Int 62:2301–2310

CASE 34

A nine-year-old girl with a newly diagnosed malignancy is in remission after recent treatment with vincristine, adrimycin, thalidomide and dexamethasone. She develops the nephritic syndrome and is found to have focal segmental glomerulosclerosis (FSGS) on renal biopsy. She has been receiving pamidronate to prevent bone resorption, and celecoxib for chronic pain.

Which ONE of the following medications is the most likely cause of her FSGS?

A. Alpha tocopherol
B. Ranitidine
C. Calcitonin
D. Dexamethasone
E. Pamidronate

The correct answer is E. Pamidronate has been documented to cause FSGS as well as several other patterns of the nephritic syndrome (MCD, mesangial hyperplasia). The course of pamidronate related FSGS is very variable when the drug is stopped, but patients with the collapsing variant of FSGS associated with pamidronate therapy do not have a good prognosis. Adriamycin, although used in animal models to induce heavy proteinuria, has only been very rarely associated with the nephritic syndrome in man. Celecoxib may cause the nephritic syndrome due to minimal change disease or membranous nephropathy but not FSGS.

Reference

Markowitz GS, Apple GB, Fine P, et al. (2001) Collapsing FSGS following treatment with high dose pamidronate. J Am Soc Nephrol 12:1164–1172

CASE 35

An 11-year-old girl with rheumatoid arthritis has been taking 400 mg of celecoxib (COX II inhibitor) twice daily for 6 months. She develops edema and nephritic syndrome with 4.5 g of proteinuria daily and a serum creatinine that increases from 0.8 mg/dl to 2.4 mg/dl over a 2-week period. She takes no other medications, and all serologic tests are negative or normal, including complement, anti-nuclear antibody (ANA), hepatitis B and C, and HIV.

Which ONE of the following pathologic diagnoses is most likely present in this patient?

A. Acute interstitial nephritis plus minimal change disease
B. Membranous nephropathy
C. Focal and segmental glomerulosclerosis with the tip lesion
D. Membranoproliferative glomerulonephritis Type I
E. Fibrillary glomerulopathy

The correct answer is A. Recently a number of forms of renal pathology not previously reported have been noted with COX II inhibitors. These include minimal change disease with or without acute interstitial nephritis, and membranous

nephropathy. MOGN and fibrillary GN have not been reported. The membranous would not be associated with a rise in serum creatinine.

References

Alper AB, Meleg-Smith S, Krane NK (2002) Nephrotic syndrome and interstitial nephritis associated with celecoxib. Am J Kidney Dis 40:1086–1090

Markowitz GS, Falkowitz DC, Isom R, et al. (2003) Membranous glomerulonephropathy and acute interstitial nephritis following treatment with celebrex. Clin Nephrol 59:137–143

CASE 36

A 10-year-old boy presents with multiple relapsing nephritic syndrome which began at age five years. With each relapse he has been treated with oral prednisone and has responded with a complete remission within 3 weeks or less of treatment. He is now manifesting growth failure and showing signs of cumulative steroid toxicity. His mother seeks your advice about what to do next. The potential risks and benefits of various therapies have been discussed with her.

Which ONE of the following would you advise?

A. A renal biopsy is necessary to determine the nature of lesion before any therapeutic recommendations can be made
B. A serum sample should be sent for circulating permeability factor to assess treatment responsiveness
C. A course of oral cyclophosphamide 2 mg/kg/day for 12 weeks should be given after induction of a remission with prednisone
D. A course of oral mycophenolate mofetile 2 g/day for 6 months should be given
E. A course of intermittent intravenous cyclophosphamide 500 mg/m^2 every moth for 6 months should be given

The correct answer is C. The patient has developed *exogenous Cushing syndrome* and has a multiple relapsing, steroid-responsive form of nephritic syndrome. The best treatment to prevent further relapses and to allow withdrawal of steroid is a course of oral cyclophosphamide. Benefits of this approach have been proven by randomized clinical trails. A renal biopsy is not needed to confirm the diagnosis of minimal change disease. The clinical utility of measuring the serum *permeability* factor is not yet established. Oral mycophenolate mofetile is not proven to have benefits in steroid responsive minimal change disease of children (no control trail). While IV cyclophosphamide can induce remissions, the relapse rate is higher than with oral cyclophosphamide.

Reference

Staderrmann MB, Lilien MR, van der Kar, et al. (2003) Is renal biopsy required prior to cyclophosphamide use in steroid sensitive nephritic syndrome? Clin Nephrol 60:315–317

CASE 37

An eight-year-old boy presents with nephritic syndrome, hematuria, and renal failure. His physical examination reveals a BP of 150/90 mmHg. He has 1+ pitting pedal edema and a gaunt appearance due to loss of subcutaneous facial fat. Laboratory examination reveals hemoglobin of 10.1 g/dl, a serum creatinine of 2.0 mg/dl, and a serum albumin of 2.3 g/dl. His serum C3 complement is 20 mg/dl, serum C4 complement is 22 mg/dl, and the total hemolytic complement (CH50) activity is less than 10 units. A urinalysis reveals 4+ protein and large blood. Anti-nuclear antibodies and anti dsDNA antibodies are negative.

Which ONE of the following glomerular lesions will most likely be found on renal biopsy?

A. Diffuse endocapillary glomerulonephritis with subepithelial electron dense deposits
B. Diffuse crescentic glomerulonephritis with absence or glomerular dense deposits
C. Membranoproliferative glomerulonephritis with extensive subendothelial electron dense deposits
D. Immunotactoid glomerulopathy
E. Membranoproliferative glomerulonephritis with diffuse intramembranous electron dense deposits

The correct answer is E. This patient has the typical clinical and laboratory features of dense deposits disease (glomerulonephritis with persistent depression of C3 complement component). The hypocomplementemia is the critical clue. Low C3 levels with normal C4 levels seldom occur in *pauci-immune* crescentic glomerulonephritis, immunotactoid glomerulopathy, or membranoproloferative glomerulonephritis with subepithelial electron dense deposits. Endocapillary glomerulonephritis with subepithelial electron dense deposits and transient depression of C3 levels may be seen in post-infectious glomerulonephritis, but the presence of partial lipodystrophy strongly points to dense deposits disease.

Reference

Appel GA, Cook HT, Hageman G, et al. (2005) Membranoprolifertaive glomerulonephritis Type II (dense deposit disease): An update. J Am Soc Nephrol 16:1392–1403

CASE 38

A six-year-old girl presents with the recent discovery of *persistent* microscopic hematuria and is referred to you for further evaluation. She claims to be in good health and takes no prescription or over-the-counter medications. She has not noticed any episodes of macroscopic hematuria, dysuria, frequency, back pain, or fever. Her older sister was evaluated several years ago for a similar finding and no cause was found, but she did not undergo a renal biopsy. Her physical examination is normal with a BP of 110/60 mmHg. Urinalysis shows trace protein and large blood. The sediment reveals 15 to 20 dysmorphic erythrocytes per high power filed, no casts and 1 to 2 white blood cells per high power field. The serum creatinine is 0.4 mg/dl, seem albumin is 4.2 g/dl, and the serum total cholesterol is 160 mg/dl. Serum C3 is normal. Urine protein-to-creatinine ratio is 0.1 mg/mg.

Which ONE of the following is the most likely pathogenesis of her hematuria?

A. Immune complexes deposits on the sub-epithelial side of the glomerular basement membrane
B. An inherited disorder involving the alfa-3 /alfa-4 chains of Type VI collagen
C. The formation of immune complexes containing under-galactosyated IgA1 and antibody to the peptide residues on IgA1 heavy chain
D. An inherited disorder involving the alfa-5 /alfa-6 chains of Type VI collagen
E. An inherited disorder involving the alfa-1 /alfa-2 chains of Type VI collagen

The correct answer is B. This patient has *persistent isolated hematuria* with normal BP and renal function and a family history of hematuria. This is most compatible with a diagnosis of *thin basement membrane nephropathy*. This disorder is now recognized as being due to a genetic abnormality affecting the alfa-3 and/or alfa-4 chains of Type IV collagen. It usually presents in an autosomal dominant fashion. IgA nephropathy is less likely, because of the absence of bouts of macroscopic hematuria and the absence of proteinuria.

Reference

Kashtan CE (2004) Familial hematuria due to Type IV collagen mutation: Alport syndrome and thin basement membrane nephropathy. Curr Opin Pediatr 16:177–181

CASE 39

A 14-year old girl presents with newly diagnosed IgA nephropathy (grade I–II in the Hass classification) discovered on a routine health exam. Her BP is 135/85 mmHg and she weighs 56 kg. The serum creatinine is 0.8 mg/dl and albumin 4.1 g/dl. The urine protein to creatinine ratio on a first morning-voided specimen is 0.9 mg/mg.

Which ONE of the following treatment regimens should be instituted initially?

A. Fish oil, 4 g daily
B. Prednisone 40 mg daily, slowly tapering to 10 mg/day over six months
C. Cyclophosphamide 2 mg/kg/day for 3 months, followed by azathioprine 2 mg/kg/day for one to two years
D. Losartan 100 mg/day
E. Amlodipine 10 mg/day

The correct diagnosis is D. The patient has a *mild* form of IgA nephropathy with abnormal proteinuria (<1.0 g/day), presumably normal renal function, and mild hypertension. The recommended initial approach to therapy would be to try angiotensin inhibition, rather than to embark in immunosuppressive therapy. While fish oil is not contraindicated, there is no proof of efficacy for a patient with this *mild* disease.

Reference

Ballaride FW (2004) IgA nephropathy treatment 25 years on: can we halt progression? The evidence based. Nephrol Dial Transpl 19:1041–1046

CASE 40

A seven-year old boy with IgA nephropathy has persistent proteinuria (2.8 g) despite six months of treatment with a combination of enalepril and candesartan at maximal dosage. His BP is 122/76 mmHg and his serum creatinine is now 1.3 mg/dl. Serum creatinine was 1.2 mg/dl six months ago. Urinary protein excretion is currently 3.0 g/day.

Which ONE of the following regimens would you recommend for current treatment?

A. A six-month course of IV methylprednisolone—1.0 g at the beginning of the first, third, and fifth months, plus oral prednisone 0.5 mg/kg every other day
B. Oral micophenolate—2.0 g/day for six months
C. Cyclosporine at 4 mg/kg/day, plus oral steroids 0.5 mg/kg every other day for six months
D. Cyclophosphamide at 2 mg/kg/day for three months followed by azathioprine 2 mg/kg for one year
E. Fish oil, 12 g daily for one year

The correct answer is A. The patient has IgA nephropathy with several features indicative of a *poor* prognosis, including proteinuria >2.5 g/day despite combined ACE inhibitor and angiotensin II inhibitor therapy. Based on these considerations,

treatment is indicated. Controlled trials have suggested that a steroid regimen similar to that described in choice A may be the best approach. No controlled trials demonstrate benefit with cyclosporine or MMF in the circumstances described by this patient. Aggressive immunosuppression would be best limited to those patients who demonstrate progressive renal disease. Fish oil is not contraindicated, but meta-analysis of reported trials has shown that any benefits are inconsistent.

References

Ballaride FW (2004) IgA nephropathy treatment 25 years on: can we halt progression? The evidence based. Nephrol Dial Transpl 19:1041–1046

Stippoli G, Manno C, Schena FP (2003) An evidence-based survey of therapeutic options for IgA nephropathy: assessment and criticism. Am J Kidney Dis 41:1129–1139

CASE 41

A 15-year old girl is discovered to have hematuria and proteinuria (2.6 g/day) and impaired renal function (serum creatinine 1.5 mg/dl and estimated GFR of 55 ml/min). She has no systemic symptoms, such as fever, alopecia, arthralgia, or skin rashes. She takes no medications other than acetaminophen and oral contraceptives. She does not abuse drugs. Her family history is negative for renal disease or rheumatic disease. A physical examination is normal except for a BP of 142/92 mmHg. Serologic studies for lupus erythematosus are negative, as is HIV, hepatitis C, and hepatic B serology. The serum C3 is 110 mg/dl and C4 is 20 mg/dl. A renal biopsy (containing 24 glomeruli) shows 15% of the glomeruli have prominent visceral epithelial cellularity and capillary collapse, while approximately 10% show segmental glomerulosclerosis. Immunofluroscent studies reveal 2+ igG, 2+ IgA, 2+ igM, 2+ C3, and 4+ C1q deposits in the glomerular mesangium. Both kappa and lambda chains are present. Numerous electron dense deposits are present in the mesangium, but no tubuloreticular inclusions are seen in endothelial cells.

Which ONE of the following statements is MOST accurate in defining the likely course her renal disease will pursue?

A. She will likely develop serologic and clinical evidence of systemic lupus erythematosus within the next five years.
B. She is likely to respond with a complete or partial remission following combined cyclosporine-steroid therapy.
C. She will likely be unresponsive to treatment with glucosteroids and progress to ESRD within five to 10 years.
D. A recurrence of disease in a renal transplant is likely.
E. She is likely to convert to HIV+ serology within the next six months.

The correct answer is C. This patient has the typical clinical, serologic, and immunosuppressive findings of C1q nephropathy, including absence of clinical or serological findings indicative of SLE, normal serum complement levels, dominant

C1q deposits, electron-dense deposits in the mesangium, and focal and segmental glomerulosclerosis. As such, she will likely fail to respond to steroids and will very likely progress to end-stage renal disease (ESRD).

Reference

Sharman A, Furness P, Fehally J (2004) Distinguishing C1q nephropathy from lupus nephritis. Nephrol Dial Trasnpl 19:1420–1426

CASE 42

Which of the following combinations of therapy is likely to have the greatest antiptoteinuric effect in patients with chronic, nondiabetic, proteinuric glomerular disease?

A. Angiotensin converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARB)
B. ACEI and nonsteroidal anti-inflammatory agents
C. ACEI and nondihydropyridine calcium channel antagonists
D. ACEI and dihydropyridine calcium channel antagonists
E. ARB alone or ACE alone in maximal dosage plus chlorothiazide

The correct answer is A. The COOPERATE study clearly demonstrated superiority of ACEI and ARB in condition of chronic proteinuria associated with nondiabetic chronic glomerular disease (mostly IgA nephropathy).

Reference

Panos J, Michelis MF, DeVita MV, et al. (2003) Combined converting enzyme inhibition and angiotensin receptor blockade reduces proteinuria greater than converting enzyme inhibitors alone: insight into mechanism. Clin Nephrol 60:13–21

CASE 43

In comparing patients with renal vasculitis who have strong positive indirect immunofluorescence assays for antineutrophil cytoplamic autoantibodies (c-ANCA), and strongly positive ELISA assays for antiproteinase 3 antibodies (anti-PR3), to those with strongly positive peripheral ANCA (p-ANCA) and antimyeloperoxidase antibodies (anti-MPO), which ONE of the following statements is CORRECT?

A. The initial response to treatment is poor for patients with p- ANCA/anti-MPO.
B. The likelihood of a relapse following initially successful treatment is greater for patients with c-ANCA/anti-PR3.

C. Initial treatment of patients with p-ANCA/anti-MPO should always include plasma exchange.
D. Patients with drug-induced renal vasculitis are more likely to have c-ANCA/anti-PR3.
E. The long-term outcome (renal survival) is similar for both p-ANCA/anti-MPO and c-ANCA/PR3-associated renal vasculitis.

The correct answer is B. Prolonged observation of patients with systemic necrotizing vasculitis has clearly shown that patients with Wegner's granulomatosis, who typically are c-ANCA/anti PR3 positive, have a much higher risk of relapse than do patients with microscopic polyangiitis (who typically are p-ANCA/ant MPO positive. Patients with p-ANCA/anti PR3 are more often associated with drug-induced diseases and may have a better prognosis if treated early before advance irreversible organ damage has occurred.

Reference

Booth AD, Pusey CD, Jayne DR (2004) Renal vasculitis: an update in 2004> Nephrol Dial Transplant 19:1964–1968

CASE 44

A nine-year old girl presents with rapid deterioration of renal function (serum creatinine level rising from 1.8 mg/dl to 6.0 mg/dl over 6 days), hematuria, and proteinuria, cough, marked hemoptysis, and severe shortness of breath. She is confused and disoriented. Physical examination reveals moist rales bilaterally and mild cyanosis of the lips. The neck veins are not distended. The sputum is dark red. Urine output is scanty. BP is 12/80 mmHg and the pulse is 120 beats per minute. Serum creatinine is now 7.0 mg/dl. Serologic tests from two days ago are reported as ANCA + (anti-MPO), anti-GNM negative, and C3/C4 normal ANA 1:40 (normal up to 1:80). The urinalysis shows 4+ protein and large blood. The arterial PO_2 is 60 torr. The hemoglobin is 9.0 g/dl.

In addition to administering oxygen and preparing for hemodialysis, which ONE of the following steps would you take next?

A. Percutaneous renal biopsy
B. Transbronchial lung biopsy
C. Start treatment with IV methylprednisolone and IV cyclosphomide
D. Start treatment with IV methylprednisone, IV cyclophosphamide, and plasma exchange
E. Start treatment with IV methylprednisone and IV immunoglobulin

The correct answer is D. The patient presents with a syndrome of rapidly progressive glomerulonephritis accompanied by hemoptysis, hypoxia, and severe dyspnea. Serologic studies indicate a p-ANCA/anti-MPO positive form of microscopic polyangiitis. She is severely anemic and has oliguric acute renal failure. The pulmonary hemorrhage may be life threatening. The best approach to this desperately ill patient is to start steroids and cyclophosphamide for the presumed vasculitis and to add plasma exchange for the severe pulmonary hemorrhage. Neither a renal biopsy nor a lung biopsy will add materially to the therapeutic decision-making. Methylprednisone and cyclophosphamide without plasma exchange could be tried, but in light of her precarious state of ventilation, a more aggressive approach is indicated. Steroids and IV immunoglobulins may also be helpful for the pulmonary hemorrhage, but the current evidence suggests a more prompt and predictable response with plasma exchange.

Reference

Klemmer PJ, Chalermskulrat W, Rief MS, et al. (2003) Plasmaphoresis therapy for diffuse alveolar hemorrhage in patients with small vessel vasculitis. Am J Kidney Dis 42:1149–1153

CASE 45

A one-year old boy presets with rapidly progressive renal failure and nephritic urine. He also has arthralgia, tinnitus, a cough, and a bloody nasal discharge. ANCA is positive for c-ANCA and anti-PR3-antibodies. A renal biopsy shows necrotizing and crescentic glomerulonephritis (GN) with negative immunofluorescnce (Pauci-immune crescentic GN Type 3). A chest x-ray shows bilateral fluffy densities in the lower lobes. He is treated with oral cyclophosphamide (2 mg/kg/day) and oral prednisone (2mg/kg/day) and responds with an improvement in all external renal signs and symptoms. After three months of treatment, his serum creatinine has decreased from 3.5 mg/dl to 1.2 mg/dl and the urinalysis now shows 2+ proteinuria and trace blood. The c-ANCA titer is negative. A chest x-ray is normal.

Based on currently available evidence, which ONE of the following would you now do?

A. Taper the prednisone to 10 to 15 mg every other day and continue the oral cyclophosphamide at 2 mg/kg/day for an additional 18 months
B. Taper the prednisone to 10 to 15 mg every other day and replace the cyclophosphamide with azathioprine at 2 mg/kg/day for the next 18 months
C. Start cyclophosphamide.
D. Taper the prednisone to 10 to 15 mg every other day and substitute mycophenolate mofetile at 1–2 mg/kg/day for cyclophosphamide for the next 18 months
E. Change daily oral prednisone to monthly IV methylprednisolone at 1.0 g for six additional months, and discontinue the cyclophosphamide

The correct answer is B. This patient has Wagener's granulomatosis and has responded to combine oral cyclophosphamide and prednisone with a clinical and serologic remission, with mild residual proteinuria at three months. Based on a randomized clinical conducted by the EUVAS group, the safest and most efficacious option would be to withdraw the cyclophosphamide and replace it with azathioprine, and to further taper the steroids. Azathioprine should be continued for at least 18 months, and perhaps longer. Prolongation of cyclophosphamide is not needed and may be hazardous. Substitution of cyclophosphamide with MMF might also be beneficial, but this has not yet been shown on a randomized clinical trial. Discontinuation of cyclophosphamide without substitution with a long-term immunosuppressant would likely expose the patient to a high risk of relapse. IV cyclophosphamide is not needed to prolong the remission and has not been shown to be effective and safe in this situation.

Reference

Jayne D, Rasmussen N, Andrassy H, et al. (2003) European vasculitis Study Group: A randomized trial of maintenance therapy for vasculitis associated with ANCA, N Engl J Med 349:36–44

CASE 46

A 14-year old female presents with proteinuria and hematuria. She was diagnosed as having systemic lupus erythematosus at age 17 because of alopecia, a molar rash, artheralgia, anemia, and thrombocytopenia. Her serum creatinine and urinalysis were normal at that time. She is currently being treated with anti-malarias, nonsteroidal anti-inflammatory agents (PRN for artheralgias) and low dose prednisone 7 mg/day. Her physical exam reveals a BP of 159/96 mmHg. There are no rashes and her joints are normal. Livedo reticularis is bilaterally present in the lower extremities. Her fluorescent nuclear antibody (ANA) is positive at 1:256, anti-dsDNA is elevated, and her serum C3 is 1 80 mg/dl (normal 90 to 140 mg/dl). Urine protein is 2.0 g/day, and the urine is 3+ for blood. Her serum creatinine is 0.9 mg/dl, hemoglobin 11 g/dl, WBC 3800/mm^3 and platelet count is 80,000/mm^3.

In addition to performing a renal biopsy, which ONE of following laboratory tests would be useful in determining prognosis and choosing a therapeutic regimen?

A. AntiSm antibody
B. Antinucleosome antibody
C. AntiC1q antibody
D. Antiphospholipids antibody
E. Indirect and direct Coombs' test

The correct answer is D. This patient has SLE with proteinuria, hematuria, hypertension, thrombocytopenia, and livedo reticularis. Her renal function is presumptively normal. These features suggest that she may well have the *antiphospholipids syndrome* accompanying SLE, for which treatment with anticoagulants may be appropriate. Detecting antiphospholipid antibodies would also indicate an unfavorable prognosis.

The antiSm and antinucleosome antibodies would provide no additional useful clinical information. AntiC1q antibodies would provide some value in determining the *activity* of the SLE with respect to renal involvement. There is no evidence of an autoimmune hemolytic anemia to warrant Coombs' testing.

Reference

Moroni G, Ventura D, Riva P, et al. (2004) Antiphospholipid antibodies are associated with an increased risk for chronic renal insufficiency in patients with lupus nephritis. Am J Kidney Dis 43:28–36

CASE 48

A 19-year old female presents with Raynaud's phenomenon, arthralgias, widely scattered purpuric lesions on the lower extremities, fever, and mild diarrhea. She also had episodes of clumsiness in the right lower extremity. She takes no medications. Her physical examination reveals a BP of 140/80 mmHg. Areas of confluent purpura are present over the dorsum of both feet. The plantar reflex is upgoing on the right. Laboratory studies show a serum creatinine of 1.0 mg/dl and urinalysis shows 2+ protein and 2+ blood. Hemoglobin is 10.0 g/dl, WBC 4500/mm3, and platelet count is 18,000 mm3. Schistocytes are present in the peripheral smear. C3 and C4 complements are normal. A fluorescent ANA is elevated at 1:160. The prothrombin time and activated partial thromboplastin time are normal.

Which ONE of the following is most likely to explain the underlying cause of her disorder?

A. AntiDNA-dDNA immune complex deposited in glomeruli vessels provoking a systemic vasculitis
B. Antibodies to ADAMTS-13 provoking impaired cleavage of von Willebrand factor multimers, platelet microthrombi, and a thrombotic microangiopathy
C. Antibodies to topo-isomerase-I provoking a sclerodermatous lesion in renal vessels
D. Peripheral embolic disease from lupus-induced marantic (nonbacterial) endocarditis of the mitral valve
E. Intestinal infection with shigella (Type B) producingverotoxin

The correct answer is B. This patient has all the features of thrombotic microangiopathy (purpura, neurological abnormalities, fever, thrombopenia, anemia, fragmented erythrocytes (schistocytes), hematuria, and proteinuria) along with a positive ANA, Raynaud's phenomenon, and arthralgias. This is most likely due to an acquired deficiency of ADAMTS-13 cleaving enzyme due to antibody formation. The lack of hypocomplementemia indicates that immune complexes are not involved. There are no features to suggest scleroderma other than Raynaud's phenomena. Infective endocarditis is a possibility (with cerebral emboli), but the normal complement levels, schistocytes, and thrombocytopenia suggest otherwise. A diarrhea-associated hemolytic uremic syndrome (Shig toxin-related) is possible, but the positive ANA and artheralgia suggest otherwise.

Reference

Coppo R, Bengoufa D, Veyradier A, et al. (2004) Severe ADAMTS-13 deficiency in adult idiopathic thrombotic microangiopathies defines a subset of patients characterized by various auto-immune manifestations, lower platelet counts and mild renal impairment. Medicine 83:233–244

CASE 49

A five-year old boy develops nephritic syndrome and is found to have focal segmental glomerulosclerosis (FSGS) upon biopsy. He is tested for genetic mutations leading to FSGS and is found to have a compound heterozygote defect in the *NPHS2* gene for podocin.

Which ONE of the following is true about this patient's FSGS?

A. He is more likely to be steroid-resistant than a patient without the podocin mutation.
B. His disease is more likely to recur in the allograft than a patient without podocin mutation.
C. He should not be treated for his FSGS because it will be resistant to all therapy.
D. The defect in this patient is an autosomal dominant one.
E. Patients with this genetic defect are likely to present at any age with the nephritic syndrome.

The correct answer is A. Patients with mutations in the *NPHS2* gene encoding for podocin, (whether homozygote or compound heterozygote are found) are likely to be children or young adults. Patients with this autosomal recessive defect typically are steroid resistant and usually do not have recurrences in the allograft. Despite this generalization about therapy, attempts at treatment should be made with immunosuppressive agents, if otherwise indicated, because not all patients have been resistant to therapy.

References

Caridi C, Bertelli R, Scolari F, et al. (2003) Broadening the spectrum of diseases related to podocin mutations. J Am Soc Nephrol 14:1278–1286

Ruf RG, Lichtenberger A, Karle SM, et al. (2004) Patients with mutations in NPHS2 (podocin) do not respond to standard steroid treatment of nephritic syndrome. J Am Soc Nephrol 15:722–732

Weber S, Gribouval O, Esquivel EL, et al. (2004) NPHS2 mutation analysis shows genetic heterogeneity of steroid-resistant nephritic syndrome and low-transplant recurrence. Kidney Int 2004; 66:571–579

CASE 50

Which ONE of the following is true about renal transplantation in children with focal segmental glomerulosclerosis?

A. For African-American children with FSGS, renal survival after transplantation is worse than for African-American patients with other causes of ESRD.
B. For children with FSGS who are NOT African-American, living-related and cadaver transplantation gives equal renal survival rates.
C. Among children with FSGS who are NOT African-American, the rate of allograft failure is higher than with other causes of ESRD.
D. Recurrence rates in children are similar to rates in adults, but the response to plasmapheresis and high-dose cyclosporine is better than in adults.
E. Recurrence rates in children are higher than in adults, but the response to plasmapheresis and high-dose cyclosporine therapy is similar to that in adults.

