Urea cycle disorders (UCDs) secondary to enzyme defects include carbamoyl phosphate synthetase 1, ornithine transcarbamylase (OTC), argininosuccinate synthetase, argininosuccinate lyase, and arginase 1 deficiencies. The most common UCD in adults is OTC deficiency, an X-linked disease. Female heterozygotes may not develop the condition until they are adults. Patients present with hyperammonemia, typically when they are exposed to precipitants such as increased protein intake, drugs, or infection. In adults, UCD diagnosis should especially be sought after refractory hyperammonemia with no acidosis, after excluding common etiologies. In suspected UCDs, serum glutamine, citrulline, and urine orotic acid should be checked. In OTC deficiency there is increased glutamine level, low citrulline level, and increased urine orotic acid level. A combined preparation of sodium phenylacetate/sodium benzoate is approved by the U.S. Food and Drug Administration for the treatment of hyperammonemic crisis in patients with inborn errors of metabolism. Arterial ammonia level greater than 200 µg/dL is strongly associated with cerebral edema and cerebral herniation. Decreasing the ammonia levels will help with decreasing the cerebral edema and intracranial pressure. Oral vancomycin can be used for the treatment of hepatic encephalopathy. The patient has hyperammonemia from UCD and is already on lactulose and rifaximin. She would benefit more from sodium benzoate to increase the urea clearance and decrease the ammonia. Sodium polystyrene sulfonate is useful for treating hyperkalemia, and a protein-rich diet would worsen the hyperammonemia.
References:
2. **Rationale**

This patient has thyroid storm. While diagnostic criteria remain controversial, her history of Graves' disease, combined with the clinical features, is strongly suggestive, and treatment should be initiated immediately, even before laboratory results are available.

Treatment involves several components:

1) Inhibition of new hormone synthesis with propylthiouracil (PTUs) or imidazoles (methimazole and carbimazole). PTU blocks the enzyme thyroidal peroxidase to inhibit thyroid hormone synthesis. It is generally preferred over methimazole because it also inhibits the peripheral conversion of thyroxine to triiodothyronine. The dosage of PTU is a 500-1000 mg loading dose, followed by 250 mg every four hours. Methimazole is dosed 60-80 mg/day in divided doses.

2) Blockade of release with iodine or lithium. Blocking release of thyroid hormone is best accomplished with iodine, but lithium can be used in iodine-allergic patients. It is important not to administer iodine until after the synthetic pathways have been blocked with PTU (at least 30 minutes); otherwise administration of iodine might cause more thyroid hormone to be formed. Options B, C, and D each have iodine being given before PTU, which make them incorrect.

3) Inhibition of peripheral effects with beta-adrenergic agents. Propranolol is the preferred treatment to block peripheral effects of thyroid hormone because of its nonselective effects and the additional benefit of inhibiting peripheral conversion of thyroxine to triiodothyronine. If a contraindication to propranolol exists (eg, asthma, congestive heart failure), then an agent such as diltiazem could be considered. Furthermore, possible inciting events should be addressed (eg, infection, diabetic ketoacidosis, trauma, etc.). Administration of glucocorticoids is recommended because thyroid storm can precipitate adrenal crisis (relative adrenal insufficiency), with similar dosing regimens. Dexamethasone may be preferred, since it also blocks the peripheral conversion of thyroxine to triiodothyronine. Antipyretics and external cooling methods may be considered, but salicylates should be avoided because they may increase free hormone levels. Most patients will benefit from IV fluids to replace significant volume loss from hyperthermia and gastrointestinal losses.

4) Inhibition of enterohepatic circulation of thyroid hormone, which is metabolized in the liver where it is conjugated to glucuronides and sulfates and excreted into the intestine in bile, while unconjugated free hormones are reabsorbed into circulation. Cholestyramine, by binding conjugated products, promotes their excretion, thereby lowering thyroid hormone levels. The recommended dose is 1-4 g twice daily.

**Reference:**

3. Rationale

Posttraumatic rhabdomyolysis is common and associated with significant morbidity and mortality. In earthquake survivors, it is the second most important cause of mortality. Nontraumatic causes of rhabdomyolysis include extreme exertion, grand mal seizures, delirium, drugs, toxins, infections, and endocrine disorders. Prolonged anesthetics can be associated with rhabdomyolysis, especially in young muscular patients. A common feature of both traumatic and nontraumatic rhabdomyolysis is massive necrosis resulting in limb weakness, myalgia, and gross pigmenturia.

The pathophysiologic process involves sarcolemmic injury as well as depletion of ATP within the myocyte. This leads to a detrimental increase in intracellular calcium. Tight calcium regulation is necessary in order to ensure proper contractile function (low concentrations at rest and increasing concentrations during a state of activation facilitate proper actin myosin-binding and contraction). Channels and pumps that regulate this calcium concentration are ATP dependent and, once ATP depletion occurs, are no longer able to maintain calcium homeostasis. The muscle persistently contracts, and calcium-dependent proteases and phospholipases are activated, eventually leading to destruction of the myocyte. Kidney injury commonly results as a consequence of renal vasoconstriction, direct and ischemic tubule injury, and tubular obstruction.

After identification and treatment of the cause of rhabdomyolysis, the important steps to prevent acute kidney injury include aggressive volume administration with the goal of maintaining and enhancing renal perfusion to minimize cast formation and/or to flush out casts that have already formed. Another goal is enhancement of urinary potassium excretion, since death from hyperkalemia is a major complication of traumatic rhabdomyolysis. Although the optimal type of fluid and rate of repletion is unclear, potassium-containing fluids should be avoided, especially in the initial phase, and administration of normal saline at 1-2 L/hr is generally recommended initially.

Despite the theoretical benefits of bicarbonate administration (prevention of nephrotoxic effects of myoglobinuria such as heme protein precipitation with Tamm-Horsfall protein, decrease of release of free iron from myoglobin and prevention of formation of uric acid crystals), the administration of bicarbonate plus mannitol over normal saline alone has not been shown to prevent renal failure, reduce the need for dialysis or prevent death in trauma patients. There was, however, a trend towards better outcome in patients with CK values over 30,000 U/L.

