A 77-year-old man presented with acute onset of right upper-quadrant and epigastric abdominal pain over the past 10 hours. He described this as “aching,” with radiation to the back. Associated symptoms included chills, nausea, and several episodes of nonbloody, nonbilious emesis.

His medical history was notable for inflammatory ileocolonic Crohn disease status post ileocolonic resection, currently on budesonide; ankylosing spondylitis, on acetaminophen as needed; gastroesophageal reflux, on once-daily omeprazole; and latent tuberculosis, on isoniazid. Patient was previously on infliximab for several years as maintenance therapy for Crohn disease, with remission of symptoms, but this had recently been stopped around the time of initiation of isoniazid 9 months ago, when he was diagnosed with latent tuberculosis. Family history was negative for gastrointestinal disorders. He denied any past or current tobacco or alcohol use.

At presentation, the patient’s vital signs were as follows: temperature 36.8 °C, heart rate 77 beats per minute, and blood pressure 96/59 mm Hg. Physical examination revealed epigastric tenderness to light palpation without peritoneal signs.

Laboratory evaluation (reference range in parenthesis) yielded the following: hemoglobin 16.5 g/dL (13.0 to 17.0 g/dL); hematocrit 40% (40% to 50%); leukocytes 12.9 x 10^9/L (4.0 to 11.0 x 10^9/L); platelets 185 x 10^9/L (140 to 400 x 10^9/L); sodium 136 mEq/L (133 to 147 mEq/L); potassium 3.5 mEq/L (3.5 to 5.3 mEq/L); creatinine 0.8 mg/dL (0.6 to 1.3 mg/dL); total bilirubin 0.6 mg/dL (0.2 to 1.3 mg/dL); aspartate aminotransferase (AST) 19 IU/L (15 to 46 IU/L); alanine aminotransferase (ALT) 10 IU/L (0 to 49 IU/L); and alkaline phosphatase 65 IU/L (42 to 140 IU/L).

1. Which of the following additional features would this patient need to meet the diagnostic criteria for acute pancreatitis?
   a. Right upper-quadrant pain that radiates to the right shoulder
   b. Right upper-quadrant ultrasound demonstrating cholelithiasis
   c. Serum lipase greater than 3 times the upper limit of normal
   d. Gamma-glutamyl transferase (GGT) greater than 3 times the upper limit of normal
   e. Serum amylase greater than 2 times the upper limit of normal

Right upper-quadrant pain that radiates to the shoulder would be more characteristic of biliary pathology, such as cholelithiasis or cholecystitis, rather than acute pancreatitis (AP). Right upper-quadrant ultrasound demonstrating cholelithiasis may increase suspicion for gallstones as a potential underlying etiology for AP but is not a diagnostic criterion. A diagnosis of AP is established by the presence of 2 of the 3 following criteria: characteristic abdominal pain, serum amylase or lipase greater than 3 times the upper limit of normal, and imaging findings suggestive of AP. Characteristic abdominal pain is described as epigastric or left upper-quadrant abdominal pain that radiates to the back. Gamma-glutamyl transferase can be elevated in various types of hepatobiliary disease and is not a required diagnostic criterion for AP. Finally, serum amylase would have to be elevated greater than 3 times the upper limit of normal to meet diagnostic criteria.
The severity of AP can be classified as mild, moderate, or severe, based on the Revised Atlanta Criteria, which incorporates the presence of transient or persistent organ failure as well as local or systemic complications. The severity of AP is not static and should be reassessed frequently while the episode of pancreatitis is evolving.

With cases in which the diagnosis of AP cannot be made using patient history and laboratory results, abdominal imaging can be helpful. Contrast-enhanced computed tomography (CT) is reported to have greater than 90% sensitivity and specificity for diagnosing AP. Magnetic resonance imaging (MRI) is reported to be more sensitive than CT imaging in detecting subtle changes of AP and may be useful in evaluating patients with high clinical suspicion for AP with negative CT findings. Imaging findings seen with AP can include fluid collections surrounding the pancreas, reticular stranding of peripancreatic fat, suggestive of inflammation, and, in severe cases, absence of normal enhancement of parts of or entire pancreas, indicative of necrosis.