The correct answer is C. African-American children with FSGS do equally as well with renal transplant survival as they do with other causes of ESRD. For children who are NOT African-American, allograft failure rates are higher with FSGS than with other causes of ESRD. Nevertheless these children who are not African-American still have better allograft survival rates with living related transplants. Recurrence rates in the allograft are higher in children than in adults, but response to plasmapheresis is better in children.

References

Ghiggeri G (2004) Recurrent focal glomerulosclerosis in the era of genetics and podocyte proteins: theory and therapy. Nephrol Dial Transplant 19:1036–1040

Huang K, Ferris ME, Andreoni KA (2004) The differential effect of race among pediatric kidney transplant recipients with FSGS. Am J Kidney Dis 43:1082–1090

CASE 51

A 12-year old girl develops mild arthralgias and edema. She is found to have a positive fluorescent ANA, a negative dsDNA antibody, and a borderline low-serum complement level. She has 4.5 g protinuria daily with a serum creatinine level of 0.8 mg/dl and a urinalysis without urinary sediment, but with 3+ proteinuria. Renal biopsy shows thickening of glomerular capillary walls, but only mesangial cell proliferation. Immunofluorescence microscopy was positive for IgG, IgA, IgM, C3, and C1q in a fine granular pattern along the glomerular capillary walls and in the mesangium. Electron microscopy shows epimembranous, mesangial deposits, and tubuloreticular inclusions in the endothelial cells, but no subendothelial deposits.

Which ONE of the following statements regarding this patient's possible therapies has been confirmed in randomized, controlled trials?

A. Oral prednisone is as likely as IV cyclophosphamide to induce a remission of proteinuria and the nephrotic syndrome.
B. Oral prednisone is as likely as IV cyclosporine to induce a remission of proteinuria and the nephritic syndrome.
C. Oral prednisone is as likely as IV cyclosporine to induce a remission of proteinuria and the nephritic syndrome.
D. Relapse of the nephritic syndrome after therapy is more likely with IV monthly pulse cyclophosphamide than with oral cyclosporine.
E. Mycophenolate mofetile is more effective than IV cyclophosphamide in inducing a remission of the nephritic syndrome.

The correct answer is C. Membranous lupus often presents with the nephritic syndrome without full serologic activity. Certain findings of the biopsy are strongly suggestive of lupus membranous nephropathy. The presence of mesangial hypercellularity and deposits does suggest this is not just idiopathic membranous, but rather a secondary form. In the presence of tubuloreticular inclusions and a positive ANA in the blood, the diagnosis of lupus membranous is confirmed. In both the older (WHO) and current (International Society of Nephrology [INS]/Renal Pathology Society [RPS]) classification of membranous lupus, mesangial deposits are considered part of the Class V pattern. The *full house* positively for immunoglobulins and complement is also very suggestive of lupus and HIV-associated nephropathy. Both lupus nephropathy biopsies and HIV-associated nephropathy have tubuloreticular inclusions in the endothelial cells, but HIV-associated nephropathy is typically a collapsing form of FSGS. In a controlled randomized trials of membranous lupus nephropathy at NIH, cyclosporine or monthly or IV of ocyclophosphamide pulses were both superior to corticosteroids in reducing remission of the proteinuria and the nephritic syndrome. Cyclosporine gave a more rapid remission than IV cyclophosphamide, but cychlophosphamide was associated with fewer relapses when therapy was discontinued. MMF has not yet been tested in any large or controlled series

of membranous lupus patients, although it has been successful in small numbers of patients with this pattern and in larger trials with patients with proliferative lesions.

Reference

Weening JJ, D'Agati VD, Schwartz MM, et al. (2004) for the ISN and Renal Pathology Society Working Group on the Classification of lupus Nephritis: The classification of glomerulonephritis in systemic lupus erythemarosus revisited. Kidney Int 65:521–530

CASE 52

Which ONE of the following statements is TRUE regarding HIV-infected patients who have lesions other than HIV-associated nephropathy (HIVAN) in a renal biopsy?

A. They are just as likely to be African-American as HIVAN patients.
B. They progress more rapidly to ESRD than HIVAN patients.
C. The use of anti-retroviral agents slows their progression to ESRD.
D. They present with the same incidence of hypertension and the same level of renal insufficiency as HIVAN patients.
E. They are less likely to be African-American and have less severe hypertension than HIVAN patients.

The correct answer is E. A recent large series of biopsied HIV-positive patients with diseases other than HIVAN found them less likely to be African-American and to have less severe hypertension and reduction of GFR than HIVAN patients. Use of antiretroviral therapy, although benefiting HIVAN patients in this analysis, did not alter the progression to ESRD of HIV-positive, non-HIVAN patients.

Reference

Szczech LA, Gupta SK, Habash R, et al. (2004) The clinical epidemiology and course of the spectrum of renal disease associated with HIV infection. Kidney Int 66:1145–1152

CASE 53

Which therapy for HIV-associated nephropathy (HIVAN) has been proven to delay the progression to renal failure in a controlled randomized trial?

A. Angiotensin converting enzyme inhibition
B. Corticosteroids
C. Highly active antiretroviral therapy (HAART)

D. Angiotensin II receptor blockade
E. None of the above

The correct answer is E. No therapy has been proven in prospective randomized controlled trials to be the treatment of choice for HIVAN. There is strong suggestive evidence of the benefit of blocking the rennin-angiotensin system, and for HAART. Corticosteroids have been shown to be effective in very select populations of HIVAN patients. Current therapy should be individualized based on the clinical features of the patient and the ability to tolerate each therapy.

Reference

Weiner NJ, Goodman JW, Kimmel PL (2003) The HIV-associated renal disease: current insight into pathogenesis and treatment. Kidney Int 63:1618–1631

CASE 54

A 10-year old boy is seen in your office for evaluation of chronic kidney disease (CKD) secondary to IgA nephropathy. He currently smokes twenty cigarettes per day. On examination, his BP is 135/85 mmHg. Laboratory studies include serum creatinine of 1.4 mg/dl and spot urine albumin-to-creatinine ratio of 200 mg/g (normal <20 mg/g). Estimated GFR is 72 ml/min/1.73 m^2. His serum total cholesterol is 190 mg/dl, and low-density lipoprotein (LDL) cholesterol is 125 mg/dl. He agrees to go on low-cholesterol diet and begins an exercise program. Fasting lipid levels are measured in three months and include serum total cholesterol of 175 mg/dl and a LDL cholesterol of 120 mg/dl.

Which ONE of the following is true regarding the MOST effective therapy for this patient?

A. You recommended that the patient continue on a low-cholesterol diet with follow-up lipid measurements in six months.
B. Therapy with fish oil should be started to reduce his risk of cardiovascular events.
C. Therapy with a fibrate such as gemfibrozil should be started.
D. Therapy with a statin should be started with a target LDL cholesterol of <100 mg/dl.
E. Therapy with niacin should be started with a target LDL cholesterol of <100 mg/dl.

The correct answer is D. Patients with CKD should be considered the highest risk group for the development of cardiovascular events. Aggressive risk factor reduction should be instituted. In this man, risk factor reduction should include smoking cessation, BP control, and lipid management. The target LDL cholesterol should be <100 mg/dl. Drug therapy needs to be started because three months of dietary

modification and exercise has not achieved the target LDL cholesterol goal. There is no evidence that fish oil can reduce the risk of cardiovascular disease. The recommended first-line drug class is the statin. Fibrates are indicated for patients with fasting triglycerides >500 mg/dl, or for patients who do not tolerate statin.

References

Kasiske BL (1998) Hperlipidemia in patients with chronic kidney disease. Am J Kidney Dis 32 (suppl 3):S142–S156

Mann JF, Gerstein H, Pogue J, et al. (2001) Renal insufficiency as a predictor of cardiovascular outcomes and the impact of ramipril: the HOPE randomized trial. Ann Intern Med 134:629636

CASE 55

A 12-year old white girl who was followed for two years for juvenile rheumatoid arthritis with known skin, joint, lung, and cardiac involvement presents with a five-day history of shortness of breath. Her past medical history, except for the above, is remarkable only for mild easily controllable hypertension. There is no history of cardiac or renal disease. Her current medications are hydrochlorothiazide 25 mg/day, fenoprofen 200 mg three times a day, and occasional acetaminophen for headaches. There is no other drug or toxin exposure elicited in the history. Her oral intake had been poor due to nausea.

BP and pulse are 90/60 mm Hg, 78 beats/min supine, and 75/50 mm Hg, 90 beats/min standing. Respiratory rate is 26 per minute, and oral temperature is 38 °C. Skin shows an erythematous, maculopapular rash on the upper arms, shoulders, and trunk, which the patient says has been present for two days. Pulmonary and cardiac examinations are unremarkable except that P2 = A2 in intensity. The remainder of the physical examination is unremarkable.

Laboratory studies: Hemoglobin 12.5/dl, hematocrit 37%, WBC 6.3/mm^3 (normal differential), sodium 142 mEq/l, potassium 4.4 mEq/l, chloride 97 mEq/l, total CO_2 29 mEq/l, BUN 29 mg/dl, creatinine 3.1 mg/dl, glucose 105 mg/dl. Urinalysis shows a specific gravity of 1.011, 2+ protein, pH 6, 4–6 RBC, 6–8 white blood cells, no epithelial cells, no bacteria, and occasional hyaline casts. Wright's stains of the urine multiplied by 2 shows no eosinophils. Urine chemistries show sodium 32 mEq/l, potassium 30 mEq/l, chloride 20 mEq/l, and fractional excretion of sodium is 3%. Chest x-ray reveals bilateral lower lobe interstitial infiltrates, unchanged from previous films, and an ECG is unremarkable. A 24-hour urine completed during the patient's first 24 hours of hospitalization reveals a creatinine clearance of 27 ml/min, 1.3 g protein, and total volume 1,100 ml. Dexamethasone at 4 mg/day was begun for her dyspnea with gradual improvement. Despite correction of her orthostatic BP with normal saline, however, her renal function deteriorates until by Day 8 she is oliguric with a BUN of 90 mg/dl and serum creatinine of 9.2 mg/dl. On Day 9, a renal biopsy is done.

What ONE of the following is the most likely pathology finding in this renal biopsy?

A. Acute tubular necrosis
B. Prenatal azotemia
C. Acute interstitial nephritis
D. Acute glomerulonephritis
E. Renal vein thrombosis

The correct answer is C. The renal biopsy showed normal glomeruli, interstitial edema, with an intense inflammatory infiltrate consisting predominantly of mononuclear cells and plasma cells, with about 5% eosinophils and no vascular lesions. The biopsy was consistent with acute interstitial nephritis. The combination of fever, skin rash, and acute deterioration of renal function strongly suggests acute interstitial nephritis. The negative history for toxins is against the diagnosis of acute tubular necrosis. The renal biopsy was done to determine the continuing need for the steroids that were started for her pulmonary problem.

Both hydrochlorothiazide and fenoprofen have been associated with acute interstitial nephritis, the latter drug also having been associated with the nephritic syndrome papillary necrosis and acute renal failure secondary to underperfusion. The reactions seen with both drugs can occur with variable times of exposure and five days to five weeks after initial exposure, even if the drug is stopped. Only a minority of patients with this type of acute interstitial necrosis present with the classic triad of fever, rash, and eosinophilia. Eosinophiluria is said to be pathognomonic of acute interstitial nephritis. The mechanism of acute interstitial nephritis is unclear, but a recent report demonstrating that the cells in the interstitial infiltrate of acute interstitial nephritis, secondary to fenoprofen, stained exclusively for T-lymphocyte markers suggesting an immunologic role. The prognosis for recovery of renal function is good, and there is suggestive evidence that steroid hastens recovery of renal function.

Reference

Schwartz A, Krause PH, Kunzendrof U, et al. (2000) The outcome of acute interstitial nephritis: Risk factors for the transition from acute to chronic interstitial nephritis. Clin Nephrol 54:179–190

CASE 56

This patient is a 16-year old white female referred to our medical center from an institution for the mentally retarded for the purpose of chronic hemodialysis. A review of the patient's history revealed that she had initially been seen at another hospital because of hematuria. Physical examination, at that time, was remarkable only for the presence of an acne-like rash over the face and a mildly tender left flank

mass. An IVP was performed that revealed bilateral renal masses. Ultrasonography demonstrated the masses to be solid in character. Renal angiography was then performed. On the basis of the angiogram, renal cell carcinoma was suspected, and the patient was sent to surgery. At the time of surgery, a frozen section of the renal lesion was obtained and interpreted as consistent with liposarcoma—on this basis, bilateral nephrectomy was carried out.

What is the most likely diagnosis?

A. Renal cell carcinoma
B. Wilm's tumor
C. Renal angiomyolipoma
D. Meduallary cystic kidney disease
E. Medullary sponge kidney

The correct diagnosis is C. Renal angiomyolipoma is a benign hemartomatous tumor of the kidney. This tumor is rare in the general population but may occur with up to 80% frequency in patients with tuberous sclerosis—a disease characterized by epilepsy and mental retardation associated with nodular lesions in the brain and the facial lesions of adenoma sebaceum. Pathologically, this tumor is composed of vascular, fatty, and smooth muscle, and may be misdiagnosed as liposarcoma. Although angiomyolipoma is frequently multicentric, this tumor is considered a benign process, because neither malignant change nor metastasis has been demonstrated. Radiologic fissures of this tumor are marked radiolucency on plain films due to high lipid content and multiple small arterial aneurysms without arteriovenous shunting on angiography. Diagnostic radiologic features in our patient may be absent, however, giving an appearance similar to renal cell carcinoma.

Reference

Narla LD, Slovis TL, Watts FB, et al. (1988) The renal lesions of tuberosclerosis (cysts and angiomyolipoma)-secreening with sonography and computerized tomography. Pediatr Nephrol 18:205–209

CASE 57

A 19-year old boy is referred to you for evaluation of rising serum creatinine and hypertension. He has a history of intravenous drug abuse and unprotected sex. He is HIV positive and hepatitis C seropositive. He has been treated with highly active anti-retroviral (HAART) therapy, including stavudine, lamivudine, and indinavir. His most recent serum creatinine was 3.1 mg/dl 3 months after a value of 2.0 mg/dl. Urine dipstick is negative for blood or protein, and ultrasound examination of the kidneys shows mildly reduced renal size without any calcifications or

nephrocalcinosis. Microscopic examination of the urine reveals 20 to 30 WBCs/hpf without hematuria. Occasional crystals were seen.

What is the most likely cause of his renal disease?

A. Collapsing FSGS
B. Vasculitis secondary to hepatitis C nephropathy
C. Tubulointerstitial fibrosis with intratubular crystals secondary to indinavir nephropathy
D. Heroin nephropathy
E. Tuburculous nephritis

The correct answer is C. Indinvir, a protease inhibitor used for treating HIV that is extremely insoluble at physiologic pH levels, is lithogenic. Patients treated with indinavir will have a very high frequency of kidney stone formation.

Reference

Saltel E, Angel JB, Futter NG, et al. (2000) Increased prevalence and analysis of risk factors for indinavir nephrolithiasis. J Urol 164:1895–1897

CASE 58

This 12-year old Hispanic boy complained of gross hematuria during the day preceding hospital admission. The hematuria was accompanied by dysuria, frequency, and left costovertebral angle tenderness. He also had a history of upper respiratory tract infection associated with chills of several days' duration.

The BP was 124/78 mm Hg. No skin rashes, edema, or pharyngeal lesions were noted. No murmurs were heard.

Laboratory studies showed hematocrit of 43.6%, WBC 9,800 mm^3, blood urea nitrogen 12 mg/dl, creatinine 1.1 mg/dl, albumin 4.2 g/dl, sodium 144 mEq/dl, potassium 4.5 mEq/l, chloride 107 mEq/l, and bicarbonate 29 mEq/l. There was gross blood and 3+ protein in the urine. Urinalysis showed many RBCs and WBCs, occasional bacteria, and rare white blood cell casts. The 24-hour urinary protein excretion was 4.4 g. C_3 was 148 mg/dl (normal 100–200) and C_4 31 mg/dl (normal 10–75). Rheumatoid factor was nonreactive, and the anti-nuclear antibody titer was less than 1:20. Culture of a clean-catch urine specimen showed 1,000 colonies/ml alpha streptococci. A percutaneous needle biopsy of the kidney was performed.

What is the most likely diagnosis?

A. IgA nephropathy
B. Idiopathic focal segmental glomerulosclerosis
C. Lupus nephritis

D. Idiopathic membranoproliferative glomerulonephritis
E. Idiopathic membranous nephritis

The correct answer is A. The light microscopic examination of the biopsy showed focal proliferative glomerulonephritis with crescents involving 8 (13%) of 62 glomeruli. One arteriole showed hyaline changes. No unequivocal vasculitis was seen, and tubules and interstitium were unremarkable.

Electron microscopy demonstrated mesangial electron-dense deposits, increased mesangial matrix and cells, segmental endothelial cell sloughing, and capillary loop collapse and fibrin deposit in Bowman's space. Epithelial cell foot processes were extensively obliterated.

Using immunofluorescence microscopy, glomeruli showed IgA and, to a lesser extent, C_3 and IgG, in a diffuse mesangial pattern. Segmental and focal staining for fibrin and fibrinogen-related antigen was also noted. These results support the diagnosis of IgA nephropathy (Berger's disease).

In retrospect, the patient recalled several episodes of gross hematuria over the year prior to hospitalization. The case, therefore, illustrates the usual presentation of IgA nephropathy, which is that of recurrent gross or microscopic hematuria in a young man. These episodes are usually precipitated by and synchronous with upper respiratory-tract infections. Although moderate proteinuria (less than 2 g/24 h) is the rule, approximately 10% of patients may show nephrotic range proteinuria, as was the case here. Hypertension and, on occasion, acute or chronic renal failure, may occur.

Reference

Yoshikawa N, Lijima K, Ito H (1999) IgA nephropathy in children. Nephron 83:1–12

CASE 59

A seven-year old girl presents after having pedal and periorbital edema for three weeks. She denies gross hematuria, a recent upper respiratory infection, arthralgias, or skin rash. She has no history of diabetes mellitus and is not pregnant.

The physical examination is normal except for 4+ pedal edema. Her BP is 130/90 mmHg. Laboratory tests reveal: BUN 26 mg/dl, plasma creatinine 1.3 mg/dl, plasma albumin concentration 2.4 g/dl, and a negative antinuclear antibody titer. The urinalysis shows 4+ proteinuria, oval fat bodies, free fat droplets, 20–25 red cells/HPF, and occasional red cell casts. A 24-hour urinary protein excretion is 6.2 g.

What is the most likely diagnosis?

A. Lupus nephritis
B. Membranoproliferative glomerulonephritis
C. Focal segmental glomerulosclerosis

D. IgA nephropathy
E. Hemolytic uremic syndrome

The correct answer is B. This woman has nephrotic syndrome but also a nephritic sediment. These findings plus edema, renal insufficiency, and mild hypertension suggest the presence of diffuse glomerulonephritis. In this age group, SLE membranoproliferative glomerulonephritis and, less often, anti-glomerular basement membrane antibody disease is the most likely diagnosis. The lack of systemic symptoms or antinuclear antibodies makes SLE improbable. Similarly, the absence of pulmonary hemorrhage and severe renal insufficiency are unusual in anti-GBM antibody disease. Thus, membranoproliferative glomerulonephritis seems to be the leading diagnosis. This was confirmed by renal biopsy.

Reference

Madaio MP, Harrington JT (2001) The diagnosis of glomerular diseases: Acute glomerulonephritis and the nephritic syndrome. Arch Intern Med 161:25–34

CASE 60

A 13-year old girl is admitted to the hospital complaining of persistent vomiting of 10 days' duration. Past history is otherwise unremarkable. Physical examination shows a thin white girl who appears somewhat confused. BP is 100/80 mm Hg, pulse is 110 beats/minute, and respiratory rate is 10/minute. The remainder of the physical examination is unremarkable except for moderate mid-epigastric tenderness.

Blood electrolytes are sodium 130 mEq/l, potassium 2.2 mEq/l, chloride 50 mEq/l, and bicarbonate 60 mEq/l. The creatinine is 4 mg/dl, the BUN is 80 mg/dl, and the glucose is 85 mg/dl. Urine sodium concentration is 62 mEq/l.

What is the most likely cause of this patient's renal failure?

A. Acute tubular necrosis
B. Prerenal azotemia
C. Acute golerulonephritis
D. Acute cortical necrosis
E. Renal vein thrombosis

The correct answer is A. The differential diagnosis of this patient's disorder rests between renal failures of undetermined cause that results in uremia and vomiting vs. vomiting that results in severe volume depletion and prerenal azotemia. The finding of high urine sodium might point to the former diagnosis. The urine sodium as a means to distinguish between renal failure due to parenchymal disease and renal failure due to underperfusion is not useful in patients who have metabolic alkalosis secondary to vomiting. The rise in bicarbonate concentration seen in this disorder

will result in the spillage of some bicarbonate into the urine. This bicarbonaturia obligates the excretion of a cation, some of which will be sodium. The critical test in this patient is to measure the urine chloride concentration. In this patient, this value was 0. Thus, the kidney retained the capacity to reabsorb all the filtered chloride. This finding, plus the patient's severe hypokalemic metabolic alkalosis, suggests vomiting is the primary disorder. The BUN, which is typically elevated out of proportion to the rise of creatinine in patients with prerenal azotemia, will not rise in this fashion in patients who vomit owing to the lack of nitrogen intake. The infusion of large amounts of sodium chloride and potassium chloride not only corrected the hypokalemic metabolic alkalosis in this patient, but resulted in the restoration of renal function to normal within three days. Subsequent evaluation showed the presence of severe peptic ulcer disease that was the cause of the patient's vomiting. Urinalysis was also helpful in this patient, showing no proteinuria or formed elements.

Reference

Esson ML, Schrier RW (2002) Diagnosis and treatment of acute tubular necrosis. Ann Int Med 137:744–752

Chapter 9
Chronic Kidney Disease

CASE 1

A 10-year old African-American girl has progressive kidney failure from biopsy-proven FSGS. Her current serum creatinine is 3.7 mg/dl and estimated GFR is 16 ml/min/1.73 m^2. A urine protein-to-creatinine ratio is 4560 mg/g. Other medical problems include hypertension, currently treated with furosemide 40 mg orally twice daily and lisinopril 40 mg once daily. Her BP is 160/85 mmHg.

Which ONE of the following statements is correct?

A. The diastolic BP is the best predictor of renal outcome.
B. Target systolic BP should be 110 mmHg to 129 mmHg.
C. Systolic BP < 110 mmHg has been associated with a lower risk of kidney disease progression.
D. Addition of a dihydropyridine CCB should be avoided because of the risk of accelerating the progression of her renal disease.
E. Studies have proven that the level of BP does not affect the rate of loss of kidney function in hypertensive African-Americans.

The correct answer is B. This patient has Stage 4 CKD secondary to FSGS. Significant proteinuria is present and the BP (BP) is elevated. Controlling BP can slow the progression of kidney failure, although the exact target BP remains somewhat controversial. In a meta-analysis of 11 randomized control trials that compared the efficacy of antihypertensive treatment with or without an ACE inhibitor for patients with nondiabetic kidney disease, it was demonstrated that a systolic BP between 110 to 129 mmHg was associated with the lowest risk of kidney disease progression. In this analysis, the systolic BP was not predictive of progression. Systolic BP less than 110 mmHg was associated with a higher risk for kidney disease progression, making answers A and C incorrect. Dihydropyridine CCBs should not be the drugs of first choice in the setting of CKD because these drugs have been associated with greater amounts of proteinuria compared to ACE inhibitors or angiotensin-receptor blockers (ARB). When used in combination with an ACE or ARB, however, dihydropyridine CCBs can effectively lower BP and do not limit the antiproteniuric effects of the ACR inhibitor or ARB. In the African-American Study of Kidney

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disease (AASK) in hypertension trial, the effects of BP-lowering and antihypertensive drug classes on the progression of hypertensive kidney disease were studied. The mean GFR slope from baseline through four years of follow-up was not different between patients randomized to a low BP group (128/78 mmHg) vs. a usual BP group (141/85 mmHg). There was also no difference in the incidence of reduction in GFR by 50%, ESRD, or death. This study did not address the issue of higher levels of BP, which undoubtedly accelerate the progression of VKD in this population. Therefore, answer E is false.

Reference

Barkis GL, Weir MR, Seic M, et al. (2004) Differential effects of calcium antagonist subclasses on markers of nephropathy progression. Kidney Int 65:1991–2002

CASE 2

Which ONE of the following is TRUE regarding cardiovascular disease (CVD) in patients with CKD?

A. Microalbuminuria is not a risk factor for CVD.
B. Most patients with CKD will die of CVD before they reach ESRD.
C. CKD is a risk factor for CVD but not for stroke or peripheral vascular disease.
D. CKD is a risk factor for CVD only when the serum creatinine is >3 mg/dl.
E. A higher prevalence of traditional risk factors such as hypertension and dyslipidemia account for the increased risk of CVD in patients with CKD.

The correct answer is B. The presence of CKD is an independent predictor of CVD. The risk holds even mild elevation in the serum creatinine, or small decreases in GFR, and not for a serum creatinine greater than 3 mg/dl. Therefore, answer D is incorrect. Microalbuminuria is an independent risk factor for CVD and may be a more general marker of disordered function of the vascular endothelium. In a study of the Medicare population, Collins et al.. demonstrated that patients with a diagnosis of CKD were 5 to 10 times more likely to die than to reach ESRD. Therefore, answer B is incorrect. Not only is CKD a risk factor for CVD, but recent analyses have also shown that the presence of CKD is a risk for both cerebral and peripheral vascular disease.

References

Collins AJ, Li S, Gilbertson DT, et al. (2003) Chronic kidney disease and cardiovascular disease in Medicare population. Kidney Int 87:S24–S31

Ritz E, McClellan W (2004) Overview: Increased cardiovascular risk in patients with minor renal dysfunction: An emerging issue with far-reaching consequences. J Am Soc Nephrol 15: 513–516

Romundstad S, Holmen J, Kvenlid K, et al. (2003) Microalbuminuria and all-cause mortality in 2089 apparently healthy individuals: a 4.4-yrat follow-up study. The Nord-Trondelag Health Study (HUNT), Norway. Am J Kidney Dis 42:466–473

CASE 3

A 16-year old male has CKD secondary to IgA nephropathy. His current GFR is 18 ml/min/1.73 m^2. He has hypertension controlled with a loop diuretic and a dihydropyridine CCB. His serum cholesterol is 169 mg/dl. C-reactive protein (CRP) level was twice the upper limit of the normal range.

Which ONE of the following statements regarding cardiovascular risk and management is correct?

A. The presence of CRP is a predictor of cardiovascular risk.
B. Homocystein levels should be checked and if elevated, treatment vitamin B6 should be initiated to reduce progression of his CKD.
C. Traditional cardiovascular risk factors such as hypertension and elevated cholesterol are minor risk factors in patients with CKD.
D. Antioxidant therapy has been demonstrated to reduce future cardiovascular events.
E. Aspirin at a dosage of 325 mg should be avoided because of the risk of worsening his renal failure and its lack of efficiency in patients with CKD.