The use of loop diuretics remains controversial. No study has shown a clear benefit to patients with rhabdomyolysis. The use of loop diuretics therefore is recommended in the same manner as that for acute kidney injury that is due to other causes.

References:

4. **Rationale**

Glomerular filtration rate (GFR) is the total amount of plasma filtered at the glomerulus. Inulin is used to estimate GFR because it is freely filterable and not secreted or absorbed by the kidneys. Creatinine can be used as an approximation but is both filtered and secreted.

Renal plasma flow is the amount of plasma that flows through the kidneys per unit of time. This is difficult to measure and is instead estimated from the effective renal plasma flow (ERPF), which is the amount of plasma cleared of para-aminohippuric acid (PAH) per unit time. PAH is primarily secreted rather than filtered, but can be used to estimate ERPF.

At a level of 3 µg/kg/min, dopamine theoretically acts solely on the D1 receptor, causing dilation of the afferent and efferent arterioles of the glomerulus, leading to increased renal plasma flow and glomerular filtration rate. Dose response studies demonstrated that the dopamine-induced increase in ERPF reaches its maximum at 3 mcg/kg/min. The increase in ERPF remained unchanged by pretreatment with metoprolol, and a comparison of dopamine and dobutamine in doses producing similar increases in cardiac output showed that only dopamine increased ERPF. These findings indicate that indirect hemodynamic effects secondary to increases in cardiac contractility and cardiac output do not contribute significantly to the increase in renal perfusion caused by dopamine in doses lower than 3 mcg/kg/min. It is important to note that, despite this mechanism of action, dopamine has not been shown to prevent renal failure.

Furosemide is a loop diuretic that acts in the ascending limb of the loop of Henle. It inhibits the cotransport of sodium, potassium and chloride out of the nephron, making the ultrafiltrate more tonic and leading to a less hypertonic interstitium. With a less hypertonic interstitium, free water is retained in the collecting duct and thus excreted. Furosemide does not affect filtration at the glomerulus by direct effects on renal plasma flow.

Lisinopril is an angiotensin-converting enzyme inhibitor (ACEI). Normally, in the setting of sympathetic stimulation or decreased afferent blood flow, the renin-angiotensin-aldosterone system (RAAS) is activated, leading to increased release of angiotensin II, which acts both to increase aldosterone secretion from the adrenal cortex and directly causes constriction of the efferent arteriole to decrease ERPF and increase GFR. By inhibiting the formation of angiotensin II, ACEIs prevent efferent arteriolar constriction and therefore decrease GFR.

Metformin has no appreciable affects on ERPF or GFR.

**References:**

5. **Rationale**

Hepatorenal syndrome (HRS) is a well-described entity in patients with end-stage liver disease, and is believed to be caused mainly by functional factors. HRS type 1 is characterized by a rapid decline of renal function over a period of several weeks whereas HRS type 2 is considered to be a more chronic disease. Pathophysiology is mostly believed to be due to arterial vasodilation with reduced systemic vascular resistance and cardiac output that cannot compensate for this vasodilation. Secondary phenomenon is activation of the renal angiotensin-aldosterone system and increase secretion of arginine vasopressin to maintain blood pressure. The problem is multifactorial, and lately an increase in an inflammatory state has been described as yet another factor potentiating this problem. The treatment of HRS is in part preventive, by administration of concentrated albumin and treatment of spontaneous bacterial peritonitis, so D is the correct answer. In some patients dual transplant of liver and kidney can be considered but this is a controversial issue since we cannot predict which patients will recover their kidney function after liver transplant.

**Reference:**

6. **Rationale**

Beta-adrenergic agents can be effective in rapidly lowering potassium. However, they are relatively contraindicated in patients with coronary artery disease. Although IV furosemide can lower serum potassium, it is ineffective in patients with end-stage renal disease and no urine output at baseline. IV calcium gluconate is the therapy of choice in patients with ECG changes secondary to hyperkalemia to stabilize the cardiac membrane against the hyperkalemia-induced depolarization of resting cardiac membrane potential. It has no direct effect in lowering serum potassium. Finally, treatment with glucose and insulin lowers serum potassium within minutes. IV insulin promotes potassium uptake intracellularly by enhancing the sodium-potassium-ATPase transporter. Onset of insulin action occurs within 10 to 20 minutes and peaks at 30 to 60 minutes. The duration of insulin in the setting of normal creatinine clearance is between 4 to 6 hours. The range of potassium lowering after insulin and glucose therapy is between 0.5 to 1.2 meq/L.

**References:**
7. **Rationale**  

The delayed onset in acute kidney injury after percutaneous angiography is suggestive of atheroembolic disease. Atheroemboli contributing to renal failure typically occurs weeks after the procedure and contrast-induced nephropathy. Rhabdomyolysis from myoglobin-induced pigment nephropathy is unlikely, given the red blood cells in the urine with a mild rise in creatine kinase. Diabetic nephropathy may be present in a patient with long-standing diabetes mellitus and may contribute to chronic kidney disease. However, diabetic nephropathy does not cause an acute worsening in renal function as in this case.

**References:**

8. **Rationale**  

IV crystalloid therapy should be administered immediately and aggressively to prevent myoglobin-induced pigment nephropathy. Aggressive fluid resuscitation with crystalloid therapy has been demonstrated to enhance renal perfusion and improve urine flow rate to prevent obstruction from renal casts. Also, volume resuscitation is required to prevent hypovolemia that may result from site of crush injury. If overt alkalosis is ruled out, alkaline crystalloid solution is preferred for volume resuscitation. If there is no evidence of volume overload, loop diuretics are not recommended, and may also increase the likelihood of volume depletion. No benefit has been demonstrated with IV colloid therapy or low-dose dopamine infusion.