Our patient presented with epigastric abdominal pain that radiated to the back and serum lipase greater than 16,000 IU/L (23 to 300 IU/L). Abdominal ultrasound was unrevealing, with evidence of surgically absent gallbladder, without evidence of choledocholithiasis or common bile and pancreatic ductal dilatation. A CT scan of the abdomen and pelvis with intravenous contrast material showed evidence of peripancreatic stranding with inflammation of the pancreas. Given his clinical symptoms, and laboratory and imaging findings, the patient met all 3 diagnostic criteria for AP.

2. Which of following is the preferred laboratory marker for guiding hydration in this patient?
   a. Sodium
   b. Alanine aminotransferase
   c. Lipase
   d. Hematocrit
   e. Chloride

   Early aggressive fluid hydration is the mainstay for medical management for AP. The basis of this intervention derives from observation of significant hypovolemia in these patients, associated with diaphoresis, vomiting, reduced oral intake, respiratory losses, and third spacing of fluids. Although hydration may be performed using normal saline or Lactated Ringer's solution, the latter may be more protective against the development of systemic inflammatory response syndrome and carries a theoretical benefit of lowering metabolic acidosis.

   Hydration is not guided by sodium, alanine aminotransferase (ALT), lipase, or chloride. Serum sodium and tonicity is tightly regulated in humans. When water is ingested or absorbed in sufficient quantity to disturb tonicity, both thirst and vasopressin release are subsequently suppressed, keeping serum tonicity in tight balance. Alanine aminotransferase is released from hepatocytes, and an elevated level is indicative of liver injury and does not correlate to pancreatitis. Elevated serum lipase reflects active pancreatic inflammation and injury. There is no literature supporting serial lipase measurements in guiding hydration strategy or its utility in predicting the severity of AP. Following laboratory markers such as hematocrit, blood urea nitrogen (BUN), and creatinine as surrogate markers of adequate hydration is, however, widely recommended. The aim is to demonstrate appropriate hemodilution by lowering hematocrit and to ensure adequate renal perfusion by decreasing BUN and normalizing creatinine. There is no gold-standard “target” value that needs to be reached. Typically, however, patients will require several liters of fluid initially, at a rate of 250 to 500 mL per hour over the first 12 to 24 hours. Measuring chloride is not clinically meaningful. There is no literature describing hydration strategies that should be guided by any other laboratory measures other than hematocrit, BUN, and creatinine.

   Although early aggressive hydration is preferred in AP, fluid resuscitation should
be performed with caution in patients at risk for volume overload, such as those with severe heart failure, as it carries the risk of respiratory compromise. The aforementioned laboratory markers can be helpful in guiding rate and duration of hydration in such patients. In addition, the timeframe for early aggressive hydration in AP is the first 12 to 24 hours after admission; aggressive hydration after this period is not as helpful.

Our patient received aggressive intravenous hydration upon admission with downtrending of hematocrit from 40% to 35% within 24 hours.

3. After ensuring adequate hydration, what is the next best step in management of this patient?
   a. Enteral nutrition
   b. Prophylactic antibiotics
   c. Imaging to evaluate for drainable fluid collections
   d. Total parenteral nutrition
   e. No oral nutrition for at least 48 hours

Several meta-analyses have demonstrated that early enteral nutrition is associated with clinically meaningful outcomes, such as decreased hospital length of admission and reduced infectious complications and risk of organ failure. Randomized controlled trials have also exhibited a trend toward decrease in mortality with enteral compared with parenteral nutrition. Absence of enteral feeding is thought to result in gastrointestinal mucosal atrophy, bacterial overgrowth, and increased intestinal permeability, leading to bacterial translocation into the systemic circulation. In experimental models, enteral nutrition was shown to reduce systemic plasma endotoxin, bacterial translocation to portal and systemic circulation, and reduced bacterial colony counts in lung, pancreas, and mesenteric lymph nodes.