The correct answer is A. In CKD and ESRD patients, CVD is linked to inflammation. CRP has been used as a surrogate for inflammation with levels being predictive of the development of CVD. Homocystein levels are often elevated in patients with CKD and have been associated with the risk of CVD. Although high levels of folic acid, vitamin B12, and vitamin B6 can lower homocystein levels, there is no evidence that such therapy reduces cardiovascular risk. There is no data that antioxidant therapy reduces CVD in predialysis CVD patients, although two randomized trials suggest CVD in dialysis patients can be reduced by antioxidant therapy with either vitamin E or acetylcystein. Finally, aspirin at a dose of 325 mg once a day should be part of the management of CKD patients.

Reference

Muntner PLLH, Kusek JW, Chen J, et al. (2004) The prevalence of nontraditional risk factors for coronary heart disease in patients with chronic kidney disease. Ann Intern Med 140:9–17

CASE 4

A six-year old boy was diagnosed with hypertension eight years ago. His current serum creatinine is 2.3 mg/dl and his estimated GFR is 37 ml/min/1.73 m2. His 24-hour urinary protein excretion is 0.6 g.

Which ONE of the following choices is TRUE regarding his therapy?

A. A target mean arterial pressure (MAP) of 92 mmHg is more effective in preventing the progression of his kidney disease than is a MAP of 102 mmHg.
B. A kidney biopsy is necessary for guiding therapy.
C. An ACE inhibitor is more effective than a β-blocker in slowing the progression of kidney disease.
D. The type of antihypertensive does not affect kidney disease outcomes.
E. A dihydropyridine CCB is more effective than a β-blocker in slowing the decline in GFR.

The correct answer is C. The African-American Study of Kidney disease and hypertension (AASK) trial examined the effects of BP-lowering on progression of hypertensive kidney disease. Patients were treated with either a β-blocker, ACE inhibitor, or a dihydropyridine CCB. None of drugs were associated with a difference in GFR slope. ACE inhibitors, however, decreased the risk of developing the clinical composite outcome by 22% compared to the β-blocker, and by 38% compared to the CCB. Thus, answers A, D, and E are incorrect. Answer B is incorrect because biopsies on a subset of patients enrolled in AASK demonstrated typical hypertensive nephrosclerosis in patients with a clinical diagnosis of hypertensive nephrosclerosis.

References

Fogo AG (2003) Hypertensive risk factors in kidney disease in African Americans. Kidney Int 63:2331–2341

Wright JT, Glassock R, Herbet I, et al. (2002) Effect of BP lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK trial. JAMA 288:2421–2431

CASE 5

A four-year old girl is admitted to the hospital with failure to thrive. Upon examination, she is cachectic and has 2+ lower extremity pitting edema. Her serum creatinine is 1.0 mg/dl. A random spot urine protein-to-creatinine ratio is 2.6 g/g. A complete 24-hour urine collected during the second hospital day reveals 1.6 g of protein and 453 mg of creatinine.

Which ONE of the following statements is TRUE?

A. The patient has nephritic range proteinuria.
B. There is contradictory information presented regarding whether or not patient has nephritic range proteinuria.
C. There is insufficient information to determine whether or not the patient has nephritic range proteinuria.

D. The random spot urine protein-to-creatinine ratio is misleading because of the low creatinine production.
E. It is not valid to use protein-to-creatinine ratios to assess proteinuria when the serum albumin level is low.

The correct answer is D. The patient's spot urine protein-to-creatinine ratio is misleading because the patient is cachectic and produces only approximately 453 mg of creatinine a day. Other mechanisms besides nephritic syndrome (such as malnutrition) are needed to account for this patient's low albumin and edema.

Reference

Hogg RJ, Portman RJ, Millimer D (2000) Evaluation of proteinuria and nephritic syndrome in children: Recommendations from a pediatric nephrology panel established at National Kidney Foundation conference on proteinuria, albuminuria, risk, detection, and elimination (PARDE). Pediatrics 105:1242–1249

CASE 6

A 10-year old boy with FSGS presents for medical care. His BP is 150/95 mmHg (on a CCB), his total cholesterol is 28 mg/dl with LDL cholesterol 130 mg/dl, and his hemoglobin A1C is 6.0. His serum creatinine is 1.3 mg/dl, and his dipstick urinalysis shows 1+ proteinuria.

Which ONE of the following interventions has NOT been shown in randomized trials to slow the progression of CKD in such a patient?

A. Lowering BP to 140/90 mmHg or less
B. Treatment with ACE inhibitors
C. Treatment with angiotensin-receptor blocker (ARB)
D. Tight glycemic control
E. Reduction in serum cholesterol

The correct answer is E. Currently, there s no convincing data that cholesterol-lowering slows the progression of CKD. Lowering of total and LDL cholesterol, of course, may have other beneficial effects such as reducing CVD in this high-risk CKD population. According to the K/DOQI guidelines, the only therapies shown to reduce progression of CKD are tight BP control, use of ACE inhibitors or ARB, and tight glycemic control among diabetic patients.

Reference

Ruggenenti P, Perna A, Remuzzi (2003) Retarding the progression of chronic renal disease: The neglected issue of residual proteinuria. Kidney Int 63:2254–2261

CASE 7

A 13-year old boy has biopsy-proven IgA nephropathy, His hypertension has been controlled with a loop diuretic and ACE inhibitors and an angiotensin-receptor blocker (ARB). Currently his serum creatinine is 4.3 mg/dl and his 24-hour urinary protein excretion is 4.1 g. A fasting lipid profile shows the following values: cholesterol 244 mg/dl, triglyceride 270 mg/dl, HDL 45 mg/dl, and LDL 16 mg/dl.

Which ONE of the following statements is true regarding his dyslipidemia?

A. Treatment with a statin can lower serum cholesterol but has no effect on LDL cholesterol.
B. Target LDL cholesterol should be <140 mg/dl.
C. Addition of a cholesterol absorption inhibitor (ezetimibe) to a statin has no additional benefit on lowering LDL cholesterol compared to the statin alone.
D. Treatment with a statin has been associated with a reduction in proteinuria.
E. Statin therapy in this patient has been demonstrated to decrease the time to a first major vascular event.

The correct answer is D. Treatment with a statin can lower both serum cholesterol, as well as LDL cholesterol, and is indicated in this patient with significant CKD. There is evidence that the addition of ezetimibe—a cholesterol absorption inhibitor—to a statin does have additional benefit in lowering LDL compared to the statin alone (SHARP study). Treatment with a statin in patients with CKD who are already being treated with an ACE inhibitor or ARB can decrease proteinuria and stabilize creatinine clearance.

Reference

Baigent C, Landry M (2003) Study of Heart and Renal Protection (SHARP). Kidney Int 63: S207–S210

CASE 8

A seven-year old boy with IgA nephropathy is admitted with sepsis. He has 1+ dipstick proteinuria and his baseline serum creatinine is 1.2 mg/dl. His estimated GFR is 66 ml/min/1.73 m^2. Patient failed to improve with antibiotic therapy and developed hypotension requiring mechanical ventilation. He received IV contrast for an abdominal CT scan. His serum creatinine rose to 2.4 mg/dl the following day.

Which ONE of the following statements is MOST correct?

A. The patient's baseline CKD is unrelated to his ARF.
B. Intravenous contrast is not contraindicated in patients with CKD.

C. The patient's IgA is not a risk factor for his ARF.
D. The patient's GFR when his serum creatinine rose to 2.4 mg/dl is approximately 30 ml/min/1.73 m^2.
E. To measure the patient's GFR, a 24-hour urine collection should have been started on the morning his serum creatinine rose to 2.4 mg/dl

The correct answer is B. It would be inappropriate to use the Schwatz or any equation to estimate GFR in a patient with ARF and not in a steady state. Similarly, 24-hour urine collection for creatinine clearance would also not be valid. Although this patient does have risk factors for contrast nephropathy, this does not mean he cannot receive IV contrast. The risks and benefits of IV contrast must be assessed on a case-by-case basis. Independent of the contrast, sepsis and hypotension are other potential causes of ARF in this patient.

Reference

Cigarroa RG, Lange RA, Williams RH (1989) Dosing of contrast material to prevent contrast nephropathy in patients with renal disease. Am J Med 86:649–652

CASE 9

A nine-year-old boy has CKD from IgA nephropathy. Two years ago he was hypertensive and his serum creatinine was 2.1 mg/dl, estimated GFR 34 ml/min/1.73 m^2. A spot urine protein-to-creatinine ratio was 2000 mg/g. Treatment was started with an ACE inhibitor. Over the last two years, his serum creatinine has increased to 3.4 mg/dl, estimated GFR has decreased to 20 ml/min/1.73 m^2, and his urinary protein-to-creatinine ratio is 2600 mg/g despite maximal dosing of his ACE inhibitor. His current BP is 125/80 mmHg.

Which ONE of the following changes in his management would be BEST?

A. Switch to a different ACE inhibitor because the current one is ineffective
B. Discontinue the ACE inhibitor and start a dihydripyridine CCB
C. Add an ARB to his current medications
D. Control BP control by starting a β-blocker
E. Reduce the dose of the ACE inhibitor to allow the BP to increase and improve perfusion to the kidney

The correct answer is C. Addition of an ARB to his current medications would be a reasonable strategy based on the results of the COOPERATE trial of patients with nondiabetic kidney disease. There is no evidence that switching to a different ACE inhibitor will be more effective. The cornerstone of therapy for this patient is inhibition of angiotensin II, therefore stopping ACE inhibitors and starting a CCB is not indicated. There is no evidence that further lowering his BP will be beneficial.

In fact, a systolic BP less than 110 mmHg has been associated with worsening renal prognosis compared to a systolic BP between 110 to 129 mmHg. His current BP is optimal.

Reference

Nakao N, Yoshimma A, Morita H, et al. (2002) Combination therapy of angiotensin II receptor blocker and angiotensin-converting enzyme inhibitor in non-diabetic renal disease: A randomized, controlled trial in Japan (CCPERATE). Lancet 361:117–124

CASE 10

A 14-year old African-American male presents with edema. BP is 150/100 mmHg. He is found to have a serum creatinine of 2.8 mg/dl and a urinary protein excretion of 6 g/24 hours. A renal biopsy shows focal and segmental glomerulosclerosis. He is started on an angiotensin-converting enzyme inhibitor and a loop diuretic. One week later, his BP is 125 mmHg, his urinary protein excretion has decreased to 3 g/day, but his serum creatinine has increased to 3.2 mg/dl.

Which of the following should be recommended?

A. Stop the ACE inhibitor, switch to a β-blocker, and evaluate for renal stenosis
B. Stop the loop diuretic
C. Continue the current antihypertensives and recheck serum creatinine in one week
D. Stop the ACE inhibitor and switch to an ARB
E. Start steroid and cyclophosphamide to treat his glomerular disease

The correct answer is C. This patient has responded to treatment with an ACE inhibitor with a decrease in BP and urinary protein excretion. His serum creatinine, however, has increased from 2.8 to 3.2 mg/dl. This is an approximately 13% increase in serum creatinine. ACE inhibitors are commonly associated with an increase in creatinine following initiation therapy, due to a preferential effect on dilating the efferent arteriol. If the increase in serum creatinine is less than 30%, the ACE inhibitor can be continued with a recheck of serum creatinine. Option A is incorrect, for the reasons discussed above. In patients with bilateral renal artery disease, serum creatinine can certainly go up on an ACE inhibitor, but it is usually more than a 30% increase, and it tends to be persistent. Option B is incorrect because it is unlikely that the loop diuretic is causing the increase in serum creatinine in the absence of evidence of volume depletion. Option D is incorrect because ARB and an ACE inhibitor are both likely to have a similar effect on an increase in serum creatinine. Option E is incorrect because there is no evidence that steroids and cyclophosphamides are indicated in the treatment of this disease.

Reference

Bakris GL, Weir MR (2000) Angiotensin-converting enzyme inhibitor-associated elevations in serum creatinine. Is this a cause for concern? Arch Intern Med 160:685–693

CASE 12

A seven-year old girl is found to have microscopic hematuria on a routine physical examination. Her mother and a maternal aunt are on hemodialysis for ESRD secondary to polycystic kidney disease. Upon examination, BP is 140/90 mmHg, pulse is 80 beats/min, and weight is 75 kg. Her serum creatinine is 1.0 mg/dl, and urinalysis shows specific gravity of 1.017, no protein, trace blood, and 5 to 10 red blood cells/high-power field. A spot urine protein/creatinine is 0.15 mg/mg. Kidney ultrasound shows multiple cysts in both kidneys.

Which of the following is true regarding her condition?

A. She does not have CKD because her serum creatinine and protein excretion are both normal.
B. Estimating GFR using the Schwatz equation is not accurate in polycystic kidney disease (PKD).
C. She has CKD based on the microscopic hematuria and abnormal renal ultrasound.
D. On the basis of her current serum creatinine, she is unlikely to develop ESRD during her lifetime.
E. GFR should be measured by 125 I-iothalamate clearance to appropriately stage her CKD.

The correct answer is C. The presence of PKD and microscopic hematuria fits the definition of CKD. Her calculated GFR based on the MDRD study equation is 65 ml/min/1.73 m^2, consistent with Stage 2 CKD. Option A is incorrect for the reasons just discussed. Option B is incorrect because there is no evidence that the Schwartz study equation is not accurate in PKD patients. Option D is incorrect because normal serum creatinine at this time point, in the setting of PKD, cannot be used to predict whether she will develop ESRD. Option E is incorrect because GFR can be calculated, and measuring GFR by 125 I-iothalamate clearance is not clinically necessary.

Which of the following should be recommended for the therapy for this patient?

A. She should be advised to lower her salt intake with follow-up BP serum creatinine in four months.
B. She should be referred for laparoscopic deroofing of her renal cysts.
C. Antihypertensive therapy should be started with a thiazide diuretic, and a β-blocker could be added if needed.

D. She should be placed on dietary protein restriction (0.6 mg/day).
E. She should be treated with angiotensin-converting enzyme inhibitor to a target BP of 130/85 mmHg.

The correct answer is E. ACE inhibitors are effective in patients with autosomal dominant PKD. In fact, hypertension tends to be an early manifestation of this disease. Part of the mechanism may be related to activation of the renin-angiotensin system secondary to local areas of renal ischemia secondary cyst compression. Option A is incorrect because her hypertension should be treated with pharmacologic agents in the setting of CKD. Option B is incorrect because laparoscopic deroofing of renal cysts does not slow the progression of PKD. Option C is incorrect for the reasons discussed above. Option D is incorrect because data from the MDRD study showed no beneficial effect of protein restriction on renal disease progression in autosomal dominant polycystic kidney disease patients.

References

Ecder T, Edelstein CL, Fick-Brosnahan GM, et al. (2001) Diuretics versus angiotensin-converting enzyme inhibitors in autosomal dominant polycystic kidney disease. Am J Nephrol 21:98–103
National Kidney Foundation: K/DOQI clinical guidelines for chronic kidney disease: evaluation, classification, and stratification (2002). Am J Kidney Dis 29 (Suppl 1) S1–S266

CASE 13

A 12-year old Asian boy has developed progressive kidney failure from IgA nephropathy. His current calculated GFR is 25 ml/min/1.73 m^2.

Which of the following statements is correct?

A. Early referral to a nephrologist is associated with increased costs of care.
B. There is no difference in hematocrit levels between patients referred early versus late to a nephrologist.
C. Patients enrolled in health maintenance organizations (HMOs) are more likely to be referred early to a nephrologist.
D. Early referral to nephrologists is associated with a higher rate of vascular access placement.
E. There is no difference in albumin levels between patients referred early versus late to a nephrologist.

The correct answer is D. Delayed referral to a nephrologist is associated with poor outcomes, more hospitalization, and higher costs. Option D is correct because early referral to nephrologists is associated with a higher rate of vascular access placement. Option A is incorrect because early referral has been demonstrated to decrease

the cost of care. Option B is incorrect, because patients referred early have higher hematocrit levels than those referred late. Option C is incorrect because health insurance provided by HMOs has been shown to be an independent predictor of late referral when examined by multivariable analysis. Option E is incorrect because early referral is also associated with higher serum albumin levels.

Reference

Arora P, Obrador GT, Ruthazer R, et al. (1999) Prevalence, predictor, and consequences of late nephrology referral at a tertiary care center. J Am Soc Nephrol 10:1281–1286

CASE 14

A 15-year old boy is seen in your office for an elevated serum creatinine level. He has focal segmental glomerulosclerosis diagnosed by renal biopsy at age 9, when he presented with nephritic syndrome. Upon examination, his BP is 140/90 mmHg, his pulse is 94 beats/min, and his weight is 68 Kg. He has 2+ peripheral edema. Laboratory studies include a serum creatinine of 3.7 mg/dl compared with a value of 2.4 mg/dl one year ago. Urinalysis shows 4+ protein, negative for blood, and 0 to 2 red blood cells/high power field. A 24-hour urine protein excretion is 6.2 g.

Which of the following statements is true regarding the pathophysiology of renal disease progression in this patient?

A. Increases in single-nephron GFR would not occur because of the presence of glomerulosclerosis.
B. Proteinuria can lead to glomerular scarring, but has not been a pathogenic factor in the development of tubulointerstitial disease.
C. Increased ammonia genesis in surviving nephrons can lead to complement activation and enhanced tubulointerstitial disease.
D. Plasma renin activity is likely to be elevated and is a major factor in the pathogenesis of his hypertension.
E. Increase glomerular size blunts the adverse effects of the increased pressures and flows in the glomerulus.

The correct answer is C. Adaptations occur in surviving nephrons in an attempt to compensate for the loss of renal mass. One of these adaptations is increased ammonia genesis. Ammonia can activate complement, which can be a risk factor in the development of tubulointerstitial disease. Option A is incorrect because the degree of glomerular involvement is heterogenous and increases in single nephron GFR is an adaptation that would occur in the less-damaged glomeruli. Option B is incorrect because reabsorption of protein in proximal tubule cells with their subsequent

activation is felt to be a mechanism leading to tubulointerstitial disease. Option E is incorrect because it presents a paradox in thinking about chronic PKD. Plasma renin activity is suppressed in most chronic kidney disease, yet inhibition of angiotensin II is a major renal protective strategy. The hypertension seen in kidney disease is related to mechanisms other than activation of the renin-angiotensin system.

Reference

Hales CN (2001) Suicide of the nephron. Lancet 357:136–137

CASE 15

A 19-year old female is seen in your office for evaluation of elevated serum creatinine. She currently has hypertension. A kidney biopsy performed two years ago showed membranous glomerulonephritis. There was severe tubulointerstitial disease, and 10 to 15 glomeruli were globally sclerosed. At that time, her serum creatinine was 2.1 mg/dl, her calculated GFR using Schwartz formula was 27 ml/min/1.73 m2, serum cholesterol was 320 mg/dl, and she had a 24-hour urinary protein excretion of 8.6 g.

Which of the following is true regarding her risk of developing progressive kidney failure?

A. Few glomeruli were globally sclerosed, therefore her renal prognosis is good.
B. The severity of tubulointerstitial disease is a good predictor of kidney disease progression.
C. Proteinuria is not a risk factor for kidney disease progression.
D. On the basis of the amount of proteinuria, she is unlikely to respond to an angiotensin-converting enzyme inhibitor.
E. The risk for kidney disease progression is lower in African-Americans in comparison to Caucasions,

The correct answer is A. This patient has Stage 4 CKD secondary to membranous glomerulonephritis. Tubulointerstitial disease accompanies most glomerular disease, and its severity is a major risk for subsequent renal disease progression. Therefore, option B is incorrect because the severity of tubulointerstitial disease is a stronger predictor of progression than the low number of globally sclerosed glomeruli in this patient. Option C is incorrect because proteinuria is another major risk factor for renal disease progression in almost all studied diseases. Option D is incorrect as the patients with the highest levels of proteinuria have the greatest response to ACE inhibitor therapy. Option E is incorrect because the risk for progression in almost all renal disease is higher in African-Americans in comparison to Caucasians.

Reference

Keane WF (2000) Proteinuria: its clinical importance and role in progressive renal disease. Am J Kidney Dis 35:S97–S105

CASE 16

A 19-year old boy has developed progressive kidney failure from Type 1 diabetes diagnosed at age seven. His BP is currently 125/75 mmHg on treatment with an ACE inhibitor, β-blocker, and loop diuretic. Laboratory studies include a serum creatinine of 2.4 mg/dl, serum cholesterol of 298 mg/dl, serum albumin of 2.8 g/dl, calculated GFR of 40 ml/min/1.73 m2, and a 24-hour urinary protein excretion of 5.3 g.

Which of the following is TRUE regarding the therapy of this patient?

A. Dietary protein restriction would be of no benefit in slowing progression of his kidney disease.
B. Dietary protein restriction is most effective in slowing progression in patients with the lowest GFR.
C. An initial reduction in proteinuria with dietary protein restriction in conjunction with aggressive BP control, with agents that inhibit the renin-system would be associated with a slower rate of progression.
D. Dietary protein restriction of 0.6 g/kg/day would likely be associated with a decrease in serum albumin.
E. Low-protein diets would be associated with an increase in plasma renin activity and more difficulty controlling hypertension.

The correct answer is C. The results of clinical trial of dietary protein restriction on slowing the progression of kidney disease have been mixed. In the primary analysis of MDRD study, no beneficial effect of dietary protein restriction was seen, although there are a number of limitations of this trial. Nonetheless, other trials have demonstrated a beneficial effect in slowing the development of ESRD. Diabetics tend to have a more beneficial response in comparison to nondiabetics. Therefore, option A is incorrect. Option B is also incorrect because a *post hoc* analysis of the MDRD study showed the greatest beneficial effect to protein restriction in the patients with the highest initial levels of GFR. Option C is incorrect because the MDRD study demonstrated that an initial reduction in proteinuria was associated with a slower rate of progression. Option D is incorrect because this level of protein restriction should not have a negative impact on nutritional parameters. Option E is incorrect because dietary protein restriction is associated with a decrease in plasma renin activity with no effect on BP.

References

Levey AS, Greene T, Beck GJ, et al. (1999) Dietary protein restriction and the progression of chronic renal disease: what have all of the results of the MDRD study shown? J Am Soc Nephrol 10:2436–2439

Pedrini MT, Levey AS, Lau J, et al. (1996) The effect of dietary protein restriction on the progression of diabetic and non-diabetic renal disease: a meta-analysis. An Intern Med 124:267–637

CASE 17

A 10-year old Asian boy is seen in your office for assessment and treatment of his elevated serum creatinine level. He was diagnosed by renal biopsy with IgA nephropathy two years ago. Laboratory studies show a serum creatinine of 2.0 mg/dl, calculated GFR of 37 ml/min/1.73 m2, hemoglobin of 10.0 g/dl, and a urine protein-to-creatinine ratio of 2.4 mg/mg.

Which of the following is TRUE regarding an assessment of his anemia?

A. Hematocrit is a more accurate way of defining anemia than hemoglobin.
B. Erythropoietin levels are useful in deciding treatment.
C. A bone marrow biopsy should be performed to rule out myelodysplastic syndrome.
D. Serum iron, transferring saturation, and ferritin should be measured to assess iron stores.
E. Proteinuria is associated with a poor response to erythropoietin therapy.

The correct answer is D. The patient has Stage 3 CKD secondary to IgA nephropathy. His anemia is most likely secondary to decreased erythropoietin production. The first step in assessing his anemia is to measure serum iron, transferring saturation and ferritin to make sure he is not iron deficient—a common contributing factor to anemia in patients with CKD. Iron studies are also important in the planning of erythropoietin therapy because it is important to maintain transferring saturation (>20%) and ferritin levels (>100 ng/ml). Therefore, option D is the correct answer. Option A is incorrect. Hemoglobin is a more accurate way of defining anemia because hematocrit measurements are more subject to shifts in plasma water, and results can vary depending on the age of the sample and the methodology used. Option B is incorrect because erythropoietin levels are not directly related to the degree of decrease in GFR and, in general, have not been found to be useful in assessing anemia of CKD—levels almost always inappropriately low for the level of hemoglobin. Option C is incorrect because amyelodysplastic syndrome is a rare cause of anemia and other clinical clues regarding its presence should be investigated prior to obtaining a bone marrow biopsy. Option E is incorrect because there is no evidence supporting a relationship between proteinuria and the response to erythropoietin treatment.

References

Cameron J (1999) European best practice guidelines for the management of anemia in patients with chronic renal failure. Nephrol Dial Transplant 14:S61–S65

National Kidney Foundation: K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification (2002). Am J Kid Dis 39:S1–S266

CASE 18

Which of the following is TRUE regarding therapy in this patient?

A. Treatment of anemia is associated with a higher rate of hospitalization.
B. Treatment of anemia can prevent the development of left-ventricular failure.
C. Erythropoietin can accelerate the progression of kidney disease.
D. Treatment with the recombinant erythropoietin should only be initiated when the hemoglobin is <10 g/dl.
E. Target hemoglobin levels with recombinant erythropoietin should be 11 g/dl.

The correct answer is B. Option B is correct because studies have demonstrated that treatment of anemia can prevent the development of left-ventricular hypertrophy. Option A is incorrect because treatment of anemia is associated with lower rates of hospitalization. Option C is incorrect because many studies have shown treatment with erythropoietin has no effect on the progression of kidney disease. Option D is incorrect because adverse consequences of anemia occur when hemoglobin levels are greater than 8 g/dl. Option E is incorrect but remains controversial. In a study by Hayashi et al., left-ventricular mass index progressively decreased as hemoglobin was normalized, suggesting target hemoglobin should be higher than 11 g/dl.

References

Hayashi T, Suzuki A, Shoji T, et al. (2000) Cardiovascular effect of normalizing the hematocrit level during erythropoietin therapy in predialysis patients with chronic renal failure. Am J Kidney Dis 35:250–256

Levin A, Thompson C, Ethier J, et al. (1999) Left ventricular mass index increase in early renal disease: impact of decline in hemoglobin. Am J Kidney Dis 34:125–134

CASE 19

A 17-year old girl with Type 2 diabetes and CKD presents to your office for treatment recommendations. She has hypertension that is being treated with furosemide, metoprolol, and lisinopril. Her major complaint is fatigue. Upon examination, her BP (BP) is 140/85 mmHg, and she has 1+ peripheral edema. Her serum creatinine is 2.2 mg/dl with a calculated GFR of 32 ml/min/1.73 m^2. A spot urine protein-to-creatinine is 4 mg/mg. Her blood sugar is 150 mg/dl.

Which of the following choices is most CORRECT regarding this patient?

A. At this stage in her kidney disease, glycemic control is likely to be beneficial in slowing the progression.
B. She has a low risk of kidney disease progression.
C. Her target BP should not be lowered because it would increase the risk of sudden cardiac death (J-point phenomena).
D. Addition of an ARB will further decrease the progression of her kidney disease.
E. Lowering his target BP can slow the progression of her kidney disease.