**References:**
9. **Rationale**

   The metabolic disturbance causing the anion gap acidosis is a combination of alcoholic ketoacidosis and lactic acidosis. This combination is often seen in patients with alcohol abuse who binge drink and are concurrently malnourished due to excessive alcohol intake and/or gastritis leading to food intolerance. The elevated anion gap is a result of ketone body production due to suppressed insulin secretion and lipolysis, due in part to the alcohol metabolism and starvation state. In addition, a mild lactic acidosis is present due to volume depletion or possibly early sepsis secondary to aspiration pneumonia.

   Distinguishing toxic alcohol ingestions, such as from ethylene glycol and isopropanol, from alcoholic ketoacidosis is challenging, and may not be feasible in the acute setting. Often empiric treatment with fomepizole may be needed until further laboratory testing can be conducted. History is usually the most important clue in suspecting toxic alcohol ingestion, in addition to detecting an anion gap acidosis with an elevated osmolar gap. Relying exclusively on an elevated anion gap and osmolar gap is ill advised, however, since there are many instances in which this will not hold true. Isopropyl alcohol ingestion does not cause acidosis and can be eliminated from the differential diagnosis. Similarly, with no history of diabetes and a normal blood sugar level, diabetic ketoacidosis is less likely in this scenario.

   **References:**

10. **Rationale**

   This patient has evidence of acute renal failure, most likely post-obstructive from nephrolithiasis. This is a medical emergency given that he has a solitary kidney, as well as evidence of severe sepsis due to the urinary tract obstruction. Bedside ultrasound was used to determine this diagnosis, showing moderate right-sided hydronephrosis. A CT may eventually be requested by the urologist to plan the intervention, but the most critical next step is to begin management for severe sepsis while consulting urology for source control and obstruction relief. Given the findings of severe sepsis and a solitary kidney, treating this patient as uncomplicated nephrolithiasis with pain management alone is inappropriate. Similarly, the patient may eventually require dialysis and nephrology consultation, but in the acute time period, treatment of the obstructive nephrolithiasis with associated severe sepsis takes precedence in hopes that dialysis may be avoided.

   **Reference:**
11. **Rationale**

The patient has acute severe hyponatremia in the setting of transurethral resection of bladder tumor (TURBT) syndrome, which develops from bladder perforation with subsequent absorption of large amount of irrigation fluids (typically glycine, sorbitol, or free water) that results in circulatory overload, hemolysis, hyponatremia, and acute renal failure. Small subclinical perforations can occur in more than 50% of patients. The hallmarks of TURBT syndrome are acute hyponatremia, hemolysis, and metabolic acidosis.

Absorption of large amounts of hypotonic fluid leads to significant plasma hypotonicity and hyponatremia. The central nervous system and brain are most susceptible to devastating changes secondary to acute hyponatremia. A rapid drop in plasma sodium concentration leads to brain swelling, increase in intracranial pressure, and potential herniation. In response to hypotonicity, astrocytes activate cell-to-cell transfer of taurine (organic osmolyte) that protects neurons from swelling at the expense of astrocytes swelling. Within 24 to 48 hours, astrocytes normalize in volume due to slow loss of taurine and glutamate. In addition to loss of organic osmolytes, the downregulation of osmolyte-accumulating transporters (taurine and myo-inositol transporters) takes place. As results of these changes, astrocytes are extremely susceptible to hypertonic injury in cases of rapid correction of hyponatremia. Hypertonic injury triggers apoptosis, disruption of the blood-brain barrier, and demyelination. Demyelination syndrome manifests as altered mental status, seizure and movement disorders, and behavioral abnormalities. Central pontine dimyelination presents with locked-in syndrome.

It is very important to distinguish the chronicity of hyponatremia. Fast correction of chronic hypernatremia (greater than 24-48 hours in duration) will lead to hypertonic injury of astrocytes, since their osmolar adjustment mechanism are exhausted. In the setting of acute (less than 24 hours in duration) and severe symptomatic hyponatremia, aggressive correction of hyponatremia is necessary to prevent fatal cerebral edema, and will not cause demyelinating injury.

In the case of acute severe hyponatremia, administration of several boluses (1-2 mL/kg) of 3% sodium chloride is indicated with the goal of raising the sodium concentration by 4 to 6 mEq/L in the first 6 hours. This approach hastens the development of acute cerebral edema. Correction of chronic hyponatremia should not exceed 8 mEq/L/day to prevent the development of demyelination. Fluid restriction is not suitable for patients with acute severe symptomatic hyponatremia. Desmopressin leads to increased reabsorption of free water and decrease of free water loss with urine.

**References:**

12. **Rationale**

The patient presents with leg weakness as a surrogate of acute ischemia of the distal spinal cord. The initial CT showed interruption of aortic flow below the celiac artery. The ischemic cells have released potassium to the extracellular space concomitantly with an underlying severe metabolic acidosis. Although metabolic acidosis has repeatedly been implicated as a causative factor of hyperkalemia via transcellular shift of potassium from the intracellular to extracellular compartment, this paradigm has been challenged. The significant elevation of potassium is secondary to reperfusion distal to the celiac artery, which explains the occurrence of a wide complex arrhythmia, peak T waves/ST elevations, and eventually asystole.

An acute coronary syndrome could have explained some of the ECG changes since most vascular patients have undetected coronary artery disease. A retrograde dissection of the aorta compromising the ascending segment, even when possible, is not a frequent presentation for a type B dissection; however, many investigators have reported the transformation to type A dissection after stent graft placement for type B dissection with an estimated rate of 2%. Mesenteric ischemia is possible but it would not be manifested so acutely.