Prophylactic administration of antibiotics is not recommended unless there is high clinical suspicion of concurrent infection such as cholangitis, urinary tract infection, pneumonia, or bacteremia. Imaging to assess for drainable fluid collection would not be indicated in the absence of signs or symptoms suggestive of secondary complications of AP such as infected fluid collection, biliary obstruction, or fistulization. Total parenteral nutrition is not advised, as it is associated with infections and line-related complications. Given aforementioned benefits associated with early enteral nutrition, patients should be allowed to initiate oral intake as soon as tolerated. For the patients who are unable to take oral nutrition, or those with severe AP, enteral nutrition through nasogastric feeding should be considered. Nasogastric-tube feeding is comparable with nasojejunal feeding in terms of safety, tolerability, and clinical outcomes such as achievement of nutritional balance and lower mortality rate.

Upon further questioning, the patient had already been hospitalized twice over the past year for episodes of AP with no definite etiology.

4. What would be the next best diagnostic test in evaluating his recurrent acute pancreatitis after conventional imaging (ie, CT)?
   a. Serum ethanol level
   b. Hereditary pancreatitis genetic panel testing
   c. Serum IgG4 level
   d. Fine-needle aspiration of the pancreas
   e. Endoscopic ultrasound

In this case, serum ethanol would not be helpful, as the patient reported lifelong abstinence from alcohol and had previous negative results from alcohol tests. Genetic panel would not be high yield, as family history did not reveal any family members with history of AP, and the patient presented with the first episode of AP in his late 70s. Genetic testing for hereditary pancreatitis may be considered in a young person with AP with no identifiable etiology. Obtaining IgG4 levels in this patient with no other diagnostic suspicion of autoimmune pancreatitis (AIP) would be low yield; IgG4 can be elevated in multiple conditions such as
pancreatic cancer, cholangiocarcinoma, primary sclerosing cholangitis, and AP. A diagnosis of AIP would require elevated IgG4 levels in addition to associated imaging features suggestive of AIP, which was not seen in this case. Invasive procedures, such as fine-needle aspiration, have the potential to cause AP—with additional risks, including bleeding and infection—and would be unlikely to change management.

The next step of evaluation would be to pursue additional imaging, such as magnetic resonance cholangiopancreatography (MRCP) or with an endoscopic ultrasound (EUS). Such imaging can help provide high-resolution images of the pancreatic parenchyma and further assess the pancreas duct and biliary tree. More specifically, these advanced imaging modalities can assess for malignancy, microlithiasis, and chronic pancreatitis, all of which can present with recurrent episodes of AP. Endoscopic ultrasound is an invaluable tool for obtaining targeted biopsies of any suspicious lesions, with a sensitivity of 89% and specificity of 100%, in diagnosing pancreatic neoplasms. In routine clinical practice, diagnostic work-up for AP should include serum calcium and triglycerides, liver chemistries, a detailed alcohol history with ethanol level, and abdominal ultrasound to evaluate for gallstones and biliary obstruction. With cases for which this routine diagnostic work-up is unrevealing, advanced imaging or other testing may be considered.

Recurrent AP is defined as 2 or more episodes of AP, with resolution of symptoms between each episode. Recurrent AP also requires exclusion of chronic pancreatitis. With such cases, in which routine work-up has been unrevealing, medications and genetic factors should be considered. The patient underwent EUS, the results of which did not demonstrate any significant structural abnormalities. In addition, a diagnosis of chronic pancreatitis was also ruled out, as he did not present with any clinical features suggestive of endocrine and exocrine pancreatic insufficiency nor had any imaging evidence of parenchymal or ductal changes suggestive of chronic pancreatitis.

5. Which of the following medications is the most likely to be associated with this patient’s presentation?
   a. Isoniazid
   b. Budesonide
   c. Infliximab
   d. Omeprazole
   e. Acetaminophen

Medication-induced AP may account for up to 2% all cases of AP. Although hundreds of medications have been implicated, the most well-recognized classes of medications associated with AP are known as the class Ia drugs (defined as at least 1 case report with positive rechallenge and exclusion of all other potential causes of AP) and include isoniazid, enalapril, furosemide, mesalamine, and pentamidine. Budesonide, infliximab, omeprazole, and acetaminophen do not have well established association with AP. Medication-induced AP should be suspected when common etiologies of AP such as gallstones, alcohol, hypertriglyceridemia, and hypercalcemia have been ruled out and when there may be a temporal association with a commonly implicated medication. Isoniazid is a first-line drug used in treatment of latent tuberculosis. In cases of isoniazid-induced AP, pancreatitis manifests within a median of 16 days after induction of isoniazid.