The correct answer is E. The patient has Stage 3 CKD secondary to diabetic nephropathy. In addition to a decrease in his GFR, he has significant proteinuria. In an analysis of the MDRD study that did not enroll diabetics, patients with more than 1 g of protein per 24 hours had a slower rate of progression with the lowered BP goal of a mean arterial pressure of 92 mmHg. Based on this study, on JNC-VI recommendations, and on expert opinion, the best option is E for lowering his target BP to 125–130/75–80 mmHg. Option A is incorrect because there is no data demonstrating that more intensive glycemic control in Type 2 diabetics with established nephropathy can allow the progression of their kidney disease. HbA1c levels, however, have been independently associated with a faster rate of decline of GFR in patients with established diabetic nephropathy. Option B is incorrect because the patient has a high risk of progression to ESRD. Option C is incorrect because no J-shaped curve—that is, worse cardiovascular or renal outcome with progressively lower BP—has been demonstrated in diabetics. Option D is incorrect because the addition of an ARB to an ACE inhibitor can reduce proteinuria in some studies but has never been demonstrated to slow progression of kidney disease. In contrast, in nondiabetic kidney disease, the COOPERATE study-demonstrated combination therapy can slow progression.

Additional laboratory tests performed on the patient demonstrate a hemoglobin of 10.1 g/dl with a serum iron of 92 mg/dl, a transferring saturation of 23%, and a ferritin of 130 ng/ml.

Which of the following should be done next?

A. Carefully follow hemoglobin and start recombinant erythropoietin therapy if it is <10 g/dl.
B. Check an echocardiogram and start recombinant erythropoietin therapy if left ventricular hypertrophy is present.
C. Start oral iron and recheck hemoglobin level in one month.
D. Start recombinant erythropoietin at 10,000 units subcutaneously once weekly along with oral iron.
E. Transfuse two units of packed red blood cells.

The correct answer is D. This patient has anemia with normal iron studies. To avoid the development of functional iron deficiency, erythropoietin should be given along with iron supplemants. Waiting for hemoglobin to fall to <8 g/dl (option A) is not recommended because of the adverse consequences of anemia (increased cardiovascular disease, cognitive impairment, and increased mortality). One of the goals of anemia treatment is to avoid left-ventricular hypertrophy as the trigger for initiating erythropoietin, so option B is incorrect. Because this patient is not iron deficient, starting oral iron is unlikely to increase hemoglobin levels, so option C is incorrect. Option E—blood transfusions—is not indicated because this patient should have a good response to erythropoietin, and the adverse effects and cost of transfusions can be avoided.

References

Levin A, Thompson C, Ethier J, et al. (1999) Left ventricular mass index increase in early renal disease: Impact of decline in hemoglobin. Am J Kid Dis 34:125–134

Ritz E, Orth SR (1999) Nephropathy in patients with Type 2 diabetes mellitus. N Engl J Med 341:1127–1951

CASE 20

A nine-year old boy has kidney dysplasia. His BP is 135/90 mmHg, his weight is 78 kg, and his exam is unremarkable. Laboratory tests include serum creatinine of 2 mg/dl, serum calcium of 7.6 mg/dl, serum phosphate of 5.1 mg/dl, serum albumin of 4.0 g/dl, serum intact PTH of 280 pg/ml, and calculated GFR using the abbreviated MDRD study equation of 46 ml/min/1.73 m^2.

Which of the following is TRUE regarding therapy?

A. Dietary phosphate should be restricted to 2 g/day.
B. He should be treated with 0.25 $\mu g/day$ calcitriol.
C. Calcium-containing phosphate binders should be avoided.
D. Long-term therapy with aluminum hydroxide should be started at a dose of 15 ml orally with meals.
E. Sevelamer therapy would be associated with an increased risk of development of osteomalacia and bone fractures.

The correct answer is B. The patient has Stage 3 CKD, and secondary hyperparathyroidism is present. Calcitriol therapy (choice B) can effectively reduce PTH secretion and is the best treatment for this patient. Dietary phosphorous restriction to 800 mg–1000 mg should be instituted when the serum phosphorous is >4.6 mg/dl (option A is incorrect). Option C is incorrect because calcium-containing

phosphate binders can be used as primary therapy but should be limited to 1500mg/day. If vascular calcification is present, current treatment guidelines suggest the noncalcium-containing phosphate binders may be preferred. Option D is incorrect because long-term treatment with aluminium-containing phosphate binders can cause osteomalacia secondary to deposition of aluminum in bone. Option E is incorrect because sevelamer has not been associated with osteomalcia or an increased risk of bone fractures.

Reference

Slatopolsky E, Burke SK, Dillon MA, et al. (1999) Renagel, a nonabsorbed calcium-and aluminum-free phosphate binder, lowers serum phosphorus and parathyroid hormone. Kidney Int 55:299–307

CASE 21

An eight-year old girl is seen in your office for evaluation of CKD. Over the last two years, her GFR has decreased from 47 to a current value of 19 ml/min/1.73 m2, despite of good BP control with an ACE inhibitor. Laboratory studies include serum creatinine of 4.1 mg/dl, potassium of 5.0 mEq/l, and bicarbonate of 17 mEq/l. An arterial blood gas confirms she has a compensated metabolic acidosis.

Which of the following is TRUE regarding her acidosis?

A. No adverse effects of acidosis are seen until the bicarbonate is <15 mEq/l.
B. Acidosis stimulates albumin synthesis by the liver.
C. Acidosis suppresses PTH release.
D. Acidosis increases calcium loss from bone.
E. Acidosis stimulates skeletal muscle hypertrophy.

The correct answer is D. Buffering of hydrogen by bone is associated with release of calcium. In addition, acidosis stimulates osteoclastic activity. Metabolic acidosis occurs when the GFR falls to .60 ml/min/1.73m^2 and can have adverse consequences even when the serum bicarbonate is between 15 to22 mEq/L. Option A is therefore incorrect. Option B is incorrect because acidosis suppresses albumin synthesis by the liver. Option C is incorrect because acidosis is associated with increased PTH release. Option E is also incorrect because acidosis-stimulated degradation of protein from skeletal muscle mediated in part by increased cortisol release and decreased release of insulin-like growth factor 1.

Reference

Caravaca F, Arrobas M, Pizarro JL, et al. (1999) Metabolic acidosis in advanced renal failure: Differences between diabetic and nondiabetic patients. Am J Kidney Dis 33:892–898

CASE 22

A 19-year old female has CKD from Type 1 diabetes. Her current GFR is 45 ml/min/1.73 m^2.

Which of the following is TRUE regarding alterations in bone and mineral metabolism in CKD?

A. The most sensitive marker of abnormal mineral metabolism is decreased clacitriol production.
B. Elevations in PTH secretion do not occur until GFR is <20 ml/min/1.73 m^2.
C. Elevated serum phosphate inhibits the 1 hydroxylase enzyme in the kidney, leading to decreased calcitriol synthesis.
D. The most common bone abnormality is osteomalacia.
E. An alteration in the set point for calcium occurs in the parathyroid glands, leading to increased PTH secretion for any increase in serum calcium.

The correct answer is C. This patient has Stage 3 CKD. Abnormalities in calcium, phosphorous, and parathyroid hormone (PTH) commonly develop as GFR declines. The earliest and most sensitive marker of abnormal mineral metabolism is an elevation in serum PTH. This develops when the GFR decreases to 40–70 ml/min/1.73 m^2. Therefore, choice A is incorrect. Calcitriol synthesis decreases in CKD, but usually not until the GFR is less than 40 ml/min/1.73m^2, and the changes are somewhat variable. Choice B is incorrect because PTH secretion occurs at an earlier stage in CKD, when the GFR is 40–70 ml/min/1.73m2. Choice C is correct because one of the mechanisms for decreased calcitriol synthesis is inhibition of the 1 hydroxylase enzyme in the kidney by elevated serum phosphorous. In regard to choice D, the set point for calcium is altered in CKD, leading to increase PTH secretion for a given decrease (not increase) in serum calcium level. Choice E is incorrect because parathyroid-related bone disease (osteitis fibrosa cystica) is more common than osteomalacia.

Reference

National Kidney Foundation: K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification (2002). Am J Kidney Dis 39: S1–S266

CASE 23

A seven-year old girl presents with nephritic syndrome secondary to focal segmental glomerulosclerosis (FSGS). A kidney biopsy is diagnostic for focal and segmental glomerulosclerosis. Her current estimated GFR by the abbreviated MDRD equation is 60 ml/min/1.73 m^2.

Which of the following is the best predictor of her risk of progressing to ESRD?

A. The percentage of glomeruli with focal changes upon biopsy
B. Angiotensin-converting enzyme (ACE) genotyping polymorphisms
C. The extent of tubulointerstitial disease on biopsy
D. The level of plasma renin activity
E. A family history of hypertension

The correct answer is C. The two most predictive risk factors for progression of glomerular diseases are the quantity of protein excreted in the urine and the extent of tubulointerstitial disease in a renal biopsy. There is no evidence that choice A is a predictive factor. There is no convincing evidence that the ACE genotype predicts progression of glomerular diseases, particularly FSGS. Therefore, choice B is also incorrect. Choice D, the level of plasma renin activity, has not been demonstrated to be a predictor of renal disease progression. In fact, in most chronic kidney diseases, plasma renin activity is suppressed, most likely related to volume expansion. Thus, the beneficial effects of ACE inhibitors in slowing progression of renal disease are somewhat of a paradox. There is no evidence that a family history of hypertension predicts progression of FSGS. Therefore, choice E is incorrect. The link between tubulointerstitial disease and progression may relate to reabsorption of proteins by proximal tubular cells, with activation of these cells and subsequent release of inflammatory mediators.

References

Hels CN (2001) Suicide of the nephron. Lancet 357:136–137
Nath K (1998) The tubulointerstitium in progressive renal disease. Kidney Int 54:992–1456

CASE 24

A 15-year old boy with CKD secondary to IgA nephropathy is seen in our office for management of his CKD. His BP is controlled to a level of 130/80 mmHg on loop diuretic, β-blocker, and ACE inhibitor. His current serum creatinine is 1.8 mg/dl, and his GFR is 45 ml/mim/1.73 m^2. You decide to add an angiotensin-receptor blocker to his ACE inhibitor.

Which of the following is TRUE regarding this combination therapy?

A. No rational therapeutic basis exists for combination therapy.
B. Hyperkalemia limits the usefulness of combination treatment.
C. A greater benefit of combination therapy has been seen in diabetic in comparison with nondiabetic kidney diseases.
D. Combination therapy can improve renal survival.
E. The benefits of combination therapy over monotherapy with an ACE inhibitor alone are dependent on a greater decrease in BP.

The correct answer is D. This patient has chronic kidney disease with heavy proteinuria secondary to IgA glomerulonephritis. His BP is well controlled on three antihypertensives, including an ACE inhibitor. In an attempt to slow progression of his kidney disease, an ARB is added to his ACE inhibitor (combination therapy). Combining an ACE inhibitor with an ARB may be more effective than either agent alone in reducing proteinuria and/or improving renal survival—particularly in patients with nondiabetic glomerulonephritis. Choice A is incorrect because an ACE inhibitor blocks angiotensin II formation and the ARB inhibits the angiotensin Type 1 receptor. Therefore, both agents act at different sites. A number of studies have shown that there is not a significant risk of hyperkalemia with combination therapy, so choice B is incorrect. Choice C is incorrect because most studies have shown that patients with nondiabetic kidney disease have a greater beneficial effect, as was seen in the COOPERATE study. In this study, BP was the same with combination therapy in comparison to monotherapy, providing evidence that the beneficial effect on renal survival was not due to a greater fall in BP.

Reference

Nakao N. Yoshimura A, Morita H, et al. (2003) Combination treatment of angiotensin II receptor blocker and angiotensin-converting enzyme inhibitor in no-diabetic renal disease (CCPERATE): a randomized controlled trial. Lancet 361:117–124

CASE 25

A six-year old girl with biopsy-proven IgA nephropathy presents for nephrology care. Her serum creatinine has increased from 0.8 mg/dl to 2.5 mg/dl over the past three years. Her BP is now 155/90 mmHg. There is no edema, rash, or arthritis upon physical examination. Hemoglobin is 10.5 g/dl, potassium 5.5 mEq/l, and intact PTH level 150 pg/ml.

Which ONE of the following statements is MOST CORRECT?

A. Her hemoglobin should be increased to 11 to 12 g/dl with human recombinant erythropoietin therapy to reduce the risk of congestive heart failure.
B. Her serum potassium should be reduced to <5.0 mEq/l to reduce the risk of sudden death.
C. Her intact PTH level should be reduced to 70 to 11 pg/ml to rescue the risk of facture.
D. None of the above

The correct answer is D. Unfortunately, none of the interventions have been shown to yield the listed clinical benefits in randomized controlled trials.

Reference

Dillon JJ (2001) Treating IgA nephropathy. J Am Soc Nephrol 2001; 12:846–847

CASE 26

Which ONE of the following statements is MOST CORRECT concerning the use of nonsteroidal anti-inflammatory drugs (NSAID) among patients with Type 1 diabetes mellitus and Stage 3 CKD?

A. Use of NSAID will lead to superimposed analgesic nephropathy in this population.
B. Development of minimal change disease associated with NSAID will lead to confusion regarding proteinuria.
C. Anemia from NSAID-induced gastrointestinal blood loss will accelerate loss of renal function.
D. Serum potassium levels may increase as a result of NSAID use and limit the use of angiotensin-converting enzyme inhibitors.

The correct answer is D. The risk of analgesic nephropathy from use of NSAIDS remains controversial.

Reference

Ibanez L, Morlans M, Vidal X, et al. (2005) Case-control study of regular analgesic and nonsteroidal anti-inflammatory use and end-stage renal

CASE 27

A 15-year old girl has chronic glomerulonephritis with advanced renal insufficiency. Her serum creatinine is 4.5 mg/dl, phosphate 5.2 mg/dl, hemoglobin 9.5 g/dl, and hematocrit 29%. Her BP is 148/90 mmHg while on therapy with furosemide, amlodipine, and enalepril. Therapy with recombinant human erythropoietin is instituted.

Which ONE of the following statements is MOST CORRECT regarding the correction of anemia in this patient?

A. It is likely to be associated with an acceleration of renal disease progression.
B. Strong evidence (from controlled clinical trials) of a beneficial effect on cardiovascular morbidity and mortality is lacking.
C. It will likely significantly reduce the development of angiographically proven coronary heart disease.
D. Increasing the hemoglobin level to normal will lead to regression to left-ventricular hypertrophy.
E. It is likely to reduce the rate of albumin excretion in the urine.

The correct answer is B. There are limited data to suggest that correction of anemia in patients with CKD is associated with regression of left ventricular hypertrophy (LVH) that could improve cardiovascular outcomes and mortality. Improvement of LVH is also associated with increase in Hb levels from less than 10 g/dl to levels of 11 to 12 g/dl. However, the hypothesis tested in clinical trials that correction of anemia ameliorate CVD outcome has not been confirmed.

Reference

Besarab A, Bolton WK, Browne JK (1998) The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. N Engl J Med 339:584–590

CASE 28

A nine-year old girl has been previously diagnosed as having chronic glomerulonephritis. Her serum creatinine is 1.0 mg/dl and estimated GFR 77 ml/min/1.73 m^2. Her BP (BP) is 150/90 mmHg and 24-hour urinary protein excretion is 2.5 g. She is prescribed enalepril at the initial dose of 5 mg/day.

Which ONE of the following is the most desirable target BP for patients with CKD and proteinuria similar to this patient (select all that apply)?

A. <125/75 mmHg
B. <110/70 mmHg
C. <120/70 mmHg
D. <130/80 mmHg
E. <140/90 mmHg

The correct answers are A and D. Based on the results of several studies, the NKF/DOQI recommends that target BP should be less than 130/80 mmHg in patients with CKD. Evidence from other studies, however, suggests that an even lower systolic pressure may be more effective in slowing progressive renal disease in patients with proteinuria. Answer A is also correct because several national committee have recommended a BP target of 125/75 mmHg in subjects with hypertension and proteinuria of the magnitude present in this patient.

Reference

K/DOQI Clinical Practice Guidelines on Hypertension and antihypertensive agents in chronic kidney disease (2004). Am J Kidney Dis 43:(Suppl 1) S5–S10

CASE 29

Which ONE of the following evaluation strategies would be MOST appropriate when ACE inhibitor therapy is initiated in a patient with CKD, serum creatinine of 3.1 mg/dl, and urinary protein excretion of 2.0 g/day?

A. Evaluate serum potassium and creatinine levels two weeks after initiating therapy, and stop therapy if hyperkalemia cannot be controlled by loop diuretics and dietary counseling, or if the serum creatinine increases >30% over baseline levels.
B. Evaluate serum potassium and serum creatinine two months after initiating therapy.
C. Use of an ACE inhibitor is contra-indicated in such patients.
D. Such therapy should only be used in patients with Type I diabetes mellitus.

The correct answer is A. The risk of hyperkalemia in patients who would benefit from ACE inhibitor or ARB therapy can be minimized by the appropriate use of diuretics, a low potassium diet, and the use of low dose of potassium-binding resin. If metabolic acidosis is present, sodium bicarbonate should be given.

Reference

Knoll GA, Sahgal A, Nair RC, et al. (2002) Renin-angiotensin system blockade and the risk of hyperkalemia in chronic hemodialysis patients. Am J Med 112:110–114

CASE 30

Which of the following statements is MOST CORRECT regarding the use and effectiveness of low-protein diets to retard the progression rate of the chronic renal disease (select all that apply)?

A. Dietary protein restriction is reliably effective if protein intake can be reduced to approximately 0.8 g/kg per day.
B. Dietary protein restriction is reliably effective and the risk of malnutrition is negligible.
C. Although definite proof that dietary protein restriction slows progression of CKD is lacking, it is advisable to suggest a moderate protein restriction to attenuate metabolic abnormalities.
D. Dietary protein restriction is not recommended because the risk of malnutrition.
E. The effects of dietary protein restriction are not known.

The correct answers are C and E. The ideal dietary for patients with CKD is not certain. It is reasonable to prescribe a regimen consisting of approximately 0.8 to 1.0 g/kg of high biologic value protein per day, while lower protein intake value

is used in patients with progressive disease. Patients with diabetic nephropathy may have a greater benefit from a low protein diet. The evidence, however, was gained before ACE inhibitors were widely used. Answer E is also correct because thaere have been no adequately powered studies of protein restriction in subjects with ADPKD, so the effect of protein restriction in such subjects is unknown—even though such restriction may attenuate metabolic abnormalities associated with CKD.

Reference

Mitch WE, Remuzzi G (2004) Diets for patients with chronic kidney disease, still worth prescribing. J Am Soc Nephrol 15:234–237

CASE 31

Which ONE of the following statements is MOST CORRECT regarding the relationship between hyperlipidemia and the future progression of renal disease?

A. Hyperlipidemia has no demonstrated adverse effect on progression in animals with experimental renal disease
B. Hyperlipidemia is a well-documented treatable risk factor for the progression of renal disease in humans.
C. Progression of renal disease is seen only in association with a plasma LDL cholesterol level >150 mg/dl.
D. Hyperlipidemia has been shown to aggravate the progression of renal disease in animals, but the evidence in humans is weak.
E. Progression of renal disease is seen only in association with a plasma triglyceride level >400 mg/dl.

The correct answer is D. Experimental studies suggest that dislipidemia may not only be a risk factor for the development of systemic atherosclerosis, but may also enhance the rate of progressive glomerular injury. Furthermore, because patients with CKD should be considered in the highest risk group for CVD, they should be treated to lower target, low-density lipoprotein cholesterol levels as recommended by the NKF-K/DOQI guidelines.

Reference

Weiner DE, Sarnak MJ (2004) Managing dyslipidemia in chronic kidney disease. J Gen Intern Med 19:1045–1052

Chapter 10
Renal Osteodystrophy

CASE 1

A 19-year old female patient has been treated with hemodialysis for the past 14 years after rejection of a cadaver transplant. Her original disease was Henoch-Schonlein purpura. She now presents with ascending pain and weakness in her hands and feet. There are prominent contractures of her extremities that have caused her to become bedridden over the last four months. Her major problems associated with hemodialysis had been hyperphosphatemia (7 to 8.5 mg/dl) and hypercalcemia (10 to 11 mg/dl) after vitamin D therapy. Her parathyroid hormone (PTH) levels are mildly elevated at 56 pg/ml, although they have been substantially higher in the past. A work-up for collagen vascular disease, including vasculitis, has been negative, as well as Lyme titer and thyroid function tests. Blood glucose has never been elevated. Electromyography and nerve conduction studies are normal. Muscle biopsy shows atrophy and intravascular calcification.

What is the most likely cause of this condition?

A. Uremic myopathy
B. Mitochondrial myopathy
C. Scleroderma
D. Calcific uremic arteriopathy
E. Recurrent HSP

The correct answer is D. In its most florid from, calcific vasculopathy may be manifested as calciphylaxis. A small fraction of patients with ESRD, particularly those treated with dialysis, develop deep skin ulcerations in association with calcification of subcutaneous arterioles. Uremic peripheral neuropathy is a distal, symmetrical, mixed sensorimotor. It occurs more commonly in men, and it is independent of the underlying disease. There is no specific myopathy associated with uremia. Arthralgia and myalgias characterize diffuse scleroderma. Early diffuse cutaneous systemic sclerosis includes arthritic symptoms. A specific myopathy is not seen. Recurrent HSP does not manifest a specific myopathic picture, as seen in this case.

F. Assadi, *Clinical Decisions in Pediatric Nephrology.*

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Reference

Kunis CL, Markowitz GS, Liu-Jarin X, et al. (2001) Painful myopathy and end-stage renal disease. Am J Kidney Dis 37:1098–1104

CASE 2

A 14-year old male patient begins hemodialysis treatments under your care. His original disease was FSGS. Physical examination is unremarkable. His serum calcium is 9.7 mg/dl, phosphate 6.1 mg/dl, and PTH 340 pg/ml. To optimize his management, you initiate therapy with sevelamer hydrochloride to maintain his serum phosphate level within an acceptable range.

Which of the following statements BEST describes the likely response of this patient to sevelamer hydrochloride in comparison with calcium acetate?

A. Sevelamer hydrochloride will be more effective in reducing serum phosphate levels.
B. Calcium acetate will be more effective in reducing serum phosphate levels.
C. Sevelamer hydrochloride will be more effective at reducing PTH levels.
D. Sevelamer hydrochloride use will result in less hypercalcemia as a later complication.
E. Sevelamer hydrochloride is as costly as calcium acetate.

The correct answer is D. Sevelamer hydrochloride (Renagel) significantly lowers serum phosphorous in hemodialysis patients but with minimal effects on serum calcium in comparison to treatment with standard calcium-based phosphate binders. Patients with the highest PTH levels (>300 pg/ml) experienced the greatest reduction in PTH. The effect on PTH levels, however, may be inconsistent.

Reference

Bleyer AJ, Burke SK, Dillon M, et al. (1999) A comparison of the calcium-free phosphate binder Sevelamer hydrochloride with calcium acetate in the treatment of hyperphosphatemia in dialysis patients. Am J Kidney Dis 33:694–701

CASE 3

An 18-year old female maintained on hemodialysis for the past six years due to congenital kidney dysplasia presents with a large necrotic lesion of the skin of her upper thigh. She is obese, has mild glucose intolerance and poorly controlled hypertension, and has been receiving large doses of iron dextran and erythropoeitin for resistant anemia as well as enalepril for hypertension. Her serum phosphate level has ranged from 6 to 9 mg/dl, serum albumin from 2.2 to 2.9 g/dl, and serum calcium from

8.8 to 9.0 mg/dl. Serum magnesium is 2.6 mg/dl, alkaline phosphatase 165 IU/l, and serum PTH 450 pg/ml. Biopsy of her skin lesion reveals medial calcification and intimal hyperplasia of small arteries and fat necrosis.

Which of her clinical characteristics is a key risk factor for this condition?

A. Iron dextrin therapy
B. Hypertension
C. Hypomagnesemia
D. Hyperphosphatemia
E. Erythropoietin therapy

The correct answer is D. Hyperphosphatemia is the strongest predictor of calciphylaxis in patients receiving hemodialysis treatment. There is a 3.5-fold increase in the risk of calciphylaxis associated with each 1 mg/dl increase in the serum phosphate concentrations. Body mass index, diabetes, hypertension, hypomagnesemia, aluminum, and higher dosages of erythropoietin and iron dextran are not independent predictors of calciphylaxis.

Reference

Mazhar AR, Johnson RJ, Gillen D, et al. (2001) Risk factors and mortality associated with calciphylaxis in end-stage renal disease. Kidney Int 60:324–332

CASE 4

A 17-year old male has been on hemodialysis for the past 10 years after a failed cadaveric renal transplant. He has had recurrent episodes of bone pain but has otherwise been well. You have attempted to control his secondary hyperparathyroidism for the past six months with intravenous calcitriol and the aggressive use of phosphate binders, including Sevelamer. Despite these efforts, serum PTH level remains at 757pg/ml, although reduced from the peak of 1011 pg/ml.

Which one of the following statements regarding parathyroidectomy in patients receiving renal replacement therapy (RRT) is correct?

A. Male patients receiving long-term RRT are twice as likely as female patients to require parathyroidectomy.
B. The incidence of parathyroidectomy to control hyperparathyroidism during long-term RRT is about 10% for those patients on therapy for 10 years.
C. Patients on peritoneal dialysis are half as likely to require parathyroidectomy as patients receiving hemodialysis.
D. Patients with diabetic nephropathy are as likely as those with other etiologies for ESRD to require parathyroidectomy.

E. White patients are more likely to require parathyroidectomy than African-American patients.

The correct answer is B. The prevalence of parathyroidectomy in patients on chronic dialysis therapy is 5.5%, and increases with the duration of dialysis therapy (9.2% after 10 to 15 years and 20.8% after 16 and 20 years). Relative risk for needing a parathyroidectomy is significantly higher in women and lower in elderly and diabetic patients. Relative risk for parathyroidectomy is also higher in patients on peritoneal dialysis than in those on hemodialysis, and decreases after transplantation. Previous study comparing blacks with whites revealed the odds ratio for hyperparathyroidism bone disease (mean PTH>500 pg/ml) is 4.4 (2.1 to 9.25).

Reference

Malberti F, Marcelli D, Conte F, et al. (2001) Parathyroidectomy in patients on renal replacement therapy: an epidemiologic study. J Am Soc Nephrol 12:1242–1248

CASE 5

A 10-year old African American girl on chronic hemodialysis treatment sustains a fracture of her left hip after a fall in her living room. She undergoes successful surgery, but she is concerned about recurrent fractures.

Which of the following factors are associated with an increased risk of subsequent fracture?

A. Her serum bicarbonate level predialysis is 18.5 mEq/l.
B. Her body mass index (BMI) is less than 23 kg/m^2.
C. She is African-American.
D. She has well-controlled Type 2 diabetes.
E. She is 10 years old.

The correct answer is C. The risk factors for hip fracture among patients treated with chronic hemodialysis include aging (age > 40 years old), female gender, black race, obesity (BMI >26 kg/m^2), and presence of peripheral vascular disease. Diabetes, serum intact PTH, aluminum, and bicarbonate levels did not appreciably influence the risk of hip fracture.