**References:**

13. **Rationale**

The endothelial glycocalyx is located on the luminal side of endothelial cells and serves as the active interface between blood and the capillary wall. Traditionally, the Starling principle has been taught as a model of semipermeable capillaries subject to hydrostatic and oncotic pressure gradients. This model employed the classic compartments of plasma, interstitial, and intracellular as locations where resuscitative fluids would filter, depending on the balance between hydrostatic and oncotic pressure gradients. Recent research has shown that the endothelial glycocalyx layer appears to have a major role in fluid exchange and volume of distribution. The glycocalyx model, an acellular layer lining the endothelium, is a paradigm shift in our understanding of the interface between the blood and the endothelial cells. It is a key determinant of vascular permeability. The glycocalyx layer has varying membrane permeability across organ systems, which changes based on timing and severity of the ongoing disease process, as well as treatment. Extravasation of fluid from the capillaries is predominately dependent on capillary hydrostatic pressure and not on decreased intravascular colloid osmotic pressure, as once thought. Various disease states (ie, sepsis and trauma) as well as over-resuscitation (leading to the release of atrial natriuretic peptide) can damage the glycocalyx layer.
References:

14. **Rationale**

**Answer: D**

Fluid resuscitation is a ubiquitous intervention in critical care medicine, and the provision of maintenance fluids is a common cornerstone of this therapy. The rationale for maintenance fluids is that they assist in fluid resuscitation and prevent preload-dependant hypoperfusion. This has not been proven. What is known is that approximately 80% of isotonic crystalloid infusions are not maintained in the vascular space, maintenance fluids contribute to volume overload, and volume overload is increasingly recognized as a direct contributor to organ failure in critically ill patients.

Intravascular circulating volume is important for patients with markers of poor perfusion or end-organ damage. There appears to be an optimal circulating fluid volume to prevent shock and multisystem organ failure. Liberal fluid strategies have shown such complications as peripheral edema, respiratory failure/lung injury, dilutional anemia and coagulopathy, neutrophil activation, poor wound healing, and delayed bowel recovery. Intravascular volume should be restored on an individualized basis with care given to the type of fluid used for resuscitation and the amount of fluid provided.

References:

15. **Rationale**

**Answer: A**

This patient has a mixed acid-base disorder. She has worsening sepsis from an ischemic small bowel obstruction leading to a metabolic lactic acidosis. There is an underlying metabolic alkalosis from vomiting and nasogastric tube drainage. The respiratory alkalosis develops with her abdominal pain and she becomes tachypneic.

Discerning acid-base problems requires a systematic approach. Here is one of several methods that can be used. Step 1: Look at the pH. The process that caused the shift to either side of 7.40 is the primary abnormality. This patient’s pH is 7.50, with a partial pressure of carbon dioxide of 24 mm Hg, consistent with acute respiratory alkalosis. Step 2: Calculate the anion gap. The body will never generate a large anion gap to compensate for the primary disorder. In this case the anion gap is 27 mEq/L.
Of note, the albumin level is normal, but if less than 4.0 g/dL, the anion gap would require correction by 2.5 mEq/L for every 1 below 4.0 g/dL. Step 3: Calculate the delta-delta gap to see if there is an underlying non-anion gap acidosis or metabolic alkalosis in addition to the anion gap acidosis. In this case the delta gap is greater than 2.0, indicating a concurrent metabolic alkalosis.

References:

16. Rationale

When solving acid/base problems, the first step is examining the pH. A normal pH is between 7.35 and 7.45. Acidemia is present when serum pH is less than 7.35, while alkalemia is present when serum pH is more than 7.45. In this case, the pH is 7.12, indicating academia.

The second step is examining the partial arterial carbon dioxide pressure (Paco$_2$) to determine whether the academia is respiratory in nature or not. A normal Paco$_2$ is 35-45 mm Hg. In this case, the Paco$_2$ is 40 mm Hg, indicating that the low pH is due to a metabolic, rather than respiratory, component. This is further validated by the low bicarbonate level (17 mEq/L).

The third step is to see whether or not there is respiratory compensation. With a metabolic acidosis, the body attempts to compensate by hyperventilating in order to remove carbon dioxide. In this case, the Paco$_2$ is 40 mm Hg. In order to be appropriately compensated, for every 1 mEq/L decrease in bicarbonate from 24 mEq/L, the Paco$_2$ should decrease by 1 mm Hg from 40 mm Hg. In this case, the bicarbonate decreases by 7 mEq/L (from 24 mEq/L to 17 mEq/L) but the Paco$_2$ does not decrease at all from 40 mm Hg.

Alternatively, the Winters formula can be used to predict the appropriate Paco$_2$ for a given bicarbonate. The Winters formula is Paco$_2$ = (1.5 x bicarbonate) + 8 ± 2. For the given question, the expected Paco$_2$ would be 33 ± 2 mm Hg. The actual Paco$_2$ is 40 mm Hg, which is too high given the level of acidosis; therefore, a concomitant respiratory acidosis is present.

When dealing with a metabolic acidosis, it is imperative to next calculate the anion gap using the anion gap formula: Anion gap = sodium - (bicarbonate + chloride); normal 10-12. In this case, the anion gap is 33 so an anion gap metabolic acidosis must be present.

Finally one must determine if there is a mixed picture present. In order to determine this, the delta anion gap must be calculated: Delta anion gap = (anion gap - 12)/(24 - bicarbonate). In this case, the delta anion gap is 3: (33-12)/(24-17) = 3.

Delta ratio assessment guidelines specify that a value less than 0.4 = hyperchloremic normal anion gap acidosis. If 0.4-0.8, consider combined high anion gap and normal anion gap acidosis but note that the
ratio is often less than 1 in acidosis associated with renal failure. A value of 1-2 is usual for uncompli-
cated high anion gap acidosis. Lactic acidosis yields an average value of 1.6. Diabetic ketoacidosis is more
likely to yield a ratio closer to 1 due to urine ketone loss (especially if the patient is not dehydrated). A
value of greater than 2 suggests a preexisting elevated bicarbonate level. Consider a concurrent meta-
bolic alkalosis or a preexisting compensated respiratory acidosis.

Since this value is greater than 2, a concomitant metabolic alkalosis is also present. The bicarbonate is
too high given the current anion gap. In this case, the patient was admitted for nausea and vomiting,
which could lead to a mixed picture, including a metabolic alkalosis. Other potential causes of metabolic
alkalosis include iatrogenic administration of bicarbonate or excessive diuretic use.