Our patient was taking all the aforementioned listed medications. After gathering additional history, his 3 episodes of AP had all occurred after initiation of isoniazid for latent tuberculosis. It was thought that his episodes of AP were related to use of isoniazid, given the temporal association; the known risk of pancreatitis with this medication; and the largely negative work-up to date, which had excluded structural and metabolic causes.

As the patient had completed his cumulative 9 months of therapy with isoniazid for latent tuberculosis, he was instructed to discontinue isoniazid, given that the risk of reactivation of tuberculosis with use of
strong immunosuppressants was calculated to be minimal at this time. At the time of last follow-up, 4 months after discontinuation of isoniazid, the patient was doing clinically well, without any additional episodes of AP.

DISCUSSION
Acute pancreatitis is one of the most common diseases of gastrointestinal tract, with incidence estimated to be between 4.9 to 73.4 cases per 100,000 worldwide.\(^1\) In the United States alone, there are approximately 220,000 hospital admissions annually attributed to AP,\(^14\) with annual health care cost spending of approximately $2.6 billion.\(^1\)

A diagnosis of AP is established by the presence of 2 of the 3 following criteria: characteristic abdominal pain, serum amylase or lipase greater than 4 times the upper limit of normal, and imaging findings suggestive of AP. The etiology of AP can be diverse. The most common cause of AP is gallstones, responsible for 40% to 70% of cases, followed by alcohol, which accounts for approximately 25% to 35% of cases.\(^1\) Other less common causes include metabolic disturbances such as hypercalcemia and hypertriglyceridemia, medications, infections, and pancreatobiliary tumors.\(^1,13\)

Management should focus on early aggressive fluid resuscitation, especially within first 24 hours following hematocrit; BUN; and creatinine as surrogate markers of adequate hydration.\(^6\) Correction of hypovolemia is critical, as failure to achieve appropriate decrease in the hematocrit at 24 hours has been reported as the best risk factor for development of pancreatic necrosis.\(^6\) In addition, initiation of early enteral nutrition is recommended, as it is associated with clinically meaningful outcomes such as decreased hospital length of admission, infectious complications, and risk of organ failure.

Advanced imaging modalities beyond conventional CT, such as MRCP and EUS, offer unique diagnostic capability with detailed pancreatic tissue characterization if no definite etiology is found. For example, MRCP allows for visualization of pancreatic ductal course, obstruction, dilatation, and abnormal side branches, which allows for comprehensive evaluation of a spectrum of pancreatic diseases.\(^3\) In addition, EUS can demonstrate enlarged pancreas with hypoechoic pattern; peripancreatic inflammation; and peripancreatic fluid collection, which can be suggestive of acute edematous pancreatitis.\(^13\)

Medications are reported to be responsible for 0.1% to 2.0% of AP cases. Medication-induced AP mechanisms are not yet clearly defined, but potential theorized mechanisms include pancreatic-duct constriction and accumulation of toxic metabolites. When patients present with AP of unclear etiology, medications should be reviewed thoroughly, as several classes of medications have been reported to be triggers of AP. Clinicians should gather history carefully to identify any potential new medication, as well as its temporal association to AP, especially in patients presenting with recurrent AP.

There are multiple reports of isoniazid-induced AP reported in the medical literature. Isoniazid is currently classified as class Ia drug for AP, which is defined as a drug class with at least 1 case report with positive rechallenge and exclusion of all potential causes of AP.\(^13\) Its mechanism is hypothesized as dose-dependent pancreatic injury from accumulation of toxic metabolites and is reported to manifest within a median of 16 days after induction of isoniazid.\(^13\) Although there is no clearly identified length of follow-up suggested for medication-induced AP, these patients should be monitored closely to ensure clinical stabilization.

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REFERENCES

CORRECT ANSWERS: 1. c. 2. d. 3. a. 4. e. 5. a.