Reference

Stehman-Breen CO, Sherrard DJ, Alem AM, et al. (2000) Risks factors for hip fracture among patients with end-stage renal disease. Kidney Int 58:22002205

CASE 6

A nine-year old patient with five-year history of chronic hemodialysis for the treatment of FSGS begins to complain of bone pain and muscle weakness. The work-up of the patient revealed the following: serum calcium 9.2 mg/dl, PO_4 5.2 mg/dl, intact PTH level 250 pg/ml, and plasma aluminum 433 $\mu g/dl$. Bone mineral density was reduced with a total Z score (SD from the mean of a healthy, age- and gender-matched reference population) of -1.25.

Which of the following should be done now?

A. Bone biopsy
B. 1,25 $(OH)_2$ vitamin D measurement
C. Bone-specific alkaline phosphatase measurement
D. Procollagen-Icarbixy-terminal propeptide level
E. β2-microglobulin level

The correct answer is A. This patient's clinical picture is consistent with low turnover bone disease, and therefore aluminum toxicity must be considered. In the presence of significant aluminum exposure, bone biopsy seems indicated in the following cases: before parathyroidectomy, and before starting long desferrioxamine treatment, given the risks of deafness and fatal mucormycosis as complications of treatment. Bone alkaline phosphatase is not sensitive enough to distinguish between low and normal turnover. Procollagen-Icarboxy-terminal propeptide is not a specific indicator of bone disease because it is not well-controlled with bone histology.

Reference

Ferreria MA (2000) Diagnosis of renal osteodystrophy: when and how to use biochemical markers and non-invasive methods; when bone biopsy is needed. Nephrol Dial Transplant 5:S8–S14

CASE 7

A 12-year old male patient on maintenance hemodialysis is referred to you from an outside hospital for help with treating his renal osteodystrophy. The patient has been poorly compliant with his phosphate binders and has multiple PTH measurements in the 1400 pg/ml range. He has also had a fractured fibula after minor trauma. The referring nephrologist has tried to suppress the patient's PTH levels with intravenous calcitriol but has produced hypercalcemia to 12.5 mg/dl on several occasions.

In reviewing a number of treatment options, which would you recommend to the patient?

A. 22-oxacalcitriol, because it will likely prove more beneficial than calcitriol
B. Paricalcitol, because it will likely prove more beneficial than calcitriol

C. Parathyroidectomy should be performed
D. 1 ά- hydroxyvitamin D_2 because it will likely prove more beneficial than calcitriol
E. 1 ά- hydroxyvitamin D_3 because it will likely prove more beneficial than calcitriol

The correct answer is C. The indications for parathyroidectomy, two of which apply to this patient, have classically included: 1) hypercalcemia and hyperphosphatemia in the presence of very high PTH levels (>800 pg/ml), as in this patient, with concurrent resistance to pharmacologic control; 2) fractures and tendon avulsions; 3) when the estimated weight of a parathyroid gland exceeds I g; and 4) calcific arteriolopathy, which some experts have considered to be an absolute indication.

Reference

Schomig M, Ritz E (2000) Management of disturbed calcium metabolism in uremic patients: 2. Indications for parathyroidectomy. Nephrol Dial Transpl 5:25–9

CASE 8

A 10-year old boy was referred to you for evaluation and treatment of persistent post-renal transplant hypophosphatemia. He has been treated with cyclosporine and prednisone, but has complained of some persistent muscle aches. Physical exam was unremarkable except for mild proximal muscle weakness in the lower extremities. He is on no medications except for his immunosuppressive agents. Laboratory values revealed the following: creatinine 1.2 mg/dl, calcium 9.6 mg/dl, phosphate 2.1 mg/dl, intact PTH 38 pg/ml, and fractional excretion of phosphate 28%.

Which of the following is the most likely cause of his renal phosphate wasting?

A. Parathyroid hormone
B. Cyclosporine
C. Phosphatonin
D. 1,25 $(OH)_2$ D_3
E. Glucocorticoids

The correct answer is C. Green et al.. studied the mechanism of post-transplant hypophosphatemia and found that sera from hypophosphatemic post-transplant patients inhibited PO_4 transport in vitro in a PTH-independent mechanism. This finding is consistent with the concept that there are PTH-independent humoral agents (phosphatonin) that dramatically reduce PO_4 reabsorption, and they may underline disorders of phosphate transport, as seen in oncogenic osteomalasis. Cyclosporine does not produce phosphate wasting, nor does 1,25 $(OH)_2$ D_3. Glucocorticoids are phosphaturic but do not produce the severe degree of phosphate wasting seen in this case.

Reference

Green J, Debby H, Lederer E, et al. (2001) Evidence for a PTH-independent humeral mechanism in post-transplant hypophosphatemia and phosphaturia. Kidney Int 60: 1182–1196

CASE 9

Which ONE of the following statements is TRUE regarding the effective prevention of hyperphosphatemia in patients receiving adequate dialysis therapy?

A. An effective level of dietary phosphate restriction can be achieved without restriction of dietary protein intake to less than 1g/kg/day.
B. Calcitriol administration does not alter dietary phosphate absorption.
C. Avoiding processed foods will reduce phosphate absorption.
D. Avoiding meat-derived phosphate will be more beneficial than avoiding plant-derived phosphate.
E. $CaCO_3$ is less effective than sevelamer hydrochloride for the control of serum phosphorus.

The correct answer is D. Any evaluation of dietary phosphorus adequacy should consider not only the content of phosphorus in food, but also the bioavailability of phosphorus because most phosphorus in plants is in the form of phytate. Because humans do not have the phytase enzyme that is required to degrade phytate and to release phosphorus, phytate is poorly digested in the human gastrointestinal tract and therefore limits phosphrous absorption from plant sources. Phosphorus in meat is well-absorbed because it is found mostly as intracellular organic compounds that are easily hydrolyzed in the gastrointestinal tract, releasing inorganic phosphorus for absorption.

Reference

Uribarri J, Calvo MS (2003) Hidden sources of phosphorus in the typical American diet: does it matter in nephrology? Semin Dial 16:186–188

CASE 10

Which ONE of the following statements about the use of calcium containing-phosphate binders (CCPB) is TRUE?

A. Patients who develop hypercalcemia on CCPB tend to have low bone density, suggesting reduced capacity for bone to buffer calcium loads.
B. Vascular calcification has been shown to occur when patients are in positive calcium balance.

C. Randomized control trails have shown that Sevelamer hydrochloride is less likely to be associated with cardiovascular mortality than comparable phosphate control with CCPB.
D. Extensive vascular calcification had been rarely seen before the advent of the use of CCPB.
E. Calcium carbonate is less likely to produce hypercalcemia than is calcium citrate.

The correct answer is A. This question addresses the fact that while many have speculated on the danger of using CCPBs, the literature does not provide any real justifications for any answer other than A.

Reference

Colandonato JA, Szczech LA, Friedman EA, et al. (2002) Does calcium kill ESRD patients-the skeptic's perspective? Nephrol Dial Transplant 17:229–232

CASE 11

A 15-year old boy is evaluated for muscle weakness and bone pain over the past five months. Physical examination reveals marked proximal myopathy but no other abnormalities. Laboratory studies reveal the following: calcium 10.2 mg/dl, phosphorous 1.2 mg/dl, immunoreactive PTH 23 pg/ml (normal; 10 to 65 pg/ml), 1,25 (OH)2 Vitamin D 8 pg/ml (normal; 10–55 pg/ml), and tubular reabsorption of phosphate 75% (normal; 90%). A CT scan shows a $3 \times 4\,\mathrm{cm}$ tumor of the right thigh. The tumor is removed and the patient fully recovers.

Which ONE of the following factor is MOST likely elevated in plasma before tumor resection?

A. PTH-related protein
B. 25 OH vitamin D
C. Fibroblast growth factor 23
D. Stanniocalcin
E. Calcitonin

The correct answer is C. Recent evidence suggests that the tumor product responsible for the phosphaturic action is fibroblast growth factor 23 (FGF-23), a member of a large family of proteins involved in regulating fibroblast function. In the oncogenic osteomalacia, there is over-production of FGF-23. In hereditary x-linked hypophosphatemic rickets there is mutation in an endopeptidase that normally inactivates PGF-23, and prevents high levels of the cytokine from migrating from bone to act systemically and in the kidney. In autosomal dominant hypophosphatemic rickets, there are mutations in the gene encoding FGF-23, so that it is a functional

molecule but cannot be efficiently degraded by an endopeptidase, and therefore acts both systemically and in the kidney.

Reference

Jonsson KB, Zahradnik R, Larsson T, et al. (2003) Fibroblast growth factor 23 in oncogenic osteomalacia and x-linked hypophosphatemia. N Engl J Med 348:1656–1563

CASE 12

Which ONE of the following statements BEST characterizes the effects of the experimental calcimimetic agent AMG 073 in modifying abnormalities in divalent ion metabolism in patients with renal failure?

A. Value is less than 400 pg/ml
B. Calcimimetics tend to raise the serum PO_4 levels in hemodialysis patients
C. In patients receiving calcimimetics, higher concomitant calcitriol administration is necessary to prevent hypocacemia than in control patients not receiving calcimimetics
D. $\mathrm{Ca} \times \mathrm{PO_4}$ product tends to slightly increase in patients not receiving calcimimetics
E. Calcimimetics reduce intact PTH levels while concurrently reducing caciumphosphate products ($\mathrm{Ca} \times \mathrm{PO_4}$)

The correct answer is E. Calcimimetic agents in early trials are effective even when PTH levels are greater than 400 pg/ml and they tend to reduce the $\mathrm{Ca} \times \mathrm{PO_4}$ product. While there may be episodes of hypocalcemia with their use, the patients receiving the calcimimetics do not require sustained increases in calcitriol dosages.

Reference

Lindberg JS, Moe SM, Goodman WG, et al. (2003) The calcimimetic AMG 073 reduces parathyroid hormone and calcium × phosphorous in secondary hyperparathyroidism. Kidney Int 63:248–254

CASE 13

A 15-year old girl on maintenance hemodialysis for eight years is transferred to your clinic and found to have severe refractory hyperparathyroidism (PTH 1400 pg/ml), serum calcium 10.6 mg/dl, and phosphorus 6.9 mg/dl. The patient has mild bone pain, and radiologic studies show moderate signs of hyperparathyroidism. The increased level of PTH is confirmed on three separate occasions. Ultrasound

revealed a single parathyroid mass with a long axis of 6 mm. The other three glands were enlarged, but each was less than 5 mm in length.

Which ONE of the following therapies should the patient receive?

A. Total parathyroidectomy with auto transplantation of parathyroid tissue
B. Two six-week trials of high-dose calcitriol
C. Increase in bath calcium level to 3.0 mEq/L
D. Calcimimetic therapy
E. Percutaneous ethanol injection therapy

The correct answer is A. The indications for percutaneous ethanol injection include: serum $\mathrm{PTH} > 800$ pg/ml, symptoms such as severe itching or bone pain, evidence of high turnover bone disease, exclusion of aluminum bone disease by desferrioxamine, resistance to medical therapy including clacitriol pulse therapy, and the long axis of the target parathyroid gland detected by ultrasonography exceeding 5 mm and shown to have a positive blood flow by power-Doppler ultrasonography. Patients failing to have adequately sized glands will likely require surgical removal. Increasing calcium in the dialysate or increasing vitamin D intake would be inappropriate in this hpercalcemic patient. Calcimimetic agents would be ineffective in this patient with the enlarged PTG greater than 5 mm in length.

Reference

Tanaka R, Kakuta T, Fujisaki T, et al.. (2003) Long-term (3-years) prognosis of parathyroid function in chronic dialysis patients after percutaneous ethanol injection therapy guided by color Doppler ultrasonography. Nephrol Dial Transpl 3: (suppl 3) 58–S58–S61

CASE 14

A 17-year old male presents with two large areas of skin necrosis on his left thigh. He has been treated with hemodialysis for the past six years for chronic kidney disease. He has received intermittent, small doses of calcitriol but has developed hypercalcemia to 12.0 mg/dl. His physical examination is unremarkable except for moderate obesity and intact pulses throughout his lower extremities. The necrotic areas of skin are superficial, but they measure $4 \times 5\,\mathrm{cm}$ each. Laboratory studies revealed calcium 9.6 mg/dl, phosphate 5.6 mg/dl, and immunoreactive PTH 180 pg/ml.

Which ONE of the following choices BEST explains this clinical condition?

A. Calciphylaxis associated with adynamic bone disease
B. Calciphylaxis with intermittent hyperphosphatemia
C. Calciphylaxis secondary to intermittent hyperparathyroidism

D. Vasculitis
E. Occult atheroembolic disease

The correct answer is A. This patient has developed skin necrosis associated with calcific vasculopathy. This syndrome is called calciphylaxis. Because he demonstrates hypercalcemia with therapeutic doses of vitamin D, he likely has adynamic bone disease, as well. The association of the two conditions has been reported and is linked by the role of recurrent episodes of hypercalcemia. Hyperphosphatemia does play a role but the elevation of serum phosphate is typically persistent. Hyperparathyroidism is frequently found associated with calciphylaxis, but in this case, the iPTH level is below that associated with the full picture of symptomatic hyperparathyroidism including accelerated bone turnover and hypercalcemia with small doses of vitamin D. Vasculitis and atheroembolic disease are important entities in the differential diagnosis of calciphylaxis but are not associated with the tendency to hypercalcemia found in this patient.

Reference

Wilmer WA, Magro CM (2002) Calciphylaxis: emerging concept in prevention, diagnosis, and treatment. Semin Dial 15:172–186

CASE 15

The finding of cardiac valvular calcifications predicts which ONE of the following clinical complications for patients on hemodialysis?

A. 2.5-fold increase in mortality in all such patients
B. A 2.5-fold increased mortality only if protein C levels are concomitantly elevated
C. A 50% increase in mortality only if valvular calcification coexists with known previous coronary artery disease
D. A 2.5-fold increased mortality only if the patient is older than 60 years
E. A 3-fold increase in aortic dissection

The correct answer is A. Recent clinical demonstrated that cardiac valve calcification was predicative of an increased all-cause mortality and cardiovascular death independent of age, gender, dialysis duration, C-reactive protein, diabetes, and atherosclerotic vascular disease.

Reference

Wang Ay, Wang M, Woo J, et al. (2003) Cardiac valve calcification as an important predictor for all cause mortality and cardiovascular mortality in long-term peritoneal dialysis patients: a prospective study. J Am Soc Nephrol 14:159–168

CASE 16

Which of the following statements regarding the measurement of serum PTH in patients with chronic kidney disease is TRUE?

A. The first generation intact PTH measures both 1–84 and 7–84 moieties of PTH.
B. The ratio of 1–84/7084 more accurately predicts the histologic state of bone than intact PTH assay.
C. A low 7–84 moiety in the face of a low 1–84 moiety rules out low turnover bone disease.
D. A low intact PTH in the face of a high 7–84 moiety indicates the presence of adynamic bone disease.
E. The 7–84 moiety solely binds to a clearance receptor.

The correct answer is A. Plasma PTH levels that remain persistently higher than the recommended target range for patients with ESRD are typically associated with bone biopsy evidence of secondary hyperparathyroidism. In contrast, PTH levels less than 150 pg/ml, particularly those below 100 pg/ml, usually indicate adynamic renal osteodystrophy. Based upon published comparisons demonstrating approximately two-fold differences between target PTH values determined by first and second generation immunoreactive assays, a target PTH of approximately 75 to 150 pg/ml as measured by a second generation PTH assay would correspond to existing guidelines for the preferred concentration of PTH in plasma for patients with ESRD.

Reference

Goodman WG, Juppner H, Salusky IB, et al. (2003) Parathyroid hormone (PTH), PTH-derived peptides, and new PTH assays in renal osteodystrophy. Kidney Int 63:1–11

CASE 17

Parathyroid hormone-related protein (PTHrP) is responsible for the humoral hypercalcemia of malignancy.

Which ONE of the following statements correctly characterizes the comparative effectiveness of PTHrP compared with intact PTH (1–84)?

A. Unlike PTH (1–84), PTHrP does not produce renal calcium reabsorption.
B. PTHrP is as equally phosphaturic as PTH (1–84).
C. Like PTH (1–84), PTHrP stimulates hydroxylation of 25-OH vitamin D_3.
D. PTHrP is less calcemic than PTH (1–84).
E. PTHrP does not influence magnesium reabsorption.

The correct answer is B. Horwitz et al.. examined the effects of PTHrP on renal calcium handling by comparing PTHrP to PTH (1–84). Both PTH (1–84) and PTHrP displayed similar calcemic and phosphaturic effects. In addition, both peptides had similar effects on renal tubular calcium handling. They also found that PTH (1–84) might be selectively more effective than PTHrP in stimulating 1,25 (OH)2 vitamin D_3.

Reference

Horwitz MJ, Tedesco MB, Sereiks SM, et al. (2003) Direct comparison of sustained infusion of human parathyroid hormone-related protein (hPTHrP-(1–36) versus hPTH-(1–34) on serum calcium, plasma 1,25-dihydroxyvitamin D concentrations, and fractional calcium excretion in healthy human volunteers. J Clin Endocrinol Metab 88:1603–1609

CASE 18

A six-year old girl has undergone renal transplantation as therapy for end-stage renal disease due to FSGS. She has received a living unrelated kidney from her husband. She has done well post-operatively. Her therapy includes a regimen of low-dose prednisone, cyclosporine and mycophenolate mofetile. At six months post-transplantation, a dual-energy x-ray absorptiometric scan demonstrates a 10% loss of bone mass compared with her pre-transplantation study.

Which ONE of the following maneuvers would have likely prevented this bone loss?

A. Low protein intake
B. Elimination of mycophenolate mofetile
C. Elimination of cyclosporine treatment
D. Use of vitamin D and calcium therapy
E. Alternate day steroid therapy

The correct answer is D. Low doses of active vitamin D and calcium partially prevents bone loss at the lumbar spine and proximal femur during the first six months after renal transplantation. Recently, prophylactic bisphosphonate treatment has shown promise, but the exact indications for its use in this setting remain to be determined. Steroid therapy contributes to bone loss, but not cyclosporine or mycophenolate.

Reference

DeSevaux RG, Hoitsma AJ, Corstens FH, et al. (2002) Treatment with vitamin D and calcium reduces bone loss after renal transplantation: a randomized study. J Am Soc Nephrol 13: 1608–1614

CASE 19

A decreasing GFR in CKD is associated with:

A. Decreasing PTH and decreasing 1,25 $(OH)_2$ D_3
B. Decreasing PTH and increasing 1,25 $(OH)_2$ D_3
C. Increasing PTH and decreasing 1,25 $(OH)_2$ D_3
D. Increasing PTH and increasing 1,25 $(OH)_2$ D_3
E. None of the above

The correct answer is C. In patients with CKD, declining GFR is associated with PTH secretion and decreasing 1, 25 $(OH)_2$ D_3. Phosphate restriction decreases PTH secretion and increases production by the kidney, which increases the absorption of dietary calcium.

Reference

Silver J, Levi R. Regulation of PTH synthesis and secretion relevant to the management of secondary hyperparathyroidism in chronic kidney disease. Kidney Int Suppl. 2005;95:S8–S12

CASE 20

Which of the following is the major regulator of PTH expression?

A. Plasma phosphate concentration
B. Plasma calcium concentration
C. Plasma level of 1,25 $(OH)_2$ D3
D. Plasma level of magnesium
E. None of the above

The correct answer is B. Calcium acting through the calcium receptor (CaR) is the major regulator of PTH transcription, secretion, and parathyroid gland hyperplasia.

Reference

Rodriguez M, Nemeth E, Martin D. The calcium-sensing receptor: a key factor in the pathogenesis of secondary hyperparathyroidism. Am J Physiol Renal Physiol 2005; 288:F253–264

CASE 21

Current therapeutic approaches for secondary PTH, which are based largely on active vitamin D analogues and phosphate binders,

A. Improve control of circulating PTH levels
B. Do not eliminate the progression of parathyroid gland hyperplasia

C. Are associated with increased Ca X P in high doses
D. Lower plasma phosphorous levels
E. All of the above

The correct answer is B. Current therapeutic approaches, based largely on an active vitamin D analogue and phosphate binders, lead to improved control of circulating PTH levels, but do not eliminate the progression of parathyroid gland hyperplasia and adenomatous transformation.

Reference

Fukagawa M, Tominaga Y, Kitaoka M, Kakuta T, Kurokawa K. Medical and surgical aspects of parathyroidectomy. Kidney Int suppl 1999; 73:S65–S69

CASE 22

According to the National Kidney Foundation's kidney disease outcome quality initiative (K/DOQI), the respective upper limits in stage 5 CKD are:

A. Serum phosphate 5.0 mg/dl; corrected serum calcium 9.5 mg/dl; $\mathrm{Ca} \times \mathrm{P} < 60$; and intact PTH 320 pg/ml
B. Serum phosphate 5.5 mg/dl; corrected serum calcium 9.5 mg/dl; $\mathrm{Ca} \times \mathrm{P} < 55$ mg/dl; and intact PTH 300 pg/ml
C. Serum phosphate 6.0 mg/dl; corrected serum calcium 9.5 mg/dl; $\mathrm{Ca} \times \mathrm{P} < 55$; and intact PTH 275 pg/ml
D. Serum phosphate 5.5 mg/dl; corrected serum calcium 9.0 mg/dl; $\mathrm{Ca} \times \mathrm{P} < 55$; and intact PTH 320 pg/ml
E. None of the above

The correct answer is B. The K/DOQI Guidelines recommend attaining serum calcium, phosphate, $\mathrm{Ca} \times \mathrm{P}$, and iPTH levels in the range that permits control of metabolic bone disease, while limiting the potential toxicity of increased $\mathrm{Ca} \times \mathrm{P}$ levels. The respective upper limit for serum phosphate in Stage 5 CKD is 5.5 mg/dl, the corrected serum calcium is 9.5 mg/dl (corrected serum calcium = serum calcium + 0.8 × [4-g/dl protein], the $\mathrm{ca} \times \mathrm{p}$ is <55, and intact PTH is 300 pg/ml.

Reference

Moe SM, Chertow GM, Coburn JW, et al. (2005) Achieving NKF-K/DOQI bone metabolism and disease treatment goals with cinacalcet HCL. Kidney Int. 67:760–771

CASE 23

Calcimimetics are thought to decrease both serum calcium and PTH levels through which of the following mechanisms of action?

A. Activation of PTH receptors in bone
B. Enhanced excretion of PTH in the kidney
C. Activation of CaR on chief cells of the parathyroid to suppress PTH secretion
D. Enhanced metabolism of PTH to inactive fragments
E. Inhibition of intestinal Ca absorption

The correct answers are B and D. Calcimimetics are calcium receptor (CaR) agonists that act on the parathyroid gland by increasing the sensitivity of the receptor to calcium. Treatment with cinacalcet HCl causes significant decreases in PTH without elevating serum calcium or phosphate levels.

Reference

Rodriguez M, Nemeth E, Martin D. The calcium-sensing receptor: a key factor in the pathogenesis of secondary hyperparathyroidism. Am J Physiol Renal Physiol 2005; 288:F253–264

CASE 24

A 12-year old boy treated with hemodialysis presents with a serum calcium level of 10.7 mg/dl, phosphate of 5.9 mg/dl, iPTH level of 1065 pg/ml, and a parathyroid gland weight of 5.0 g as determined by ultrasonography. Previous attempts with oral calcitriol therapy to suppress PTH had produced a 15% fall in PTH levels.

Which of the following treatments should be ordered next?

A. Aggressive use of Sevelamer to lower serum phosphate level
B. Intravenous calcitriol (1.0 ug) at the time of dialysis treatment
C. Intravenous 1-α vitamin D2 (1.0 ug) at the time of dialysis
D. Intravenous 25 (OH) vitamin D
E. Parathyroidectomy

The correct answer is E. The indications for parathyroidectomy include 1) hypercalcemia and hyperphosphatemia in the presence of very high PTH level (>800 pg/ml) with failure to lower PTH levels after six to eight weeks of vitamin D analogue and/or calcimimetics agents therapy; 2) fractures and tendon avulsions; 3) calcific arteriolopathy; and 4) hypertrophied gland and weight >4.0 g as determined by ultrasonography.

Reference

Ritz E (1994) Which is the preferred treatment of advanced hyperparathyroidism in a renal patient? II. Early parathyroidectomy should be considered as the first choice. Nephrol Dial Transplant 9:1819–1821

CASE 25

A 14-year old boy with ESRD has been treated with hemodialysis three times weekly for the past four years. He has adhered to his medication regimen, which included the use of calcium-containing phosphate binders and calcitriol. Current laboratory values include serum intact PTH 710 pg/ml, calcium 9.9 mg/dl, and phosphate 6.2 mg/dl. You decide to begin therapy with the calcimimetics agent, cinacalcet.

Which ONE of the following patterns of response compared to pretreatment values would be typical for patients receiving cinacalcet 30 mg/day (titrated up to 180 mg/day) based on changes in the intact PTH level?

A. 40% reduction in intact PTH level, 7% reduction in calcium, 10% reduction in phosphate
B. 10% reduction in PTH level, 10% reduction in calcium, 10% reduction in phosphate
C. 70% reduction in intact PTH level, 10% reduction in calcium, 10% reduction in phosphate
D. 80% reduction in intact PTH level, 7% reduction in calcium, 10% reduction in phosphate
E. 90% reduction in intact PTH level, 10% reduction in calcium, 10% reduction in phosphate

The correct answer is A. Forty-three percent of the cinacalcet group reached the primary end point, in comparison with 5 percent of the placebo group. Overall, mean parathyroid hormone values decreased 43 percent in those receiving cinacalcet but increased 9 percent in the placebo group. The serum calcium-phosphorus product declined by 15 percent in the cinacalcet group because calcium fell by 6.8% and phosphorus by 8.4%, and remained unchanged in the placebo group.

Reference

Block GA, Martin KJ, de Francisco AL, et al. (2004) Cinacalcet for secondary hyperparathyroidism in patients receiving hemodialysis. N Engl J Med 350:1516–1525

CASE 26

Which ONE of the following statements regarding recent prospective trials of phosphate-binding agents is correct?

A. The Calcium Acetate/Rangel (Sevelamer) Evaluation (CARE) study found that both agents were equally effective in lowering serum phosphate.
B. The CARE study found that vascular calcification was stable in both calcium acetate- and Sevelamer-treated patients.
C. The CARE study found that the incidence of hypercalcemia (>11.0 mg/dl) was equivalent to Sevelamer and calcium acetate.
D. The cost of treatment with calcium acetate is $<20\%$ of the cost of treatment with Sevelamer.
E. Sevelamer has been shown in a prospective, randomized, double-blind study to prevent progression of vascular calcifications.