It is also important to note how hypoalbuminemia can affect acid/base status. Since albumin is a nega-
tively charged anion that greatly contributes to the anion gap, when albumin levels are decreased, the
anion gap may be falsely decreased. It is important then to be aware of the albumin corrected anion
gap: Albumin corrected anion gap = observed anion gap + 2.5 (normal albumin-observed albumin)
where the normal albumin is 4 g/dL. In this case, the albumin corrected anion gap = 33 + 2.5 (4-2.5) =
36.75.

References:
1. Matthes K, Urman R, Ehrenfeld J, eds. Anesthesiology: A Comprehensive Board Review for Prima-
Williams & Wilkins; 2012:236-237.

17. Rationale

The patient has mild alkelemia, with a pH of 7.45. His carbon dioxide level is 23 mm Hg, consistent
with respiratory alkalosis. However, the pH is lower than would be expected for a carbon dioxide value
of 23 mm Hg, indicating a mixed process. Bicarbonate level is 18 mEq/L, indicating a metabolic acido-
sis. The anion gap is calculated to be 11 mEq/L (133 - (104 +18)). However, albumin is only 1.4 g/dL, as
opposed to the normal level of 4 g/dL. For every 1 g/dL decrease in albumin, the anion gap should be
raised by approximately 2.5 mEq/L, leading to a final value of 17.5 mEq/L.

References:
18. **Rationale**

Proper assessment and management of the airway of the status epilepticus patient with ongoing convulsions can be difficult. Most patients will have a profound metabolic acidosis (as severe as arterial pH < 7.0) with attempted respiratory compensation. Patients in status epilepticus continue to breathe with appropriate gas exchange as long as the airway remains clear. This metabolic acidosis will correct itself once the seizures are controlled. Antiseizure drugs with sedating side effects can impede the drive for respiratory compensation, creating a secondary acid-base disturbance (worsening the overall acidosis) with a respiratory acidosis. This respiratory compensation is of paramount importance as a patient is placed on the ventilator, and clinicians should plan on a high minute ventilation requirement. This patient has no oxygenation issues, and increasing positive end-expiratory pressure is not the correct intervention for increasing ventilation. Propofol is a sedating medication that usually impedes respiratory drive, leading to an increase in carbon dioxide levels. Decreasing the set respiratory rate could worsen respiratory acidosis, negatively impacting the clinical situation. Dead space is calculated from correlating the measured expiratory carbon dioxide and the blood gas measurement that is still pending; however, this end-tidal carbon dioxide value is not consistent with a dead space issue.

**References:**

19. **Rationale**

This patient has elevated anion gap metabolic acidosis, which is often caused by methanol, ethanol, uremia, diabetic ketoacidosis, propylene glycol, oxoproline, lactate, or salicylates. A normal anion gap ranges from 8 to 16 mEq/L, with a value over 16 mEq/L considered an elevated anion gap. In this case, the anion gap is calculated to be 35 mEq/L (145 - (106 + 4)). The patient is nonadherent with her insulin, but her blood glucose on arrival is 134, making diabetic ketoacidosis less likely. Intoxication from vast quantities of ethanol is similarly unlikely since her ethanol level was less than 5 on admission. Salicylates such as aspirin can cause an elevated anion gap metabolic acidosis and a respiratory alkalosis, but her aspirin level is negative and she has a compensated metabolic acidosis.

Acetaminophen overdose is the most common cause of acute liver failure in the United States. Signs and symptoms of an overdose include nausea, vomiting, sweating, lethargy, and elevated liver enzymes. Aside from causing an elevation in liver enzymes, ingesting a large quantity of acetaminophen also causes an elevation in 5-oxoproline. 5-Oxoproline is a metabolite of acetaminophen, and if it accumulates in the body it can cause an elevated anion gap metabolic acidosis. 5-Oxoproline is an intermediate in the gamma-glutamyl pathway, which is the metabolic cycle responsible for creating glutathione and pushing amino acids into the cytosol. When glutathione levels are diminished, feedback inhibition ceases, causing an overproduction of gamma-glutamylcysteine, which is then metabolized to 5-oxoproline. Treatment with N-acetylcysteine should be initiated and referral to a liver transplant center should be considered.
References:

20. Rationale

This patient at baseline has a compensated chronic respiratory acidosis; her baseline partial pressure of carbon dioxide (pCO₂) is 60 mm Hg with a relatively normal pH (7.35-7.45) and bicarbonate of 32 mEq/L. This can be explained by this equation:

\[ \text{Expected [bicarbonate]} = 24 + 4 \times \frac{(\text{Actual } pCO_2 - 40)}{10} \]

or 32 = 24 + 4(60-40)/10).

She is experiencing a chronic obstructive pulmonary disease exacerbation, mostly likely due to an underlying respiratory infection. This has led to an acute rise in pCO₂ 12 mm Hg, without time for metabolic compensation, which takes 48 hours. Her pH can be calculated as follows:

\[ \text{Change in pH} = .008 \times (\text{new } pCO_2 - \text{baseline } pCO_2) \]

or .008 \times (72-60) = 0.096, or 7.34, which is the patient’s current pH. 0.096 = 7.24.

References:
21. **Rationale**

In a case of digitalis toxicity, during the patient’s stabilization and transport, it is possible to use atropine to attempt to reverse the pronounced bradycardia. Ephedrine and, eventually, epinephrine in small doses can be considered as well. Electrolytes should be corrected quickly, especially in the case of hypokalemia and hypomagnesemia. Hypercalcemia enhances digitalis-induced increases in intracellular calcium, which can lead to calcium overload and increased susceptibility to digitalis-induced arrhythmias.