The correct answer is D. The CARE study, a randomized, double-blind comparison between calcium acetate and Sevelamer found the calcium salt-controlled phosphorus more effective, and was more likely to produce acceptable phosphorus levels. As expected, the calcium levels were significantly higher with calcium acetate and transient hypercalcemia developed in 8 of 48 (16.7%) calcium acetate-treated subjects, but in none of the patients receiving Sevelamer. The projected annual per patient cost for treatment with calcium acetate would be $732 compared to $4283 for Sevelamer. The Treat to Goal study found that at study completion the median absolute calcium score in the coronary and aorta increased significantly in the calcium treated subjects, but not in the Sevelamer-treated subjects.

Reference

Emmett M (2004) A comparison of clinically useful phosphorus binders for patients with chronic kidney failure. Kidney Int 90: S25–S32

CASE 27

A 10-year old girl has begun hemodialysis treatments and you are considering which of the available parathyroid hormone (PTH) assays to use. You decide to try a new, whole-molecule, 1–84 assay, but are informed of an additional expense involved in the newer assays.

Which ONE of the following statements is TRUE regarding the decision to use the newer assay?

A. You should use the older, intact PTH assay because it yields more reliable results than the newer 1-84 whole or bio-intact assays.

B. The NKF K-DOQI guidelines strongly recommend that you use the newer bio-intact or whole PTH assays.
C. The older intact PTH assays will yield a higher level of PTH than the newer 1–84 bio-intact or whole PTH assays.
D. Subtracting the results of the newer bio-intact or whole PTH assays from the older intact PTH assay results will provide the only reliable data on the presence of adynamic bone disease.
E. You cannot successfully monitor the benefits of serum phosphate reduction using the older intact PTH assay systems.

The correct answer is C. A comparison of PTH determinations in patients on hemodialysis using intact and whole/bioactive immunometric assays shows very good concordance, so neither assay is *more reliable*. NKF K/DOQI guidelines did not recommend the newer tests because the work group felt it was premature to utilize the new assays as bone biopsy data with the new specific PTH 1–84 immunometric assays are limited at the present time. Because the older assays measured fragments as well as intact hormone, they gave a higher value for PTH than the newer, more specific assays. There is little data that the use of ratios or other derivatives involving PTH assays gives more information on adynamic bone disease than that derived from any single assay. Because the assays correlate well with each other, each of the assays will demonstrate a reduction in PTH level if serum phosphate reduction does reduce PTH secretion.

Reference

Martin KJ, Olgaard K, Coburn JW, et al. (2004) Bone Turnover Work Group: Diagnosis, assessment, and treatment of bone turnover abnormalities in renal osteodystrophy. Am J Kidney Dis 43:558

CASE 28

A 16-year old boy on trice-weekly hemodialysis develops an elevated intact PTH level of 415 pg/ml. The patient has been moderately compliant with phosphate-binder therapy and serum phosphate has been consistently <6.0 mg/dl. You decide to institute vitamin D therapy.

Which ONE of the following statements is correct regarding vitamin D therapy in this or similar patients?

A. Prospective controlled trials show that using paricalcitol as the vitamin D analogue will convey a survival advantage compared to using calcitriol.
B. Retrospective data show that using paricalcitol as the vitamin D analogue will convey a survival advantage compared to using calcitriol.

C. Prospective data show that using doxercalciferol as the vitamin D analogue will convey a survival advantage compared to using calcitriol.
D. Retrospective data show that using doxercalciferol as the vitamin D analogue will convey a survival advantage compared to using calcitriol.
E. Retrospective data show that using doxercalciferol as the vitamin D analogue will convey a survival advantage compared to using paricalcitol.

The correct answer is B. The study found that patients who receive paricalcitol while undergoing long-term hemodialysis appear to have a significant survival advantage over those who receive calcitriol. A prospective, randomized study is critical to confirm these retrospective findings. There are no definitive prospective studies of the effects of these agents on survival nor are there retrospective data supporting the beneficial effect of doxercalciferol on survival.

Reference

Teng M, Wolf M, Lowrie E, et al. (2003) Survival of patients undergoing hemodialysis with paricalcitol or calcitriol therapy. N Engl J Med 349:446–456

CASE 29

Which ONE of the following statements is TRUE regarding bone disease after renal transplantation?

A. Use of a short course of bisphosphonate zoledronate confers sustained preservation of bone mass for at least three years after transplantation.
B. Vitamin D therapy will prevent a decline in bone mineral density after transplantation, but will be associated with a significant increase in serum creatinine.
C. A short course of bisphosphonate zoledronate, but not pamidronate therapy, will preserve bone mass in patients for six months after renal transplantation.
D. Bone mass will typically remain stable in most patients after renal transplantation in the absence of specific therapy to retard bone loss.
E. Prospective studies suggest that vitamin D therapy is effective in preventing bone loss for one year after renal transplantation without a decline in GFR.

The correct answer is E. The study showed that the early bone loss that occurs during the first year after renal transplantation could be prevented by alfacalcidol without a sustained rise in serum creatinine. This bone loss is commonly seen in all patients who are not given some prophylaxis. The bisphosphonates are not effective in preventing long-term loss if they are prescribed as short term therapy.

Reference

El-Agroudy AE, El-Husseini AA, El-Sayed M, et al. (2003) Preventing bone loss in renal transplant recipients with vitamin D. J Am Soc Nephrol 14:2975–2979

CASE 30

Which ONE of the following choices is NOT a characteristic response to the use of Sevelamer as a phosphate-binding agent?

A. An increase in acid load
B. Reduced progression of coronary artery calcifications
C. An elevation of calcium-phosphate product
D. Reduction in LDL-cholesterol
E. An increased need for vitamin D supplementation

The correct answer is C. Sevelamer does convey a substantial acid load to treated patients because it is formulated as Sevelamer hydrochloride. The agent is associated with reduced progression of coronary artery calcifications and with a reduced LDL-cholesterol level. Typically, if patients are not given supplemental calcium, they will require vitamin D supplementation to maintain serum calcium levels while receiving Sevelamer.

Reference

Emmett M (2004) A comparison of clinically useful phosphorus binders for patients with chronic kidney failure. Kidney Int Suppl 90:S25–S32

CASE 31

A seven-year old boy with dialysis-dependent ESRD and chronic hip pain had an MRI scan that revealed aseptic necrosis that was attributed to previous glucocorticoid therapy for asthma. Two hours after the MRI, he had his scheduled hemodialysis treatment. His predialysis serum calcium was 5.4 mg/dl, phosphorus 5.6 mg/dl, and albumin 3.6 g/dl. He has been closely followed for moderate secondary hyperparathyroidism, and has received vitamin D supplementation.

Which is the MOST likely explanation for these findings?

A. Gadodiamide (Omniscan)-induced spurious hypocalcemia
B. Parathyroid infarction
C. Gadopentate (Magnevest)-induced spurious hypocalcemia
D. Inadvertent barium administration
E. Defective calcium ion electrode determination

The correct answer is A. Gadodiamide binds with colorimetric agents used in assaying serum calcium and produces a spurious hypocalcemia. Parathyroid infarct is a rare event. Gadopentate does not produce the same effect. Barium administration is associated with hypokalemia and barium sulfate used in radiologic studies does not enter the circulation. A defective lab instrument is always possible, but Gadodiamide predictably produces this artificial finding.

Reference

Choyke PL, Knopp MV (2003) Pseudohypocalcemia with MR imaging contrast agents: a cautionary tale. Radiology 227:627–628

CASE 32

Lanthanum carbonate is a phosphate binder. Which ONE of the following statements regarding its use is correct?

A. 90% of lanthanum excretion is via nonrenal pathway.
B. Lanthanum is less tightly bound to phosphate than is calcium in the GI tract.
C. Lanthanum directly induces osteomalacia in the bones of experimental animals.
D. Lanthanum has been shown to produce a higher frequency of nausea than placebo.
E. Lanthanum has been shown to be safe after 10 year of human use.

The correct answer is A. Lanthanum is predominately excreted via nonrenal routes through hepatic excretion. It is bound tightly to phosphates as a trivalent element. Its effects on bone are complex, but if it does produce osteomlacia changes in bone, it appears to be mediated by hypophosphatemia and not a direct effect of lanthanium. The side effect profile of lanthanium carbonate is good with no increased frequency of nausea, but the potential for long-term adverse effects has yet to be fully evaluated because no 10-year, post-marketing data are yet available.

Reference

Behets GJ, Verberckmoes SC, D'Haese PC, et al. (2004) Lanthanum carbonate:a new phosphate binder. Curr Opin Nephrol Hypertens 13:403–409

CASE 33

Which ONE of the following statements is TRUE regarding vascular calcification in patients with chronic kidney disease?

A. Calcification occurs primarily in the medial aspect of blood vessels.
B. Calcifications seen on electron beam computed tomography (EBCT) do not correlate with atherosclerotic burden in vessels.

C. Calcifications are primarily the result of calcium-phosphate deposited through simple mass action-induced precipitation.
D. Calcification, unlike atherosclerotic calcifications, have no inflammatory component.
E. Calcifications are unrelated to any changes in protein C levels.

The correct answer is A. Calcifications seen in patients with chronic kidney disease is primarily in the media of vessels. Calcifications seen on EBCT, however, are also correlated with intimal atherosclerosis and generally correlate with total atherosclerotic burden. Calcifications arise in response to metabolic, mechanical, infectious, and inflammatory injuries. Protein C levels, indicating systemic inflammation, do correlate with the degree of vascular calcifications.

Reference

Vattikuti R, Towler DA (2004) Osteogenic regulation of vascular calcification: an early perspective. Am J Physiol Endocrinol Metab 286:E686–696

Chapter 11
End-Stage Renal Disease and Dialysis

CASE 1

An 18-year old male with end-stage renal disease secondary to FSGS initiates chronic maintenance hemodialysis therapy. He receives 40 μg of recombinant hepatitis B vaccine intramuscularly in the deltoid, receiving three separate doses. Six weeks after the primary series is completed, antibody levels against hepatitis B surface antigen are <10 mU/ml.

Which ONE of the following is the MOST appropriate course of action at this time?

A. No further hepatitis B vaccine administration or antibody testing
B. Repeat antihepatitis B surface antigen after three months
C. Revaccinate with up to three additional intramuscular doses
D. Revaccinate with up to three intradermal doses
E. Revaccinate using Freund adjuvant

The correct answer is C. The Center for Disease Control Advisory Committee on Immunization Practices recommends revaccination with recombinant hepatitis B vaccine with up to three additional doses for susceptible persons who do not develop protective antibody levels after an initial vaccination series. The intramuscular route is preferred because there are no data regarding long-term protection following intradermal vaccination and the vaccine is not licensed for the intradermal route of administration. Freund's adjuvant is not used with the hepatitis B vaccine.

Reference

Rnagel MC, Coronado VG, Euler GI, et al. (2000) Vaccine recommendations on patient on chronic hemodialysis. Seminar 13:101–107

F. Assadi, *Clinical Decisions in Pediatric Nephrology.*

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CASE 2

A 14-year old girl on dialysis has recurrent hyperkalemia, prompting dietary intervention. Her dietitian notes that she has had an excessive consumption of strawberries and oranges, which may be contributing to her hyperkalemia. She is asked to remove these from her diet. One week later she presents to the dialysis unit with new symptoms of altered mental status, hiccoughs, and paresthesias of the limbs.

Consumption of which one of the following is the most likely explanation for her symptomatalogy?

A. Papayas
B. Passion fruit
C. Star fruit
D. Avocado
E. Cantaloupe

The correct answer is C. Star fruit, an exotic fruit, has potent neurotoxicity in uremic patients. Ingestion of 1–2 fruits is reported to be associated with the development of neurological symptoms within hours, an overall 40% morbidity, and 80% mortality in patients with altered mental status. Papayas, passion fruit, avocados, and cantaloupe are not associated with neurotoxicity in uremic patients.

Reference

Chang IM, Hwang SJ, Kuo HT, et al. (2000) Fatal outcomes after ingestion of star fruit (averrhoa, Carambola) in uremic patients. Am J Kidney Dis 35:189–193

CASE 3

A 15-year old boy on dialysis has recurrent intradialytic hypotension, often necessitating that he remain in the dialysis unit until his BP has stabilized. His mother confides in you that her son is contemplating discontinuation of dialysis therapy because of this problem, and she asks if you can adjust the dialysis prescription to improve the problem.

Which ONE of the following is least effective in reducing intradialytic hypotension?

A. Sequential ultrafiltration followed by dialysis
B. High-sodium dialysate
C. Use of sodium modeling
D. Low-temperature dialysate (35°C)
E. Administration of midodrine

The correct answer is A. Intradialytic hypotension occurs in 15–25% of all hemodialysis treatments. Although many strategies to prevent this complication are at least partly successful, a recent prospective crossover study did not support the use of isolated ultrafiltration followed by isovolemic dialysis. Each of the other four choices has demonstrated utility in preventing dialysis hypotension, albeit a head-to-head comparison of these four strategies has not been performed in a single study.

Reference

Dheenan S, Henrich WL (2001) preventing dialysis hypotension: A comparison of usual protective measures. Kidney Int 59:1175–1181

CASE 4

Which ONE of the following intradialytic acute symptoms has been observed with the use of outdated cellulose acetate dialyzers?

A. Sudden death
B. Visual and auditory changes
C. Chest pain
D. Hypotension
E. Acute hypoxemia

The correct answer is B. In a recent report by Hutter et al., seven out of nine patients exposed to the use of outdated cellulose acetate dialyzers developed acute onset of diminished vision and hearing associated with other neurologic symptoms. Other answers are possible, but are less characteristic.

Reference

Hutter JC, Kuehnart MJ, Willis RR, et al. (2000) Acute onset of decreased vision and hearing, traced to hemodialysis treatment with aged dialyzers. JAMA 283: 2128–2134

CASE 5

In comparing transposed brachiobasilic fistula to brachiocephalic fistula and upper arm arterioveous grafts, which ONE of the following statements is correct?

A. Mature brachiobasilic fistula have a lower thrombosis rate than mature brachiocephalic fistula.

B. Transposed brachiobasilic fistulas mature more quickly than brachiocephalic fistulas.
C. Transposed brachiobasilic fistulas have a higher thrombosis rate than upper arm grafts.
D. Transposed brachiobasilic fistulas require more interventions than upper arm grafts.
E. Transposed brachiobasilic fistulas have a higher infection rate than upper arm grafts.

The correct answer is B. Transposed brachiobasilic fistulas are more likely to mature and mature more rapidly than brachiocephalic fistulas. Once mature, however, brachiocephalic fistulas are less likely to fail than mature brachiobasilic fistulas. Both types of upper arm arteriovenous fistulas have better results than upper arm grafts.

Reference

Oliver MJ, McCann RL, Indridason OS, et al. (2001) Comparison of transposed brachiobasilic fistulas to upper arm grafts and brachiocephalic fistulas. Kidney Int 60:1532–1539

CASE 6

Which ONE of the following surveillance techniques has the least utility in detecting hemodynamically significant stenoses in arteriovenous grafts?

A. Measurement of access recirculation
B. Measurement of dynamic venous pressure
C. Measurement of static venous pressure
D. Measurement of intra-access flow
E. Physical examination of the access

The correct answer is A. Detection of recirculation in an arteriovenous graft is now recognized to be a late finding and thus is less useful in vascular access surveillance programs. All of the other choices have greater sensitivity and thus greater utility as surveillance techniques.

Reference

National Kidney Foundation (2000) K/DOQ1 Clinical Practice Guidelines for Vascular Access. Am J Kidney Dis (suppl 1) 37:S137–S181

CASE 7

A 17-year old male is receiving hemodialysis therapy using a cuffed tunneled catheter. At the dialysis unit, he is found to have a low-grade fever and erythema at the catheter exit site. Two blood cultures are obtained, and mupirocin ointment is prescribed for a suspected exit-site infection. Vancomycin 1000 mg is also administered intravenously. Two days later, blood cultures are growing staphylococcus aureus sensitive to both vancomycin and cephalosporins. The patient is afebrile, and there is no erythema and no drainage from the catheter exit-site. He has no drug allergies.

Which ONE of the following is the most appropriate course of action?

A. Complete a three-week course of vancomycin (500 mg) after each dialysis treatment.
B. Complete a three-week course of cefazolin (1000 mg) intravenously with each dialysis treatment.
C. Arrange for catheter removal and exchange.
D. Arrange for catheter removal and exchange, and complete a three-week course of intravenous cefazolin (1000 mg) with each dialysis treatment
E. Continue treatment with mupirocin ointment, and use cefazolin (1000 mg) after each dialysis treatment for 3 weeks if the patient develops recurrent fever

The correct answer is D. Strategies involving catheter removal coupled with a three-week course of cefazolin intravenously have been demonstrated to be successful in achieving high cure rates. Antibiotic therapy alone results in an insufficient cure rate.

Reference

Beathard GA (1999) Management of bacteremia associated with tunneled-cuffed hemodialysis catheters. J Am Soc Nephrol 10:1049–1045

CASE 8

At the conclusion of a hemodialysis treatment, a dialysis nurse notes that there is a significant kink in the dialysis tubing. The patient is asymptomatic. Six hours later, the patients presents to emergency room complaining of severe epigastric abdominal pain radiating into the back.

Which ONE of the following is the most likely diagnosis?

A. Acute pancreatitis
B. Acute gastritis

C. Acute myocardial infarction
D. Acute colitis
E. Acute cholelithiasis

The correct answer is A. Intradialytic acute hemolysis can occur as a consequence of turbulent flow through hemodialysis lines, inducing mechanical trauma. Severe abdominal or back pain is common, along with clinical evidence of pancreatitis. Mortality has been reported.

Reference

Duffy R, Tomascheck K, Spangenberger M, et al. (2000) Multicites outbreak of hemolysis in hemodialysis patients traced to faulty blood tubing sets. Kidney Int 57:1667–1674

CASE 9

A nine-year old boy on hemodialysis is found to have hemoglobin of 9.0 g/dl despite of receiving 10,000 units of intravenous erythropoietin with each dialysis treatment. His transferring saturation is 8% and serum ferritin is measured at 40 ng/ml. Stool guaiac cards are negative. The patient is currently taking oral iron polysaccharide (150 mg daily). He has a history of anaphylactoid reaction to iron therapy.

Which ONE of the following is the most appropriate course of action?

A. Provide packed red cell transfusions to achieve target hemoglobin between 11 and 12 g/dl.
B. Increase oral iron to twice daily as tolerated.
C. Transfuse with packed red cells if hemoglobin drops below 8.0 g/dl.
D. Begin therapy with intravenous iron sucrose or iron gluconate.
E. Refer the patient for colonoscopy.

The correct answer is D. In most cases, anaphylactoid reaction to iron dextran administration is related to the presence of antidextran antibodies. Because neither iron sucrose nor iron gluconate have dextran, these preparations can be utilized in patients with previous anaphylactoid reactions to iron dextran. Iron sucrose and iron gluconate are associated with fewer anaphylactoid reactions than iron dextran, but can not be administered in higher total iron doses than iron dextran due to more rapid association of iron from the corresponding sugar. Increased oral iron is unlikely to replete iron stores when significant iron deficiency already exists. Most patients can not maintain adequate iron stores on oral iron therapy. Most patients on maintenance hemodialysis will require weekly intravenous iron and weekly intravenous iron therapy results in an improved erythropoietic index compared to intermittent bolus therapy.

References

Michael B, Coyne DW, Fishbane S, et al. (2002) Sodium gluconate complex in hemodialysis patients: adverse reactions compared to placebo and iron dextran. Kidney Int 61:1830–1839
Van Wyck DB, Cavallo G, Spinowitz BS, et al. (2000) Safety and efficacy of iron sucrose in patients sensitive to iron dextran: North American Clinical Trial. AM J Kidney Dis 36:88–97

CASE 10

An anemic patient on chronic hemodialysis is found to have a persistently low transferring saturation, and high serum ferritin levels.

Which ONE of the following laboratory tests will likely provide the most valuable information concerning the etiology of this problem?

A. Serum creatinine
B. Serum anion gap
C. Serum bicarbonate
D. Serum haptoglobin
E. Serum C-reactive protein

The correct answer is E. A persistently low transferring saturation coupled with high serum ferritin suggests an acute phase inflammatory process. This can be most clearly demonstrated by the measurement of C-reactive protein.

Reference

Gunnell J, Yeun JY, Depner TA, et al. (1999) Acute-phase response predicts erythropoietin resistance in hemodialysis and peritoneal dialysis patients. Am J Kidney Dis 33:63–72

CASE 11

A 12-year old dialysis patient is sent for fistulography because of the development of high static venous pressure and the increased time required to achieve access-site hemostasis after dialysis. At the procedure, she is found to have a high-grade stenosis at the graft-vein anastomosis, which is successfully angioplastied.

Which ONE of the following is the best predictor of long-term patency after angioplasty of a venous stenosis in dialysis graft?

A. Angiographic appearance of the lesion post-angioplasty
B. Degree of improvement in vascular access blood flow after angioplasty
C. Degree of improvement in KT/V urea

D. Degree of improvement in dynamic venous pressure
E. Decrease in length of time required to gain hemostasis at access sites after the dialysis procedure

The correct answer is B. Recent data suggest that monitoring vascular access blood flow before and after angioplasty of a venous stenosis in arteriovenous grafts may have efficacy in predicting subsequent access patency.

Reference

Ahya SN, Windus DW, Vesely TM, et al. (2001) Flow in hemodialysis grafts after angioplasty: Do radiologic criteria predict success? Kidney Int 59:1974–1978

CASE 12

A 19-year old patient on chronic hemodialysis has an estimated dry weight of 85 kg. His dialysis prescription consists of the following: treatment time, 4.5 hours; dialysis access, arteriovenous fistula; blood flow, 35 ml/min; dialysis flow, 600 ml/min; dialyzer, high-flux polysulfone. His measured single pool variable volume Kt/V urea is consistently less than 1.2.

Which ONE of the following approaches will likely lead to the greatest improvement in weekly urea clearance?

A. Increasing blood flow to 400 ml/min
B. Increasing dialysate flow to 800 ml/min
C. Adding a tandem dialyzer to the extracorporeal circuit
D. Adding a fourth weekly dialysis treatment
E. Increasing dialysis time to five hours for each treatment

The correct answer is D. As an index of solute clearance, KT/V urea <1.2 serves as a generally accepted marker of inadequate dialysis doses. Patients with large body mass are less likely to achieve an individual treatment target KT/V urea of 1.2. Although each of the proposed solutions will increase weekly KT/V urea, increasing the frequency of hemodialysis will have the greatest effect on weekly urea clearance by increasing the efficiency of the hemodialysis procedure.

References

Depner TA (2002) Daily hemodialysis efficiency: An analysis of solute kinetics. Adv Ren Replace Ther 8:227–235

Frankenfield DL, McClellan WM, Helgerson SD, et al. (1999) Relationship between urea reduction ratio, demographic characteristics, and body weight for patients in 1996 National ESRD Core Indicators Project. Am J Kidney Dis 33:584–591

CASE 13

A 17-year old male receiving chronic hemodialysis therapy has multiple comorbidities, including dilated cardiomyopathy, anemia despite high doses of erythropoietin, hypertension, hyperlipidemia, and generalized muscle weakness. You are considering adding L-carnitine to his medical regimen.

What is the single MOST consistent clinical effect observed in prospective trials of L-carnitine supplementation in the maintenance hemodialysis patient?

A. Improvement in myocardial function
B. Reduction in triglyceides
C. Reduction in serum cholesterol
D. Improvement in erythropoietin resistance
E. Improvement in excercisie capacity and muscle weakness

The correct answer is D. L-carnitine is a readily dialyzed, low molecular weight, metabolic intermediate. L-carnitine deficiency has been proposed as a contributor to myocardial dysfunction, hyperlipidemia, muscle weakness, and erythropoietin resistance in dialysis patients. The best evidence for benefit of L-carnitine in maintenance dialysis patients is for the treatment of erythropoietin resistance.

Reference

Hurot JM, Cucherat M, Haugh M, et al. (2002) Effects of L-carnitine supplementation in maintenance hemodialysis patients: A systematic review. J Am Soc Nephrol 13:708–714

CASE 14

A 15-year old hemodialysis patient has developed intradialytic palpitation on several occasions. His ECG demonstrates increased QT dispersion (variation in the QT interval).

Which ONE of the following maneuvers would be most appropriate in attempting to reduce QT dispersion?

A. Increased dialysate sodium concentration
B. Increased dialysis time to reduce net hourly required ultrafiltration
C. Administer oxygen during the dialysis procedure
D. Increased dialysate calcium concentration from 2.5 mg/dl to 3.5 mg/dl
E. Increased blood flow and dialysate flow rate to increase Kt/V urea

The correct answer is D. QT dispersion, defined as the difference in duration between the longest and shortest QT interval on an electrocardiogram, is a method

of approximating repolarization abnormalities. QT dispersion has been shown to independently predict cardiovascular mortality in incident dialysis patients. Intradialytic QT dispersion has been demonstrated to be inversely related to a dialysate calcium composition.

References

Beaubien ER, Pylypchuk GB, Akhtar J, et al. (2002) Value of corrected QT interval dispersion in identifying patients initiating dialysis at increased risk of total and cardiovascular mortality. Am J Kidney Dis 39:834–842

Nappi SE, Virtanen VK, Saha HHT, et al. (2000) QT dispersion increases during hemodialysis with low-calcium dialysate. Kidney Int 57:2117–2122

CASE 15

Which ONE of the following statements concerning cardiac arrest and sudden death in the dialysis unit is TRUE?

A. Patients who experience cardiac arrest and sudden death are more frequently prescribed a dialysate potassium concentration of less than 2 mEq/l.
B. Cardiac arrest and sudden death is sufficiently uncommon that they are unlikely to incur over the course of the year in the averaged sized dialysis unit.
C. The type of dialysis vascular access has no effect on predicting the likelihood of cardiac arrest.
D. The day of week has no significant effect on the likelihood of cardiac arrest and sudden death.
E. Virtually all patients who experience cardiac arrest and sudden death in a dialysis unit have a history of dilated cardiomyopathy.

The correct answer is A. Cardiac arrest and sudden death in dialysis unit occurs more frequently when patients have been dialyzed against a small dose of potassium dialysate (0 or 1.0 mEq/l). Cardiac arrest, while infrequent, occurs in 7 per 100,000 hemodialysis sessions. Only 48% of patients who experience cardiac arrest have a known cardiac history. Both day of the week and type of vascular access contribute to the likelihood of cardiac arrest.

Reference

Karnik JA, Young BS, Hew NL, et al. (2001) Cardiac arrest and sudden death in dialysis units. Kidney Int 60:350–357

CASE 16

A new patient starting regular maintenance hemodialysis treatments has a higher than average risk of mortality over the next five years if he or she belongs to which ONE of the following ethnic/racial group?

A. Caucasian
B. Hispanic
C. Asian-American
D. African-American
E. Mixed ethnic/racial

The correct answer is A. Several studies have shown higher mortality rates in Caucasians. A recent analysis of Dialysis Outcomes and Practice Patterns Study (DOPPS) data comparing Caucasians with other ethnic/racial groups showed a relative risk of 0.78 ($p<0.001$) for African-American, 0.68 ($p<0.01$) for Asians, 0.51 ($p<0.001$) for Native Americans and 0.92 (p=NS) for Hispanics. The higher risk of death in Caucasians with ESRD contrasts with the lower incidence and prevalence of ESRD in Caucasians compared with other ethnic/racial groups.

Reference

Lopes AA, Bragg-Gresham JL, Satayathum S, et al. (2003) Health-related quality of life and associated outcomes among hemodialysis patients of different ethnicities in the United States: the Dialysis Outcomes and Practice Patterns Study (DOPPS). Am J Kidney Dis 41:605–615

CASE 17

Prophylaxis against dialysis catheter-related bacteremia includes which ONE of the following?

A. Intravenous antibiotic near the end of each dialysis treatment
B. Gentamicin/citrate catheter lock
C. Ultrapure water
D. Ultrapure dialysate
E. Replacement of the catheter

The correct answer is B. Several controlled studies have shown that locking the catheter with an antibiotic or antiseptic solution can reduce the incidence of bacteremia as much as tenfold. While the use of ultra pure water and ultra pure dialysate is recommended in general to combat a subtle inflammatory influence of dialysis, such measures will not protect against catheter-induced sepsis. Antibiotics given

to the patient near the end of the dialysis treatment have little effect on catheter biofilm because the exposure is limited to both concentration and time. Replacing the catheter will resolve the problem, but it cannot be considered a prophylactic measure.

Reference

Allon M (2003) Prophylaxis against dialysis catheter-related bacteremia with a novel antimicrobial lock solution. Clin Infect Dis 36:1539–1544

CASE 18

An 18-year old woman with ESRD managed with hemodialysis develops acute substernal chest pain and requires help in choosing the least toxic form of angiography.
Which ONE of the following choices regarding this issue is TRUE?

A. Over 75% of injected gadolinium can be removed by a single dialysis.
B. Iodinated radiographic contrast agents are slowly removed by dialysis.
C. Iodinated radiographic contrast agents are easily removed by hemofiltration.
D. Gadolinium and iodinated contrast agents are large molecules that cannot be removed by dialysis.
E. There is no risk from injection of radiographic contrast agents in anuric patients.

The correct answer is A. Hemodialyzed patients are especially prone to acute volume overload after intravenous injection radiographic contrast agents, including aortography or contrast-enhanced MRI. Recent studies have shown that both gadolinium and iodinated radiographic contrast agents are rapidly and efficiently removed by hemodialysis and hemofiltration. Average removal rates of gadolinium were 78%, 95%, 98%, and after the first to fourth hemodialysis sessions. Physicians must also be alert to the significantly low serum calcium levels that may last up to 4 ½ days after the gadolinium administration. This effect of gadolinium is apparently dose-related.

References

Marenzi G, Marana I, Lauri G, et al. (2003) The prevention of radiocontrast-agent-induced nephropathy by hemofiltration. N Engl J Med 349:1333–1340
Okada S, Katagiri K, Kumazaki T, et al. (2001) Safety of gadolinium contrast agent in hemodialysis patients. Acta Radiol 42:339–341
Prince MR, Erel HE, Lent RW, et al. (2003) Gadolinium administration causes spurious hypocalcemia. Radiology 22&:639

CASE 19

A nine-year old girl with ESTD resulting from IgA nephropathy is on peritoneal dialysis (PD) and is found to be hypertensive. Her current weight is 48 kg and has no signs of volume overload and no peripheral edema, and there are no abdominal bruits. In the past two years of PD therapy, she has been on cycler therapy doing four 2.5% dextrose exchanges over nine hours and a 15-hour daytime dwell with 2.5% dextrose. She was normotensive on no antihypertensives. She is adequately dialyzed in terms of small solute clearance, but over the last two months she has become hypertensive (BP 155/90 mmHg) despite using two antihypertensive medications.

In addition to decreasing dietary sodium intake, which ONE of the options listed below would be the best change in her current prescription that would MOST likely improve her BP control?

A. Change the overnight prescription to three 2.5% dextrose dwells over nine hours and add a daytime dwell of icodextrin.
B. Continue current overnight prescription, but change daytime dwell to 4.25% dextrose during day.
C. Change her nightly prescription to three 2.5% dextrose dwells over 10 hours and continue 2.5% dextrose during day.
D. Continue current overnight prescription and add a 1.5% dextrose last bag fill and a 1.5% dextrose midday exchange.
E. Change overnight prescription to five 4.25% exchanges and a 4.25% daytime dextrose exchange.

The correct answer is A. It has been well-documented that with glucose (dextrose)-containing fluids the crystalloid-induced transcapillary ultrafiltration (UF) is dependent on maintaining an osmotic gradient between the peritoneum and the blood which favors movement of fluid from the blood to the peritoneum. The peritoneal membrane functions as an impermeable membrane and allows movement of most solutes down their concentration gradients. Unfortunately, glucose (dextrose) is readily absorbed and eventually the concentration gradient for transcapillary UF no longer exists. At that time, UF ceases and lymphatic absorption predominates. An ideal osmotic agent for PD solutions would either not be absorbed or, would only very slowly be absorbed so that the osmotic gradient is maintained throughout the dwell. Icodextrin is such a solution. Icodextrin is a polymer that induces ultrafiltration via a colloid osmotic force. By substituting icodextrin for dextrose, one may be able to increase UF volume during long dwells (8 to 15 hours) when compared to dextrose-containing fluids. Because attention has returned to optimizing BP and volume control, it has been recognized that at times, the UF volume may be relatively sodium free. Crystalloid-induced UF is via small pores (salt and water removal) and transcellular aquapores (water removal only). Therefore, during short dwells one may remove relatively less sodium than water. In contrast,

colloid-induced UF is almost exclusively via small pores, so there is no discrepancy between the relative amounts of salt and water removed during a typical dwell with a colloid osmotic agent. These differences must be appreciated when attempting to optimize BP control in PD patients.

Reference

Konings C, Kooman JP, Schonck M, et al. (2003) Effect of icodextrin on volume status, BP and echocardiographic parameters: A randomized study. Kidney Int 63:1556–1563

CASE 20

Which ONE of the following statements is true concerning hepatitis B viral infections (HBV) in the end-stage renal disease population?

A. Due to the low seroconversion rate of HBV in dialysis units, HBV vaccinations of all incident ESRD patients are not recommended.
B. As with HIV, those with active HBV infections do not need to be isolated.
C. On the basis of worldwide data from Dialysis Outcomes and Practice Patterns (DOPPS), mean facility HBV prevalence was 3.0%.
D. Most patients respond to maintain their seroprotection at two years.
E. There is frequent documented transmission from patient to staff from accidental needle sticks.

The correct answer is C. Epidemiologic data would suggest that seroconversion rates are extremely low. The prevalence of patients with active hepatitis B surface ranges from 0 to 5% of patients in over 75% of units. Vaccinations (usually a total of 4 injections: 0,1,1 and 12 months) is recommended. Most patients (about 75%) respond to the complete course at one year, however about 66% of primary responders have lost documented seroprotection at two years. Isolation is recommended with universal precautions.

Reference

Burdick RA, Bragg-Gresham JL, Woods JD, et al. (2003) Patterns of hepatitis B prevalence and seroconversion in hemodialysis units from three continents: The DOPPS. Kidney Int 63:2222–2229

CASE 21

One week after being changed to icodextrin for the daytime dwell, a 14-year old girl who has been on automated PD for four years presents with peritonitis. She is empirically placed on the appropriate dose of gentamicin and vancomycin during

her 15-hour daytime dwell. Five days after presentation, the patient looks well, but continues to have cloudy fluid. Peritoneal fluid cultures at baseline and after two days on therapy, remains negative. There are no eosinophils noted in the peritoneal fluid.

Which ONE of the following options given below would be the most appropriate intervention at this time?

A. Discontinue all antibiotics due to possibility of an allergic reaction to the intraperitoneal medications and negative cultures.
B. Discontinue icodextrin dwells, substitute dextrose-containing solutions, and continue current antibiotics.
C. Continue current antibiotics because she is clinically better but has not had enough *time* for the antibiotics to clear the infection.
D. Remove the catheter, place a tunneled catheter, and transfer to hemodialysis because the peritonitis has failed to respond.
E. This likely presents a *chemical* peritonitis from vancomycin—switch to cephalosporine and continue the gentamicin.

The correct answer is B. Icodextrin is an alternative osmotic agent that has been developed to improve ultrafiltration on PD. There are documented benefits to the use of icodextrin, but as with any other intervention, side effects may occur. Sterile peritonitis has been seen as an allergic reaction to intraperitoneal icodextrin use.

Reference

William PF, Foggensteiner L (2002) Sterile/allergic peritonitis with icodextrin in CAPD patients. Perit Dial Int 22:89–90

CASE 22

A five-year old girl with ESRD being treated with PD presents with a rapidly decreasing hemoglobin (Hb) level. There are no signs of gastrointestinal blood loss. She has been taking her subcutaneous recombinant human erythropoietin (RhuEPO) regularly. Because of her decreasing Hb, the dose of the rHuEPO has been markedly increased over the past two months. You suspect pure red blood cell aplasia (PRCA).

Which ONE of the following findings would be most consistent with that diagnosis?

A. A decline in Hb level from 11.6 g/dl to 8.3 g/dl over the past two months and declining iron saturation.
B. A decline in Hb from 11.6 g/dl to 8.3 g/dl over the past two months and a reticulocyte count of 3%.

C. Normal transferring and ferritin levels and an elevated alkaline phosphatase level.
D. Finding a low peritoneal WBC but normal WBC precursors and platelet precursors and 7% RBC precursors on bone marrow examination.
E. A decline in HB from 11.6 g/dl to 8.3 g/dl over the past two months, 3% erythroblasts, normal WBC precursors, and platelet precursors on bone marrow examination.

The correct answer is E. PRCA is a rare, but serious, complication of treating the anemia of CKD with rHuEPO. This disease must be considered as part of differential diagnosis in a patient with documented rHEPO resistance. Other causes of rHEPO resistance include iron deficiency, hyperparathyroid states, chronic inflammation, and vitamin B12 or folic acid deficiency. Patients with PRCA often have a rapid decline in their Hb levels, decreased erythrocyte precursors on bone marrow exam, and a peripheral reticulocyte count of $<1\%$. Other causes of rHEPO unresponsiveness need to be ruled out. Treatment is to discontinue the rHuEPO and avoid transfusion if possible.

Reference

Arand S, Nissenson AR (2003) Pure red-cell aplasia (2003) An emerging epidemic in dialysis patients. Peri Dial Int 23:317–319

Chapter 12
Transplantation

CASE 1

An 18-year old female with lupus nephritis and a panel reactive antibody (PRA) of 65% receives her third renal transplant. Her postoperative course is complicated by delayed graft function, and her serum creatinine eventually stabilizes at 1.8 mg/dl by six weeks post-transplantation. Her immunosuppressive medications are tacrolimus, mycophenolate mofetile (MMF), and prednisone. At 10 months post-transplantation, she presents with epigastric discomfort and dysphasia. Upper GI endoscopy reveals a gastric lesion, which is found to be Epstein-Barr Virus (EBV)-related post-transplant lymphoproliferative disease on histology.

Which ONE of the following therapeutic approaches is the best initial option for this patient?

A. Immunosuppression should be reduced.
B. Immunosuppression should be withdrawn.
C. Rituximab should be started and immunosuppression maintained at its current levels.
D. Immunosuppression should be reduced and valganciclovir initiated.
E. Surgical resection of the lesion should be performed.

The correct answer is A. Post-transplant lymphoproliferative disease (PTLD) carries a high mortality of about 70%, according to various reports, and several factors—including the number of involved organs, primary CNS involvement, and monoclonality—suggest a poorer prognosis. Therapeutic interventions include the reduction of immunosuppression, antiviral therapy, anti-B cell antibodies, anti-IL6 antibodies, alpha-interferon, cytotoxic T-cells, chemotherapy, radiation, and surgical resection. The reduction of immunosuppression forms the cornerstone of all treatment and may be sufficient by itself, with complete remission in 63% of cases in some reports. This woman is a high immunological-risk patient with localized PTLD. Withdrawal of immunosuppression will almost certainly result in acute rejection in an individual who is not at a very high risk of dying due to PTLD. Currently, many transplant programs would also administer rituximab in addition to reducing immunosuppression. Rituximab has been shown to induce remission in

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transplant recipients, including lung, liver, small bowel and stem cells transplants. However, there is insufficient data to maintain immunosuppression at current levels in combination with rituximab therapy. Neither acyclovir nor ganciclovir have an effect on EBV persistence associated with latent infection, and their use has not been effective in the treatment of PTLD.

Reference

Green M (2001) Management of Epstien-Barr virus-induced post-transplant lymphoproliferative disease in recipient of solid organ transplantation. Am J Transplant 1:103–108

CASE 2

A 19-year old female with chronic renal failure secondary to Type 1 diabetes mellitus is refereed for evaluation for pancreas transplantation. Her creatinine clearance is 38 ml/min. She has no evidence of neuropathy; however, she has had two laser treatments for retinopathy and has had two episodes of severe hypoglycemia in the last year. She has no potential living donors.

Which ONE of the following therapies would you now recommend?

A. List now for simultaneous pancreas-kidney transplantation
B. List now for pancreas transplantation alone
C. List for cadaveric renal transplant when her renal function has declined further
D. List for simultaneous pancreas-kidney transplant when her renal function declined further
E. Arrange for islet cell transplantation

The correct answer is D. Both pancreas and islet transplantation are usually reserved for patients that have recurrent life-threatening hypoglycemic episodes, or in some cases with severe complications of diabetes, such as crippling neuropathy. The reasons for these restrictions are because of the risks of long-term immunosuppression. The incidence of kidney failure after pancreas transplant alone is 2% at one year and increasing to 12% by five years post-transplant. This patient has only two hypoglycemic episodes in the last year. She is therefore not a candidate for either pancreas transplant or islet transplantation. In addition, she has a relatively good renal reserve with no symptoms, and does not qualify for listing for renal transplantation. She has no living donor. She should be listed for cadaveric transplantation once her renal function has declined further. Because patient and graft survival for simultaneous pancreas and kidney (SPK) transplantation are better than that for cadaveric kidney transplantation alone, she should be advised to be listed for SPK.

Reference

Gross CR, Limwattananon C, Maththees B, et al. (2000) Impact of transplantation on quality of life in patients with diabetes and renal dysfunction. Transplantation 70:1736–1746

CASE 3

An 18-year old male with chronic renal failure secondary to Type 1 diabetes mellitus presents for evaluation for renal transplantation. He has a creatinine clearance of 20 ml/min and has not yet initiated dialysis. His 26-year old brother is the same blood group and is willing to donate a kidney.

Which ONE of the following options would you now recommend?

A. List the patient for cadaveric renal transplant alone
B. List the patient for SKP transplantation
C. Arrange for living donor renal transplantation alone
D. Arrange for living donor renal transplantation before initiating dialysis followed by pancreas after kidney transplantation
E. Arrange for donor renal transplantation after the patient has initiated dialysis

The correct answer is D. Recent studies have shown increased patient survival following SPK transplantation (95%) and kidney graft survival (92%) at one year for recipient of SPK transplant, representing a higher kidney graft survival than that for diabetic recipients of cadaveric kidney transplants alone. SPK offers the best survival advantage and represents the treatment of choice for Type 1 diabetic patients with renal failure. Patients who have received one to six months of dialysis prior to transplantation, have had at least a 15% increase in mortality risk in comparison to those that underwent preemptive transplantation. A 75% higher risk of death was seen in those patients that were on dilyalsis for greater than 24 months.

References

Becker BN, Odorico JS, Becker YT, et al. (2001) Simultaneous pancreas-kidney and pancreas transplantation J Am Soc Nephrol 12:2527–2527

Rayhill SC, D'Alessandro AM, Odorico JS, et al. (2000) Simultaneous pancreas-kidney transplantation and living donor renal transplant in patients with diabetes: Is there a difference in survival? Ann Surge 231:417–423

CASE 4

Which ONE of the following statements regarding anti-lymphocytic induction therapy is CORRECT?

A. It is not associated with an increased risk of cardiovascular death.
B. Polyclonal antilymphocytic antibodies usually do not cause thrombocytopenia.
C. It has not been shown to increase allograft survival.
D. It is not associated with an increased risk of cytomegalovirus (CMV) infection.
E. It is not associated with long-term risk of malignancy.

The correct answer is C. Overall, clinical studies have not definitely shown an improvement in long-term allograft survival. In a recent paper, Meier-Kriesche et al. found that induction therapy was associated with an increased relative risk of cardiovascular death (1.17), infection related death (1.16), and death due to malignancy (1.16) on mulivariant analysis of cause of death after six months post-transplant. Because polyclonal anti-lymphocytic antibodies are directed toward several cell surface molecules, it may affect cells other than lymphocytes. These antibodies may all cause thrombocytopenia.

Reference

Meier-Kriesche HU, Arndorfer JA, Kaplan B (2002) Association of antibody induction with short and long-term cause-specific mortality in renal transplant recipients. J Am Soc Nephrol 13:769–772

CASE 5

All of the following statements with regard to corticosteroids withdrawal after renal transplantation are true EXCEPT for one.

Which ONE is the INCORRECT answer?

A. Acute rejection is more likely in African-Americans.
B. Avoidance of corticosteroids may be more effective than withdrawal of corticosteroids.
C. If it is achieved without rejection, it does not affect graft survival.
D. Withdrawal results in acute rejection in approximately 30% of patients.
E. Withdrawal reduces the need for antihypertensive therapy.

The correct answer is C. A recent meta-analysis of 10 studies in which steroid reduction was attempted concluded that steroid withdrawal was associated with increased risk of acute rejection and graft survival. The Canadian multicenter steroid withdrawal trial emphasized the importance of long-term follow-up in patients in whom steroids have been withdrawn, because despite the encouraging initial results, there was an increase in graft loss by five years post-transplantation. Recent data suggest that rapid withdrawal of steroids immediately post-transplantation, or complete avoidance, may be more successful and result in less acute rejection episodes. There is no long-term follow-up of these protocols and therefore the impact on long-term graft survival is not known.

References

Birkeland SA (2001) Steroid-free immunosuppression in renal transplantation: a long-term follow-up of 100 consecutive patients. Transplantation 71:108901090

Kasiske BL, Chakkera HA, Louis TA, et al. (2000) Ameta-analysis of immunosuppression withdrawal trials in renal transplantation. J Am Soc Nephrol 11:1910–1917
Sarwal MM, Yorgin PD, Alexander S, et al. (2001) Promising early outcomes with a novel, complete avoidance immunosuppression protocol in pediatric renal transplantation. Transplantation 72:13–21

CASE 6

Post-transplantation anemia is NOT related to which ONE of the following?

A. Mycophenolate mofetile therapy
B. ACE inhibitor therapy
C. Paravirous infection
D. Tacrolimus therapy
E. Sirolimus therapy

The correct answer is D. Mycophenolate mofetile has been associated with leucopenia and anemia. Both ACE-inhibitors and ARB have been shown to cause anemia in renal transplant patients. Anemia has been infrequently reported as a side effect of sirulimus, but it has been reported. There have been many reports documenting the association between paravirus B19 as a cause of anemia in renal transplant recipients.

References

Ersoy A, Dilek K, Usta M, et al. (2002) Angiotensin-II receptor antagonist losartan reduces microalbuminuria in hypertensive renal transplant recipients. Clin Transplant 16:202–205
Hernandez D, Lacalzada J, Salido E, et al. (2000) Regression of left ventricular hypertrophy by lisinopril after renal transplantation: role of ACE gene polymorphism. Kidney Int 58:889–897
MacDonald AS (2001) A worldwide, phase III, randomized, controlled, safety and efficacy study of a sirulimus/cyclosporine regimen for prevention of acute rejection in recipients of primary mismatched renal allografts. Transplantation 71:271–280
Mycophenolate mofetile in renal transplantation: 3-year results from the placebo-controlled trial (1999) European Mycophenolate Mofetile Cooperative Study Group. Transplantation 68:391–396
Yango A, Morrissey P, Gohl R, Wahbeh A (2002) Donor-transmitted paravirus infection in a kidney transplant recipient presenting as pancytopenia and allograft dysfunction. Transpl Infect Dis 4:163–166

CASE 7

Which ONE of the following immunosuppressives may improve long-term graft survival?

A. Tarcrolimus
B. Mycophenolate mofetile (MMF)

C. Rapamycin
D. Anti-CD25 antibodies
E. FTY720

The correct answer is B. No individual randomized, controlled double-blind trial of any immunosuppressive has demonstrated a definite improvement in long-term allograft survival associated with any of the currently available immunosuppressive agents. Ojo et al., however, found in the USRD database that MMF was associated with 27% decreased risk of chronic allograft failure, and this effect was independent of the effect of MMF on acute rejection. These data suggest that MMF may impact long-term allograft survival.

Reference

Ojo AO, Meier-Kriesche HU, Hanson JA, et al. (2000) Mycophenolate mofetile reduces late renal allograft loss independent of acute rejection. Transplantation 69:2405–2409

CASE 8

Which ONE of the following statements regarding CMV in renal transplantation is the correct answer?

A. CMV-positive donor to CMV-negative recipient is the lowest-risk combination.
B. Ganciclovir is not an effective form of prophylaxis for CMV.
C. Quantitative polymerase chain reaction (PCR) is an insensitive method of detection of CMV.
D. Younger recipients are not at increased risk of CMV.
E. The use of pp65 and DNA hybrid capture does not improve the quantitation of CMV viral load.

The correct answer is C. Demonstration of the presence of CMV based on qualitative PCR has been shown to be less sensitive than other methods of detection in several studies, especially pp65 antigenemia and quantitative PCR. Qualitative PCR may detect viral DNA in the asymptomatic patient, even in the case of latent CMV infection, thus limiting its usefulness clinically.

Reference

Piiparinen H, Hockerstedt K, Gronhagen-Riska C et al. (2001) Comparison of plasma polymerase chain reaction and pp65 antigenemia assay in the quantification of cytomegaloviurus in liver and kidney transplant recipients. J Clin Virol 22:111–116

CASE 9

Which ONE of the following recipient—hepatitis B (HbsAg) and/or hepatitis C (HCV)—serologies are associated with the WORST patient survival after transplantation?

A. HCV antibody-positive
B. HbsAg-positive, HbeAg-negative
C. HbsAg-positive, HbeAg-positive
D. HbsAg-negative, anti-HBc-positive
E. HbsAG-negative, HbsAb-positive

The correct answer is C. The risk of death is significantly increased for HBV+ and patients with coinfection. The risk of death in patients that are HBsAg+HBeAg+ is increased by 90%. HBsAg+ HBeAg-, and HBsAg-antiHBc+ patients have no increased risk of death. In addition, HBeAg+ patients had a significantly higher risk of graft loss, with an increase of 66%, suggesting that post-transplant mortality in chronic HBV carriers is mainly confined to HBeAg+ patients.

Reference

Breitenfeldt MK, Rasenack J, Berthold H, et al. (2002) Impact of hepatitis B and C on graft loss and mortality of patients after kidney transplantation. Clin Tranplant 16:130–136

CASE 10

A 14-year old African-American boy with a primary diagnosis of FSGS receives his second cadaveric renal transplant and is initiated on a maintenance immunosuppressive protocol of tacrolimus, mycophenolate mofetile, and prednisone. He experienced two allograft rejection episodes with his first transplant and eventually lost the graft to chronic rejection at three years. On this occasion, his post-transplant course is uncomplicated, and his serum creatinine is stable at 1.8 mg/dl over the last three months. Six months post-transplant, he is found to have persistently elevated blood glucose concentrations and is diagnosed as having post-transplant diabetes mellitus (PTDM) with fasting blood glucose persistently >250 mg/dl. He is receiving 10 mg/day prednisone, mycophenolate mofetile 1 g twice daily, and tacrolimus 3.0 mg twice daily, with trough tacrolimus levels in the range of 12 ng/ml. Insulin is started.

Which ONE of the following additional therapeutic changes represents the best option with regard to the management of his immunosuppression?

A. Withdraw corticosteroids and maintain tacrolimus at current levels
B. Withdraw corticosteroids and reduce the dose of tacrolimus to target trough level <10 ng/ml

C. Reduce corticosteroids to 5 mg/day and maintain tacrolimus at its current levels
D. Reduce corticosteroids to 5 mg/day and reduce tacrolimus to target trough levels of <10 ng/ml
E. Switch from tacrolimus to cyclosporine

The correct answer is D. Both corticosteroids and calcineurin inhibitors contribute to the development of PTDM. While cyclosporine and tacrolimus can cause PTDM, the incidence is higher with tacrolimus. The precise mechanism of the diabetogenic effects of calcineurin inhibitors is not known, but they are known to impair synthesis, storage, and secretion of insulin. In the case of this patient who is African-American, it may not be appropriate to consider steroid withdrawal at present, because in the past such protocols been associated with a high risk of rejection in this population. In addition, the patient has experienced two rejection episodes. Therefore, reduction in the dose of maintenance prednisone to 5 mg may benefit the patient without substantially increasing his risk of rejection. The development of PTDM may be associated with high trough levels of tacrolimus. Therefore, the patient may benefit from a reduction in the target trough levels.

References

Cosio FG, Pesavento TE, Osei K, et al. (2001) Post-transplant disbetes mellitus: increasing incidence in renal allograft recipients transplanted in recent years. Kidney Int 59:732–737
First MR, Gerber DA, Hariharan S, et al. (2002) Post-transplant diabetes mellitus in kidney allograft receipients: incidence, risk factors, and management. Transplantation 73:379–386.

CASE 11

The use of which ONE of the following immunosuppressive agents is NOT associated with hyperlipidemia?

A. Tacrolimus
B. Cyclosporine
C. Rapamycin
D. Mycophenolate mofetile (MMF)
E. Prednisone

The correct answer is D. Both cyclosporine and tacrolimus can cause hyperlipidemia; however, the risk is greater with cyclosporine. Hyperlipidemia has been reported as one of the major side effects of sirolimus therapy (35–50%) as compared to azathioprine (18%). Hyperlipidemia is also a known side effect of corticosteroids. MMF has not been associated with lipid abnormalities.

Reference

Kendrick E (2001) Cardiovascular disease and the renal transplant recipient. Am J Kidney Dis 38:S36–S43

CASE 12

Which ONE of the following statements concerning shipping of kidneys for transplantation is correct?

A. An HLA A1, A1, B6, B27, DR3, DR3 kidney would not be shipped to a HLA A1, A2, B6, B27, DR3, DR27.
B. HLA antigen-matched transplants have similar outcomes compared with phenotypically matched kidneys.
C. The difference in graft survival of matched and mismatched transplants due to cold ischemia time (CIT) was demonstrated at >12 hours.
D. Shipments of HLA-mismatched kidneys has been shown to be associated with increased graft survival due to lower acute rejection episodes.
E. The age of the donor does not negatively impact the effect of HLA matching.

The correct answer is B. In 1987 UNOS established a program whereby kidneys were shipped anywhere in the country to a recipient that was a six-antigen match for that donor. Since then, the policy has been amended twice—first to allow donors and recipients that were both homozygous for one antigen to be considered phenotypically matched, and then to allow for the shipment of zero mishmash kidneys, where the donor doe not express any antigen different from the recipient, but the recipient may have an antigen that is not expressed by the donor. Sharing of HLA-matched kidneys resulted in an increase in the number of transplants of HLA-matched recipients from 2% before 1987 to 13% most recently. No difference in survival was detected between six-antigen matched, homozygous for one antigen phenotypically matched, and no mismatched kidneys. The half-life of matched transplants was significantly longer than unmatched at 12.5 years compared to 8.6 years, respectively, with a 10-year graft survival of 52% for the HLA matched kidneys compared to 37% for HLA mismatched. In addition, HLA-matched kidneys experienced less acute rejection episodes.