**References:**

22. **Rationale**

Hypercalcemic crisis is an endocrine disorder that is seen in the ICU, most often in the setting of malignancy or hyperparathyroidism. This young, relatively healthy patient is found to have hypercalcemia, along with renal dysfunction. In this setting, the clinician must be concerned about hyperparathyroidism, with a main goal of restoring her volume status. IV resuscitation in the acute setting would have the most benefit for the patient because she is probably dehydrated from hypercalcemia-induced urinary salt wasting. Calcimimetic agents, such as cinacalcet, reduce calcium levels by activating the calcium-sensing receptor in the parathyroid gland, thereby inhibiting parathyroid hormone secretion. They have shown clinical benefit in secondary hyperparathyroidism associated with renal failure and in parathyroid carcinoma.

Glucocorticoids, such as prednisone, reduce serum calcium concentrations by decreasing calcitriol production by activated mononuclear cells. Clinical studies have shown the most benefit in hypercalcemia secondary to granulomatous disease; they take effect in two days. Bisphosphonates, such as zoledronate, act by inhibiting calcium release by interfering with osteoclast-mediated bone resorption, and have shown clinical benefit in hypercalcemia secondary to malignancy. Although bisphosphonates may be used in conjunction with isotonic solution, their maximal effect usually takes two to four days.

**References:**

23. **Rationale**

Thyroid storm is a challenging diagnosis to make, especially without prior history of disease and other confounding factors. This patient had undiagnosed hyperthyroidism as evidenced by her preoperative weakness, fatigue, and palpitations. She subsequently developed appendicitis, and the stress of the infection as well as the surgery, sent her into thyroid storm.

Thyroid storm is a rare but potentially life-threatening complication of hyperthyroidism that is often triggered by a stress to the body, such as infection. Symptoms include high fever, tachycardia, mental status changes, gastrointestinal symptoms, and potentially high-output heart failure. Treatment must be immediately initiated, often before laboratory results are available, to achieve the best outcome. IV beta-blockers, such as propranolol, are effective for rate control and help block peripheral thyroxine to triiodothyronine conversion. Antithyroid drugs such as propylthiouracil and methimazole are also needed to block production of thyroid hormone. Steroids are given to protect against concomitant adrenal insufficiency and prevent peripheral thyroid conversion. Iodine may be added only after antithyroid drugs are started.

Malignant hyperthermia and serotonin syndrome may look similar to thyroid storm, but there are some subtle differences. In malignant hyperthermia, a more rapid onset after induction might be expected as well as muscle rigidity and respiratory acidosis. Serotonin syndrome is also associated with muscle rigidity and often clonus. The hypertension can be controlled with the IV ACE inhibitor enalaprilat, but the initial treatment of her thyroid storm will treat the underlying cause of her increased blood pressure.

**Reference:**

24. **Rationale**

Critical illness-related corticosteroid insufficiency (CIRCI) is encountered in the ICU. This patient was on prednisone for lupus before being hospitalized and had a suppressed hypothalamic-pituitary-adrenal axis that prevented an appropriate response to the severe infection. As a result, despite appropriate fluid resuscitation, antibiotics, and vasopressor support, she remained in refractory shock requiring IV stress-dose steroids to support her blood pressure.

CIRCI is a form of relative adrenal insufficiency in which blood corticosteroid levels are inadequate for the stress imparted during critical illness. Features include refractory shock as well as electrolyte abnormalities including hypoglycemia, hyperkalemia, and hyponatremia. The diagnosis is often challenging based on laboratory test parameters, with no agreed-upon values in the literature. Conflicting results from trials such as Annane’s and the CORTICUS study (albeit with different patient populations) have led to a Surviving Sepsis Guideline recommendation to treat CIRCI on clinical grounds alone, if it
is suspected. Exact dosing and duration of steroids is undefined, but lower, intermittent dosing of IV hydrocortisone is often used and weaned once shock is resolved.

Adding antifungal coverage could be considered, although it is less likely to be of benefit in this scenario. The patient has received more than adequate resuscitation and does not meet any hard criteria for starting epinephrine.

References:

25. Rationale Answer: B

Tumor lysis syndrome (TLS) describes the physiologic disturbances that can occur after initiation of cancer treatment. Spontaneous cases of TLS may also occur. The potential to develop TLS exists with any cancer, but is more common with hematologic malignancies or when a large cancer burden is present. In TLS, rapid cancer cell lysis releases intracellular contents and metabolites (potassium, phosphate, purines, and cytokines) beyond the body’s ability to manage, leading to hyperkalemia, hyperphosphatemia, hypocalcemia, and hyperuricemia.

Signs and symptoms may develop at any time, but commonly within the first few days of starting cytotoxic medication. Examples include nausea, emesis, cramps, tetany, or seizures due to hypocalcemia. Cardiac dysrhythmias may occur due to hyperkalemia and hypocalcemia. Uremia can lead to metallic taste, pruritus, restless legs, ecchymoses or pericarditis. Hypotension and inflammation may occur with release of cytokines. Acute kidney injury can develop as a result of the precipitation of uric acid crystals and calcium phosphate crystals, and can be exacerbated by dehydration and acidosis.

Uric acid is a product of the metabolic breakdown of purine nucleotides, the building blocks of DNA and RNA. After cell lysis, enzymes break down DNA and RNA, leading to the release of purines, which are then broken down to hypoxanthine through purine catabolism. The enzyme xanthine oxidase catalyzes the formation of uric acid from xanthine and hypoxanthine. Uric acid is excreted in the urine, but higher levels lead to precipitation and crystal-induced nephropathy. Urate oxidase is an enzyme that does not exist in humans, but exists in other animals, and is used as a therapeutic drug target to further break down uric acid into the water-soluble molecule allantoin, which is excreted in the urine.

Identifying patients at high risk for TLS before initiation of cancer therapy and early recognition of these metabolic complications is important. Hydration is essential to prevent hypotension and improve renal perfusion. There are two main mechanisms for treating elevated uric acid levels: xanthine oxidase inhibitors and recombinant urate oxidase. Xanthine oxidase inhibitors (allopurinol, febuxostat) prevent the formation of uric acid; however, existing uric acid still must be cleared and can take several days to improve. Furthermore, xanthine levels can increase and lead to nephropa-
thy secondary to xanthine precipitation. Therefore, allopurinol is recommended only for patients at low risk for TLS or in combination with rasburicase.