Reference

Takemoto SK, Terasak PI, Gjertson DW, et al. (2000) Twelve years' experience with national sharing of HLA-matched cadaveric kidneys for transplantation. N Engl J Med 343:1078–1084

CASE 13

Which ONE of the following statements concerning preemptive renal transplantation is INCORRECT?

A. Patients on dialysis for 6 to 12 months have about 20% increase in mortality compared with preemptively transplanted patients.
B. Time on dialysis is associated with an increase in death-censored graft loss after transplantation.
C. Preemptive transplantation is associated with approximately 50% reduction in graft loss in the first year.
D. The improved patient and graft survival associated with preemptive transplantation is accounted for by socioeconomic advantage.
E. Regarding end-stage renal disease patients, women are equally likely as men to receive preemptive transplants.

The correct answer is D. Several studies demonstrated that the mortality for preemptive transplant recipient patients that had been on dialysis for 6 to 12 months, 13 to 24 months, 25 to 36 months, 37 to 48 months, and longer than 4 years had a 20, 28, 41, 53 and 72% increase in mortality, respectively. In addition, time on dialysis was associated with a decrease graft survival. These data further demonstrate that preemptive transplantation in living donor transplants was associated with a 52% reduction in the rate of allograft failure in the first year post transplant, 82% in the second year, and 86% in subsequent years.

Reference

Meier-Kriesche HU, Kaplan B (2002) Waiting time on dialysis as the strongest modifiable risk factor for renal transplant outcomes: a paired donor kidney analysis. Transplantation 74: 1377–1381

CASE 14

A six-year old girl received a cadaveric renal transplant three weeks ago, and she now presents with worsening dyspnea upon excretion. Her current immunosuppression therapy includes sirolimus, mycophenolate mofetile, and prednisone. Her baseline post-transplant creatinine was 0.8 mg/dl. Findings on physical examination are BP 130/86 mmHg, pulse100 beats/min, temperature 37°C, and oxygen saturation 90%. She is tachypneic, but in no distress. Her jugular venous pressure is not increased, nor is she cyanotic. Her heart sounds are normal, but a mitral incompetence murmur (2/6) is present. Occasional fine crackles are present at both lung bases, posteriorly. The abdominal examination is normal. No peripheral edema is present. Laboratory results show the following: hemoglobin 10.8 g/dl, WBC 5600/ml, platelet 178,000/ml, sodium 135 mEq/l, potassium 4.5 mEq/l, chloride

100 mEq/l, bicarbonate 26 mEq/l, and LDH 120 U/l. Liver function tests are normal. Chest x-ray and CT scan show diffuse bilateral pulmonary infiltrates.

Given these findings, which ONE of the following is the MOST likely diagnosis for this patient?

A. CMV pneumonitis
B. Pneumocystis pneumonia
C. Aspergillosis
D. Sirolimus-related pneumonitis
E. Legionella pneumonia

The correct answer is D. The patient is only three weeks post-renal transplantation. This makes infections such as CMV and pneumocystis pneumonia (PCP) or other opportunistic infections less likely. They are, however, in the differential diagnosis. She is afebrile with a normal WBC, suggesting that this is not an infectious case. Her LDH, which may be raised in PCP, is normal. She has no findings on exam to suggest congestive heart failure. The patient has recently started on sirolimus. There have been at least 34 reported cases of interstitial pneumonitis in patients treated with sirolimus. The pneumonitis is not dose-related and responds to discontinuation of sirolimus, with complete resolution within three months in all reported cases.

Reference

Singer SJ, Tiernan R, Sullivan EJ (2000) interstitial pneumonitis associated with sirolimus therapy in renal transplant recipients. N Engl J Med 343:1815–1816

CASE 15

A four-year old girl with end-stage renal disease of unknown etiology is due to receive her first kidney transplant with her father as a donor. She has a panel reactive antibody (PRA) of 68%. Donor and recipient serum are sent for AHG-CDC and flow cystometry crossmatch.

Which ONE of the following statements is CORRECT regarding this patient?

A. The high PRA will not affect allograft survival because this is a first transplant.
B. If the AHG-CDC T-cell crossmatch is positive, the transplantation should proceed, but the patient should receive intravenous immunoglobulin (IVIG) immediately post-transplantation.
C. A positive flow cystometry T-cell crossmatch does not affect the risk of acute rejection.
D. A positive AHG-CDC B-cell crossmatch is not a contraindication to transplantation.

E. Because she is receiving a transplant from her father, she should be tested for antidonor antibodies before transplantation, even if the AHG-CDC and flow cytometry T- and B-cell crossmatches are negative.

The correct answer is D. The patient is highly sensitized with a PRA of 68% and therefore represents a high immunological risk. A positive AHG-CDC T-cell cross-match is a contraindication to transplantation. A recent paper by Mahoney et al. analyzed data from the UNOS database, which demonstrated that between 1994 and 1995, 3.7% of patients were transplanted with a positive B-cell cross-match, and these patients experienced earlier graft loss and more acute rejection episodes. While these patients are of high immunological risk, the positive B-cell crossmatch is not a contraindication to transplantation. In the event that the patient does have a positive B-cell crossmatch, she should be tested for donor specific antibodies, because this will help further stratify her risk for rejection.

Reference

Mahoney RJ, Taranto S, Edwards E (2002) B-cell crossmatch and kidney allograft outcome in 9031 United States transplant recipients. Hum Immunol 63:324–335

CASE 16

An eight-year old boy received a cadaveric renal transplant two years ago. While taking tacrolimus, sirolimus, and prednisone, he is started on clarithromycin by his primary care physician for a respiratory tract infection. One week later, he is seen in the renal transplant clinic and found to have a hemoglobin 9.6 g/dl, WBC 3200/ml, platelets 68000/ml, and BUN of 42 mg/dl. Serum creatinine has increased from his baseline value of 1.2 mg/dl to 2.2 mg/dl, sodium 142 mEq/l, potassium 5.9 mEq/l, chloride 110 mEq/l, bicarbonate 18 mEq/l, and LDH 136 U/l. Liver function tests are normal.

Which ONE of the following diagnoses is most likely in this patient?

A. Hemolytic uremic syndrome/thrombotic thrombocytopenic induced by sirolimus
B. Tacrolimus nephropathy
C. Mycoplasma pneumonia
D. Sirolimus nephrotoxicity
E. Sirolimus and tacrolimus nephrotoxicity

The correct answer is E. The patient has anemia, leucopenia, thrombocytopenia, hyperkalemia, nonanion gap acidosis, and renal failure. Clarithromycin increases the levels of tacrolimus, cyclosporine, and sirolimus by decreasing their metabolism by the cytochrome P450 system. Therefore, it should not be administered to transplant patients unless absolutely necessary. This is also true for erythromycin.

Azithromycin does not have the same effect on the metabolism of cyclosporine, tacrolimus, or sirolimus, and may be used safely in transplant patients. Very high levels of tacrolimus can cause acute renal failure due to the vasoconstriction effect on the renal arteries, and may be associated with a Type IV renal tubular acidosis. High levels of sirolimus may cause thrombocytopenia and leucopenia. Tacrolimus and cyclosporine may cause HUS—sirolimus does not.

Reference

Kahan BD, Napoli KL, Podbielski J, et al. (2001) Therapeutic drug monitoring of sirolimus for optimal renal transplant outcomes. Transplant proc 33:1278–1278

CASE 17

A 10-year old girl receives a cadaver transplant with a 1A, 1B, 1DR matched kidney from a 40-year old male donor.

Which ONE of the outcome measures listed below is the most predictive of long-term (≥10 year) renal allograft survival?

A. Survival of the graft at one year
B. Serum creatinine at one year
C. Acute rejection rate
D. C-reactive protein at three months
E. Need for dialysis in the first week post-transplant

The correct answer is B. Serum creatinine is a predictor of long-term graft survivals. The risk of graft survival with each 1 mg/dl increment of serum creatinine is 1.63. Survival of the graft at one year with serum creatinine >2 mg/dl is actually a bad prognostic sign, thus choice A is incorrect. Choice C, acute rejection rate, is not a good surrogate marker for long-term graft function. C-reactive protein has not been tested in this regard, although it is biologically plausible that this measurement might correlate with graft inflammation and thus long-term outcome. Delayed graft function is a predictor of long-term lower survivals, but by itself is not sufficient to predict the course of the transplant in the absence of other factors such as presence or absence of rejection, calcineurin inhibitor toxicity, or the age of the donor.

Reference

Hariharan, McBride MA, Cherikh, et al. (2002) Post-transplant renal function in the first year predicts long-term kidney transplant survival. Kidney Int 62:311–318

CASE 18

Which ONE of the following patients has the BEST chance for a cadaver donor renal transplant functioning at one year with a normal serum creatinine?

A. A 12-year old boy with ESRD secondary to cystic dysplastic kidneys
B. Second renal transplant for an African-American male with renal failure from primary hypertension
C. 18-year old female with ESRD from Type 2 diabetes mellitus
D. 16-year old female with ESRD with a panel reactive antibody greater than 75%
E. 15-year old female who receives a cadaver kidney from a 60-year old male with a brief history of untreated hypertension

The correct answer is A. Patients with cystic dysplastic kidneys do better than other etiologies of renal failure when undergoing renal transplant, thus choice A is correct. Second renal transplants do slightly worse than first renal transplants, even with good donor-recipient matches. In particular, African-American recipients do worse than most other groups, thus answer B is correct. Patients with diabetes mellitus and African-American ethnicity would not be expected to do as well as a patient with cystic kidney disease, thus answer C is incorrect. Patients with high-panel reactive antibodies who are thus sanitized to HLA antigens also have inferior outcomes compared to other groups of patients, while donor age is an important negative predictive factor in long-term allograft function—thus, answers D and E are incorrect.

Reference

Port FK, Bragg-Gresham JL, Metzger RA, et al. (2002) Donor characteristics associated with reduced graft survival: an approach to expanding the pool of kidney donors. Transplantation 74:1281–1286

CASE 19

A six-year old African-American boy received a 2DR-matched kidney from a 24-year old donor whose heart had stopped beating.

Which ONE of the following choices regarding the recipient's course is TRUE?

A. 10-year graft survival rates are inferior to kidneys from heart-beating donors.
B. There will be an increased incidence of delayed graft function.
C. Such kidneys should never be used for recipients of second transplants.
D. Such kidneys have an increased propensity to transmit CMV infection.
E. The recipient is more likely to have hypertension compared to recipients of kidneys from heart-beating donors.

The correct answer is B. The use of donors without a heartbeat is increasing world wide due to the shortage of donors and the increased presence of patients who qualify for the transplant waiting list. A long-term comparison of 10-year graft survivals from this donor source compared to heart beating donors is not available, so choice A is not a good answer. Clearly, there is an increased incidence of delayed graft function due to the nonbeating status of the donor, therefore answer B is the correct answer. These kidneys can be used for any recipients, including recipients of second transplants. There is no evidence that these kidneys have an increased propensity to transfer virus infections or cause hypertension compared to a conventional donor, thus answers C, D, and E are incorrect.

Reference

Droupy S, Blanchet P, Eschwege P, et al. (2003) Long-term results of renal transplantation using kidneys harvested from non-heart beating donors: a 15-year experience. J Urol 169:28–31

CASE 20

A 12-year old boy had successful renal transplant two years ago and now has a serum creatinine of 1.0 mg/dl. He is on prednisone, MMF, and cyclosporine. He asks you about surveillance for skin cancer.

Which ONE of the following choices is the BEST for this patient?

A. Do not worry about skin cancer because he is a male subject.
B. He should undergo surveillance by dermatologists at least yearly for premalignant lesions.
C. His immunosuppression therapy should be progressively reduced to decrease the incidence of skin cancer.
D. All viral warts should be removed to prevent malignant transformation.
E. Patient should switch from MMF to azathioprine for better protection against skin malignancy.

The correct answer is B. Skin cancers are the most frequent malignant conditions seen in transplant recipients and can cause increased morbidity and mortality. Standard practice is to undergo surveillance aggressively to remove all basal and squamous cell carcinomas—thus, answer B is correct. There is no evidence that male subjects have less skin cancer than female. Reducing immunosuppression will result in an increased risk of rejection and probably not do much to prevent skin cancer after two years of immunosuppressive therapy. Viral warts do suggest some degree of overimmunosuppression. There is no evidence, however, that these warts need to be removed to prevent malignant transformation. They probably should be removed

on their own merits. There is no evidence that MMF is better than azathioprine for prevention of malignancy—in fact, there is some anecdotal evidence that the opposite is true.

Reference

Euvrad S, Kanitakis J, Claudy A (2003) Skin cancer after organ transplantation. N Engl J Med 348:1681–1691

CASE 21

Which ONE of the following statements about recurrent primary FSGS following renal transplant is TRUE?

A. Disease recurrence is reported in FSGS due to mutations of the podocin gene (autosomal recessive FSGS).
B. Plasmapheresis with or without cyclophosphamide is usually effective in reversing proteinuria and preserving graft function.
C. The disease frequently recurs in familial forms of the condition.
D. The disease always recurs more than six6 months after transplantation.
E. Second transplants often fare better than first transplants with recurrent primary (idiopathic) FSGS.

The correct answers are A. Recurrent FSGS commonly recurs after renal transplantation with an incidence estimated at 30-40% following a first transplant. The mutations of the podocin gene have recently been reported to be associated with recurrent disease particularly in an autosomal recessive form, thus A is correct. While plasmaphoresis and plasma exchange is sometimes effective, these therapies are ineffective overall in reversing proteinuria and preserving graft function—thus, answer B is incorrect. It is particularly common in the nonfamilial or nonhereditary causes of the disease, but does occur in familial forms as well, thus C is correct. While the disease can recur late after transplantation (greater than six months), most often the recurrence is early, so answer D is incorrect. Finally, second transplants fair much worse than do first transplants with recurrent disease. As a matter of fact, the recurrence rate is 75-80% after the second transplant, so answer E is incorrect.

Reference

Bertelli R, Ginevri F, Caridi G, et al. (2003) Recurrent of focal segmental glomerulosclerosis after renal transplantation in patients with mutations of podocin. Am J Kidney Dis 41:1314–1321

CASE 22

A seven-year old girl receives a 6-antigen mismatch deceased donor kidney transplant. Initial immunosuppression is with immunoglobulin, prednisone, cyclosporine, and mycophenolate mofetile. Six weeks after transplantation, her serum creatinine rises from 0.8 to 2.1 mg/dl. The allograft biopsy shows a Banff Grade 1a acute cellular rejection.

Which ONE of the following statements pertaining to acute allograft rejection is TRUE?

A. The incidence of acute rejection within the first year post-transplantation is less than 10%.
B. The increasing use of live donor kidney transplants has dramatically reduced the incidence of acute rejections.
C. Acute rejection may be routinely diagnosed by measurement of urinary granzyme-B and perforin excretion.
D. Steroids can be safely withdrawn from patients treated with induction therapy without increasing the risk of acute rejection.
E. Renal allograft biopsy remains the gold standard diagnostic test for rejection.

The correct answer is E. The incidence of acute rejection is generally reported as less than 20%, although the results with some newer protocols have been disappointing with higher incidence reported. The incidence of rejection has been reported higher in recipients of living donor kidneys, presumably due to less aggressive initial immunotherapy. While novel biomarkers are under development, such an assay is not generally available and the allograft biopsy remains the gold standard diagnostic test for rejection. Steroid withdrawal results in improvements in hypertension, hyperlipidemia, and glycemic control. However, many such protocols have been associated with a higher incidence of rejection.

Reference

Strom TB, Suthanthiran M (2000) Prospect and applicability of molecular diagnosis of allograft rejection. Semin Nephrol 20:103–107

CASE 23

Which ONE of the following tests identifies the highest risk of antibody-mediated rejection and graft loss?

A. A negative complement-dependent cytotoxicity crossmatch
B. A current positive flow cytometry crossmatch
C. A history of positive flow cytometry crossmatch

D. A history of a positive antihuman globulin-enhanced complement-dependent cytotoxicity crossmatch
E. A current positive antihuman globulin-enhanced complement-dependent catholicity crossmatch

The correct answer is E. The most important functions of the histocompatibility laboratory are to confirm that the recipient lacks donor specific antibodies to prevent hyperacute or antibody-mediated rejection and also to confirm blood group compatibility. A current positive antihuman globulin enhanced complement dependent cytotoxicity crossmatch poses an extremely high risk of antibody-mediated or hyperacute rejection, and is a contraindication to transplantation.

Reference

Takemoto SK, Zeevi A, Feng S, et al. (2004) National conference to assess antibody-mediated rejection in solid organ transplantation. Am J Transplant 4:1033–1041

CASE 24

A nine-year old boy known to be broadly sensitized receives a second renal transplant from a deceased donor. He subsequently develops acute renal failure within two weeks of surgery after having good initial graft function.

Which ONE of the following statements regarding this patient is TRUE?

A. Pulse solumedrol therapy for his presumed rejection precludes the need for a kidney biopsy.
B. Obtaining a single core of tissue at biopsy is sufficient as one only needs to perform light microscopy to diagnose rejection.
C. A post-transplant serum sample must be sent to the HLA laboratory to determine whether he has developed donor-specific antibodies.
D. Determination of weakly positive C4d staining by monoclonal antibody immunofluorescence in a scarred area of medulla confirms the presence of antibody-mediated rejection.
E. Demonstration of strongly positive C4d in peritubular capillaries has no prognostic significance.

The correct answer is C. The case describes an immunologically high-risk retransplant that develops acute renal failure early post-transplantation. The diagnosis is *rejection* until proven otherwise, and is likely antibody mediated. Pulse solumedrol is not sufficient therapy because he may also require an ant-thymocyte antibody, plasmapheresis, and IVIg. At least two cores of tissue need to be obtained at kidney biopsy—one that is sent to C4d staining. A serum sample should be sent to the HLA laboratory for donor specific antibody analysis. Demonstration of strongly positive C4d staining in peritubular capillaries, along with demonstration of donor specific

antibodies by flow cystometry and histologic evidence of rejection during an episode of acute renal failure fulfills the diagnostic criteria for antibody-mediated rejection. Demonstration of weakly positive C4d staining in a scarred area of medulla does not confirm the presence of antibody-mediated rejection.

References

Mauiyyedi S, Colvin RB (2002) Humoral rejection in kidney transplantation: new concepts in diagnosis and treatment. Curr Opin Nephrol Hypertens 11: 609–618

Takemoto SK, Zeevi A, Feng S, et al. (2004) National conference to assess antibody-mediated rejection in solid organ transplantation. Am J Transplant 4:1033–1041

CASE 25

A 10-year old boy with ESRD has a Class I PRA of 92% as a consequence of numerous transfusions and a prior failed transplant. Numerous family members and friends have volunteered to be tested as potential living donors.

Which ONE of the following statements is TRUE regarding his chance of receiving a second transplant?

A. Numerous prospective randomized studies have demonstrated that his best chance is with plasmapheresis and (IVIG) therapy to reduce his PRA before a live donor kidney transplant.
B. There is no point in evaluating his family as potential donors because he is so highly sanitized.
C. If given at a dose of 2 g/kg monthly, IVIG is uniformly effective in reducing alloantibody level.
D. His siblings should be evaluated first as potential live donors because one of them may be a phenotype match, thus avoiding his alloantibody problem.
E. Spelenectomy and rituximab should be considered safe and effective options for obtaining a negative crossmatch to permit transplantation.

The correct answer is D. The chance of each sibling donor being (at least) a phenotype match is 25%. High-dose IVIG is not uniformely successful in abrogating a positive cross match, particularly for recipients with high titers of donor-specific antibodies. Splenectomy and rituximab have been utilized in experimental protocols particularly to permit the transplantation of ABO-incompatible kidneys. The safety of such an approach is uncertain and cannot be broadly recommended at this time.

References

Mauiyyedi S, Colvin RB (2002) Humoral rejection in kidney transplantation: new concepts in diagnosis and treatment. Curr Opin Nephrol Hypertens 11: 609–618

Takemoto SK, Zeevi A, Feng S, et al. (2004) National conference to assess antibody-mediated rejection in solid organ transplantation. Am J Transplant 4:1033–1041

CASE 26

A 14-year old girl with hepatitis C develops a febrile illness associated with leucopenia eight weeks after pulse steroids for acute rejection. Apart from a fever, the physical examination is unremarkable. Graft function is excellent while she continues cyclosporine and prednisone. Mycophenolate mofetile has been discontinued because of the leucopenia.

Which ONE of the following statements is correct regarding the pathogenesis of this patient's disease?

A. Reactivation of latent hepatitis C is the most likely cause of the current illness.
B. Knowledge of the donor and recipient's CMV serology status is not germane to developing the differential diagnosis.
C. Up to 90% of patients with proven CMV disease post-transplant will be coinfected with either human herpes virus 6 or 7 (HHV-6 or HHV-7).
D. The clinical presentation may be explained by an isolated infection with HIV-8.
E. If the patient's bilirubin concentration is elevated, the patient is more likely to be infected with HHV-7 than HHV-6.

The correct answer is C. Reactivation of hepatitis C is associated with hepatitis, liver failure, and glomerulonephritis—not fever and leucopenia. Knowledge of the donor and recipient CMV serology status is extremely germane to this case because the clinical features and timing of presentation are typical for a post-transplant human herpes virus infection. Ninety percent of patients infected with CMV are found to be coinfected with either HHV-6 or HHV-7 by PCR. The degree of HHV-6 coinfection is significantly correlated with hyperbilirubinemia, while HHV-7 coinfection demonstrated a trend toward a cytopenias. Infection with HHV-8 is associated with development of post-transplant Kaposi's sarcoma and not the viremia syndrome described in the question.

Reference

Cotler SJ, Diaz G, Gundlapalli S, et al. (2002) Characteristics of hepatitis C in renal transplant candidates. J Clin Gastroentrol 35:191–195

CASE 27

A 13-year old girl who is dialysis-dependent and is known to be infected with hepatitis C (HCV), comes for an evaluation for transplantation.

Which ONE of the following choices provides the BEST advice for this patient?

A. Renal transplantation confers a survival benefit when compared with dialysis, although her risk of long-term mortality from liver disease is increased.

B. Pretransplant treatment with interferon will reduce her risk of HCV-associated de novo glomerulonephritis to 20%.
C. The patient should receive cyclosporine post-transplantation as the risk of post-transplantation diabetes is almost 60% if she receives tacrolimus-based immunotherapy.
D. In spite of initial concerns about the risk of rejection with interferon post-transplantation, more recent studies have shown that interferon and ribavirin are safe and effective in the transplant population.
E. Liver biopsies performed on HCV-positive patients who receive transplants uniformly revealed more inflammation with bridging fibrosis as compared with non-transplant patients with HCV.

The correct answer is C. Renal transplantation confers a survival benefit when compared with dialysis. However, long-term studies have shown an increase of both liver-related and infection-related mortality in HCV-infected patients. Pre-transplant treatment of HCV with interferon abrogates viremia in 70% of patients, of whom 10% developed post-transplant de novo glomerulonephritis. Hepatitis C infection has been associated with new onset diabetes post-transplantation. The risk is augmented by the use of tacrolimus. The use of interferon post-transplantation is associated with a high risk of rejection, which is often antibody mediated and leads to graft loss. Liver biopsies in transplanted HCV-positive patients generally reveal less inflammation and a lower proportion of bridging fibrosis or cirrhosis than control subjects.

Reference

Bloom RD, Rao V, Weng F, et al. (2002) Association of hepatitis C with post-transplant diabetes in renal transplant patients on tacrolimus. J Am Soc Nephrol 13:1374–1380

CASE 28

A seven-year old patient develops allograft dysfunction eight months post-transplant, having received thymoglobulin induction therapy while taking tacrolimus, MMF, and prednisone. The urine cytology suggests polyoma virus infection. Confirmation of BK viremia is provided by PCR.

Which ONE of the following statements concerning post-transplantation polyoma virus nephropathy is TRUE?

A. At diagnosis, the patient's viral load is directly proportional to the level of immunosuppression.
B. After diagnosing polyoma virus nephropathy, reducing immunosuppression reduces viral load in approximately 80% of patients infected with polyoma virus.

C. Reducing immunosuppression reduces viral load and is correlated with an improvement in graft function in 60% in patients infected with polyoma virus
D. Prospective, randomized, clinical trial data indicates that cidofovir—when used at a dose of 0.25 mg/kg every 2 week—is safe and effective for the treatment of polyoma virus nephropathy.
E. When a kidney transplant is lost to polyoma virus infection, the graft must be removed before retransplantation to minimize the risk of recurrent infection in the new kidney.

The correct answer is B. A correlation between BK viral load and level of immunosuppression has not been clearly identified. While reducing immunosuppression therapy for established BKV-associated nephropathy reduces viral load in 83% of cases, renal function improves in only 15% of patients. The major concern about use of cidofovir is nephrotoxicity. Successful retransplantation has been reported after BKV-induced graft failure, both after the initial allograft had been left in, as well as following graft nephrectomy.

Reference

Celik B, Shapiro R, Vats A, et al. (2003) Polyoma virus allograft nephropathy: sequential assessment of histologic viral load, tubulitis, and graft function following changes in immunosuppression. Am J Transplant 3:1378–1382

CASE 29

A nine-year old boy receives a successful second transplant after plasmapheresis and IVIG desensitization. Within six months post-transplantation, he develops ARF and is found to have tubulitis on a kidney biopsy. His blood and urine BK virus OCR levels are extremely elevated.

Which ONE of the following therapeutic interventions would be the BEST?

A. Administer high-dose cidofovir to eradicate BK virus
B. Administer intravenous steroids to treat the underlying rejection
C. Reduce immunosuppression and consider administration of leflunomide
D. Switch mycophenolate to leflunomide, even though therapeutic drug monitoring of leflunomide is not available in your institution
E. Administer OK3 (anti-CD3 monoclonal antibody)

The correct answer is C. The case describes an immunologic high-risk patient who received aggressive immunotherapy to permit transplantation, who subsequently developed a significant viral complication. Most authors agree that augmenting immunosuppression such as a high dose steroid or antibody therapy is associated with poor graft survival. Antiviral chemotherapy with conventional doses of

cidofovir, while efficacious in reducing BK viral loads, has been associated with substantial nephrotoxicity. Consequently, this agent should be used with caution. Some successes have been reported with the use of low-dose cidofovir, although randomized control trial data is not available. Reports of the successful use of leflunomide for polyoma virus infection have been presented in abstract form. There is no randomized controlled trial data in publication. Both the liver and kidney metabolize leflunomide. Consequently, it may be important to measure levels, although levels are not readily available commercially.

Reference

Kadambi PV, Josephson MA, Williams J, et al. (2003) Treatment of refractory BK virus-associated nephropathy with cidofovir. Am J Transplant 3:186–191

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