Rasburicase is a recombinant urate oxidase, converting uric acid to water-soluble allantoin, which is excreted in the urine. Because rasburicase does not increase xanthine levels and directly reduces uric acid levels, it is recommended as the first-line agent for patients at high risk for TLS. In severe situations, hemodialysis may be used.

Although urinary alkalinization increases uric acid solubility, it decreases calcium phosphate solubility. Because it is more difficult to correct hyperphosphatemia than hyperuricemia, urinary alkalinization is approached with caution in TLS. Purine analogs are antimetabolites that mimic the structure of metabolic purines. They act as inhibitors of DNA synthesis and are used to treat certain cancers and autoimmune disorders. Phosphate binders are medications used to reduce the absorption of phosphate and are typically used in people with chronic kidney failure. They are taken with meals, binding to phosphate in the gastrointestinal tract and excreted, preventing phosphate absorption.

References:

26. Rationale

Carcinoids are neuroendocrine tumors that originate mainly in the gastrointestinal (GI) tract and lungs. They synthesize and release a variety of bioactive substances (mainly serotonin, histamine, tachykinins, kallikreins, and prostaglandins), which are responsible for the symptoms and manifestations known as carcinoid syndrome. Most GI carcinoid tumors do not initially manifest with these symptoms, however, because their humoral substances are released into the portal circulation and inactivated by the liver. Carcinoid syndrome develops in patients with gastrointestinal carcinoid tumors that have metastasized to the liver. Once liver disease is present, the liver is unable to protect the body from the actions of these substances.

The most significant long-term sequela of chronic exposure to these bioactive chemicals is carcinoid heart disease, which consists of pathognomonic plaque-like fibrous deposits on the heart valves, chambers, and intima of the great vessels. Typically only the right side of the heart is affected due to inactivation of these substances by the lungs. Surgical resection is the primary treatment for carcinoid tumors. Before resection, symptom management is controlled mainly with the somatostatin analogs, such as octreotide. Somatostatin is an endogenous peptide that inhibits the release of a broad range of hormones, including many of those released by carcinoid tumors. The majority of carcinoid tumors express somatostatin receptors and, therefore, its administration will inhibit the release of its bioactive substances. Carcinoid crisis is a life-threatening form of this syndrome that may be triggered by tumor
manipulation, as in this patient. The somatostatin analogs are the primary treatment since the admin-
istration of catecholamines can worsen the situation by potentiating further hormone release from the
tumors. Therefore, systemic catecholamines are recommended only in life-threatening situations or
sustained vasodilatory shock following administration of a somatostatin analog. IV furosemide in the
setting of hypotension is not recommended and, furthermore, the findings of jugular venous distention
and right-sided regurgitant murmurs in this patient likely reflect primary valvular carcinoid heart disease
rather than fluid overload. Histamine blockers will not do much to treat the hypotension in this disease,
which is due not just to histamine, but to a number of substances.

References:
1. Fox DJ, Khattar RS. Carcinoid heart disease: presentation, diagnosis, and management. Heart.
   11;116(24):2860-2865.

27. Rationale

Risk factors for acute kidney injury (AKI) in the postoperative period include age older than 70, history
of diabetes mellitus, high-risk surgical procedures, and use of IV contrast dye. Many agents have been
evaluated for prevention of AKI; however no agent has been shown to be more effective than maintain-
ing optimal volume status and hemodynamics. Avoidance of hypotension is important in order to main-
tain renal perfusion pressure. N-acetylcysteine, mannitol, and isotonic bicarbonate have all been studied
for their efficacy in prevention and have shown benefit in some studies. However, none of these inter-
ventions has proven to be more efficacious than maintaining optimal hydration and blood pressure.

Reference:

28. Rationale

This patient has abdominal compartment syndrome (ACS) due to extensive volume resuscitation in the
setting of severe burns. Bladder pressure should be urgently checked to formally diagnose this condi-
tion and expedite further management. ACS is often under-recognized in critically ill patients because
organ failure is often multifactorial and attributed to the underlying disease process. When abdominal
pressures are found to be greater than 20 mm Hg with associated organ failure, criteria are met for a
diagnosis of ACS. Organ failure can be manifested as hypotension due to pressure on the vena cava
and a decrease in venous return and subsequent drop in cardiac output. Patients on mechanical venti-
lation often have high peak airway pressures due to a distended abdomen. However, this patient was
on pressure-control ventilation, in which airway pressures are regulated, and thus ACS manifests as
a reduction in tidal volume on this mode of ventilation. Renal failure is another common finding, and
thought to be secondary to decreased renal perfusion from renal vein compression and diminished cardiac output. Management is abdominal decompression. Providing more IV fluids is likely to worsen compartment pressures. With a low pulse pressure variation, it is highly unlikely that he will respond to more fluid boluses. Acute tubular necrosis from rhabdomyolysis is possible, but less likely given the time frame from the contrast bolus and the relatively low creatinine kinase level.

References:

29. **Rationale**

Intra-abdominal hypertension is defined as intra-abdominal pressure (IAP) of greater than 10 mm Hg. Abdominal compartment syndrome (ACS) is the effective end-organ hypoperfusion that results from prolonged intra-abdominal hypertension. IAP higher than 20 to 25 mm Hg may cause ACS and, in this way, acute functional loss of various abdominal and extra-abdominal organs. Inflammatory and hemodynamic factors caused by intra-abdominal hypertension may affect pelvic, thoracic, cranial and muscular areas beside abdominal organs. Urinary bladder pressure is the gold standard for measuring IAP and is valid up to an IAP of 70 mm Hg. Factors affecting its reliability include pregnancy, obesity, and ascites.

Option A is incorrect because the patient has remained normotensive throughout his hospitalization and we can assume that after 7 liters of crystalloid, he is close to intravascularly replete. Furthermore, administration of IV fluids in this situation is be appropriate given the evidence of increased abdominal pressures. Oliguria progressing to anuria, and prerenal azotemia unresponsive to volume expansion characterize the renal dysfunction of ACS.

Ureteral compression by increased IAP was felt to at one time be the cause of renal failure in ACS but this has since been disproven because ureteral stents do not prevent the development of renal failure in this setting. In 1947, studies examined subjects undergoing external compression to 20 mm Hg. In these models, measurements of renal vein pressure, inferior vena cava pressure, renal plasma flow and glomerular filtration rate were studied. The effective renal plasma flow and glomerular filtration rate dropped by 24.4% and 27.5%, respectively. All patients became oliguric and the absence of a sudden increase in urine flow on release of pressure suggested that ureteral compression was unlikely to be the cause of oliguria. Instead, it was discovered that elevations in renal vein pressure was probably the culprit, making option D the correct answer.

Intra-abdominal hypertension causing venous congestion and decreased preload can certainly impact
cardiac output, especially when pressures enter the range to cause ACS; however, this is not felt to be the primary cause of renal failure because correcting cardiac output with fluid and inotropes has not shown to be of benefit in this instance. It is important to note that, when fluid is administered, it should be done through an internal jugular vein rather than a femoral line given the likely impedement in venous return below the diaphragm.

Reference:

30. **Rationale**

Unfortunately, there is no such thing as an ideal resuscitation fluid; all resuscitative fluids have some physiologic impact as parenteral medications. Saline’s designation as “normal” was based on an erroneous calculation of the salt concentration in blood as 0.9% in the 1800s (the actual salt concentration of blood is closer to 0.6%). Saline frequently causes a hyperchloremic metabolic acidosis with large-volume resuscitation. While this is a transient effect, the acidosis has been associated with immune suppression and coagulopathy. Saline has also been found to be associated with renal injury; both in humans and animal models, the data suggests that the increased chloride load decreases renal perfusion and may interfere with renal hemostasis. High-chloride loads have also been associated with increased renal replacement therapy requirements. Individual studies looking at both septic patients and abdominal surgery patients have shown increased all-cause in-hospital mortality in high-chloride resuscitative strategies.

References:

31. **Rationale**

Adequate nutrition is recognized as an important component of critical care and is believed to improve clinical outcomes. Temporary cessation of enteric tube feeding occurs in as many as 68% to 83% of surgical patients admitted to the ICU and accounts for up to 32% of potential feeding time. The purpose of nothing-by-mouth status is to prevent gastric aspiration during the induction of anesthesia. However, for mechanically intubated patients who are scheduled to undergo procedures in the supine
position, there will be no airway manipulation. Enteric feeding may be continued up until or even during the procedure. Although the practice of reducing the duration of nothing-by-mouth status or providing compensatory nutrition is already being practiced at some centers, there is little published literature on this topic. The Society of Critical Care Medicine and American Society for Parenteral and Enteral Nutrition recommend that nothing-by-mouth status surrounding the duration of diagnostic tests or procedures should be minimized to prevent inadequate delivery of nutrients and prolonged periods of ileus.

References:

32. Rationale

The metabolic response of critical illness is characterized by an increase in resting energy expenditure (REE). Energy needs of the critically ill patient are dynamic, changing throughout the ICU stay. Nutrition may affect clinical outcomes in critically ill patients, and providing either fewer or more calories than the patient needs can adversely affect outcomes. It is therefore essential to have a precise measurements of energy needs in these patients in order to avoid underfeeding and overfeeding, loss of critical lean body mass, and worsening of any existing nutrient deficiencies.

In clinical practice, energy needs are determined either by using predictive equations (eg, Harris-Benedict) or by actual measurement using indirect calorimetry (IC). Although many equations exist for predicting resting energy expenditure, most studies have reached the conclusion that current predictive equations do not accurately predict required energy needs in the critically ill population. The epidemic of obesity further renders the calculations of requirements by predictive equations increasingly inaccurate at extremes of body mass index. The IC technique most accurately reflects the exact rate of energy production and substrate oxidation in critically ill patients in the clinical practice setting. IC calculates REE by measuring whole-body oxygen and carbon dioxide gas exchange. This concept is based on the strong correlation between intake of oxygen and release of carbon dioxide with energy production. It is estimated that approximately 80% of energy expenditure is due to oxygen consumption, and the remaining 20% is due to carbon dioxide production.

The Nutrition Risk in Critically Ill (NUTRIC) score is a recently developed tool to help discriminate which ICU patients will benefit more (or less) from aggressive protein-energy provision. The score, ranging from 1-10, is based on six variables (age, Acute Physiologic and Chronic Health Evaluation [APACHE] II score, Sequential Organ Failure Assessment [SOFA] score, number of comorbidities, days from hospital to ICU admission and interleukin 6 levels). Patients with a score greater than 5 are most likely to benefit from aggressive nutrition therapy.
The SOFA score allows for calculation of both the amount and severity of organ dysfunction in six organ systems (respiratory, coagulatory, liver, cardiovascular, renal, and neurologic). It is used to quantify the severity of the patient's illness based on the degree of organ dysfunction serially over time.

References:

33. Rationale

A major problem in the ICU is malnutrition. One of the reasons for this is that most critically ill patients are in a catabolic state due to a proinflammatory state and thus have increased caloric demands. Current guidelines promote early enteral nutrition due to the benefits of decreased gut atrophy, as well as preserving normal gut flora. Initiating enteral feeding compared to parenteral nutrition has also been shown to result in less infection. Multiple clinical trials have shown that gastric residual volumes are unnecessary and may contribute to malnutrition. Therefore, reducing or discontinuing enteral feeding would prevent patients from meeting their increased caloric demands. No evidence exists that low-volume elemental feeding has clinical benefit compared to full enteral feeding. Pro-motility agents may decrease gastric residuals, but have no effect on mortality.

References: