A 31-year-old woman presented to the emergency department (ED) with a 4-week history of new-onset diarrhea. The stool was described as brown, loose, occurring 12 to 14 times a day, and having progressed to bright red bloody diarrhea during the last week. Additional symptoms included crampy abdominal pain and nausea that resolved after 1 week. Past medical history was significant for migraine headaches treated with as-needed ibuprofen and recent uncomplicated pregnancy. She denied associated fever, weight loss, heartburn, vomiting, intermittent constipation, fecal incontinence, pain with defecation, urgency, nocturnal symptoms, known allergies, correlation with diet or food intolerance (including dairy), steatorrhea, recent travel, or history of upper endoscopy or colonoscopy. Alleviating efforts included probiotics, a 3-day course of metronidazole prescribed by an outside provider, and loperamide, all without benefit.

In the ED, the patient presented afebrile (36.8°C), with a heart rate of 64 beats/min, and blood pressure of 104/68 mm Hg. She was alert, orientated, and did not appear to be in distress. Her mucous membranes were moist, head and neck examination was insignificant for lymphadenopathy, and heart sounds and pulmonary effort were normal. Abdominal exam was significant for mild, right upper quadrant pain without rebound, rigidity, or distention. No abnormalities were found on skin examination.

1. What is the most likely etiology based on this patient’s initial presentation and symptom history?
   a) Colonic ischemia
   b) Infection/inflammatory
   c) Malabsorption
   d) Colorectal cancer
   e) Diverticulosis

Colonic ischemia is a differential that must be considered in the setting of bloody diarrhea or hematochezia, and accounts for 9% to 24% of hospitalized cases of lower gastrointestinal (GI) bleeding. Although nonsteroidal anti-inflammatory drug use can lead to intestinal ischemia, this patient’s intermittent use of ibuprofen, age, lack of cardiac comorbidities, and duration of diarrhea make intestinal ischemia less likely. Symptoms of colonic ischemia typically resolve within 2 to 3 days of symptom onset. Infectious/inflammatory etiology is the most common cause of bloody diarrhea in children and young adults. The insidious nature, frequency of bowel movements, and transition from secretory to bloody diarrhea make an infectious or inflammatory source most likely in this patient. Further evaluation in the form of inflammatory markers and stool studies (culture, toxins, erythrocyte sedimentation rate, and lactoferrin) can help delineate the diagnosis. Malabsorption is less likely in the setting of bloody diarrhea and absence of steatorrhea, weight loss, or history of atopy. Stool assessment for fecal fat can rule out malabsorption if symptom history is questionable. Colorectal cancer (CRC) typically presents with weight loss, changes in stool caliber, and microscopic, low volume bleeding leading to iron-deficiency anemia. Although this patient has not had a colonoscopy or CRC screening, additional symptoms of weight loss, fatigue, and family history of CRC would likely be present if CRC were to present in a patient this young. Diverticulosis is an event-type arterial bleed and the most common cause of hematochezia, especially in patients with advanced age. It does not cause diarrhea, and would not last 4 weeks.

Initial laboratory workup in the ED (reference ranges shown parenthetically) included complete blood count significant
for leukocytosis (15.9 × 10^9/L [3.5 to 10.5 × 10^9/L]) with differential significant for eosinophilia of 36% (1.0% to 3.0%), and an absolute eosinophil count of 5.73 (0.03 to 0.48 × 10^9/L). Hemoglobin (15.7 g/dL [12.0 to 15.5 g/dL]), mean corpuscular volume (87.3 fL [78.2 to 97.9 fL]), and platelet count (276 × 10^9/L [157 to 371 × 10^9/L]) were normal. Basic metabolic panel was normal and yielded sodium, 140 mEq/L (135 to 145 mEq/L); potassium, 3.7 mEq/L (3.6 to 5.2 mEq/L); bicarbonate, 22 mEq/L (22 to 26 mEq/L); chloride, 107 mEq/L (98 to 107 mEq/L); blood urea nitrogen, 17 mg/dL (7 to 20 mg/dL); creatinine, 1.09 mg/dL (0.84 to 1.21 mg/dL); glucose, 79 mg/dL (<140 mg/dL); and anion gap, 11 mEq/L (3 to 10 mEq/L). Liver function tests, troponin, and lactate, 1.5 (0.5 to 2.2 mmol/L) results were also within normal limits. Pregnancy test was negative.

2. What is the best approach to initial workup of this patient?
   a) Computed tomography (CT) angiogram to assess intestinal ischemia
   b) Surgical evaluation for peritonitis including General Surgery consultation
   c) Stool studies — stool culture, enteric toxins, C. difficile testing, ova/parasites
   d) Empiric antibiotics, such as ciprofloxacin and metronidazole
   e) Human immunodeficiency virus testing

Colonic ischemia is a differential guided by history and physical examination. Computed tomography angiogram is not used routinely to assess the vasculature in suspected colonic ischemia; it would be indicated if dealing with isolated right colon ischemia. Patients with obvious signs of peritonitis (fever, abdominal pain, rigidity, or distention) should be evaluated surgically and would warrant a General Surgery consultation. This patient's age, lack of cardiac history, and lack of peritoneal signs do not support CT angiography or General Surgery consultation. Although symptom history is not typical of infectious diarrhea based on duration, her leukocytosis with eosinophilic predominance supports an infectious or inflammatory etiology. Initial evaluation should include stool studies such as stool culture, enteric toxins, erythrocyte sedimentation rate, lactoferrin, C. difficile testing in the setting of recent antibiotic use/surgery (such as a Caesarean section), and ova/parasites to evaluate parasitic sources of diarrhea due to eosinophilia. Stool culture, toxin evaluation, and polymerase chain reaction can be helpful in clinical decision-making if antibiotics are necessary. Empiric antibiotics or antimicrobials in the setting of diarrhea are not typical unless it is clear a pathogen appropriately amendable to therapy is present. Patient history did not support a sexual or illicit drug history to warrant HIV testing on initial evaluation.

Laboratory workup was significant for positive E.coli Shiga toxin. Stool culture for enteric pathogens including Shiga toxin-producing E.coli, Shigella, E. coli 0157H7, Salmonella, Yersinia, Campylobacter, and Aeromonas were negative. Additional stool studies for C. difficile, Giardia, and parasitic ova/parasites were negative. Abdominal CT scan in the setting of mild abdominal pain and bloody diarrhea was negative for acute pathology including colitis, obstruction, mass, or lymphadenopathy. In the ED, the patient remained hemodynamically stable throughout evaluation, and treatment measures in the form of intravenous fluid resuscitation or intravenous antibiotics were not given.

3. Subsequent workup and evaluation should initially involve?
   a) Outpatient pulmonary function testing, chest imaging, and Pulmonology consultation
   b) Outpatient bone marrow aspirate, biopsy, and Hematology consultation
   c) Outpatient endoscopic evaluation and Gastroenterology consultation
   d) Inpatient admission, intravenous antibiotics, and supportive therapy
   e) Inpatient admission, nothing by mouth orders, and General Surgery consultation

Eosinophilia is often associated with pulmonary pathology such as asthma, allergic bronchopulmonary aspergillosis, and vasculitides such as eosinophilic granulomatosis with polyangiitis (formerly Churg-Strauss
syndrome). Idiopathic hypereosinophilia is a diagnosis of exclusion following extensive history, tissue biopsy, smear studies, and multidisciplinary evaluation including Hematological evaluation. History and symptomatology in this patient suggest a GI source; therefore, pulmonary and hematological workup would not be efficacious at this time. This patient with intermittent bloody diarrhea would benefit more from upper and lower endoscopic evaluation with intestinal biopsy to delineate the extensiveness of eosinophilia. Negative cardiac troponins support local involvement of the GI tract only and no other organ systems. Physical exam, imaging, and laboratory evaluation did not support an inpatient admission. Current international guidelines support the use of antibiotics in infants younger than 3 months, malnourished, immunocompromised, or elderly patients. First-line therapy is fluoroquinolones such as ciprofloxacin. This patient did not meet criteria for antibiotic therapy and did not have peritoneal signs to warrant surgical evaluation or exploration. The patient remained hemodynamically stable while in the ED without evidence of imminent compromise; therefore, she would not have met criteria for inpatient admission and management.

The patient was discharged from the ED in stable condition with a 1-week course of oral sulfamethoxazole and trimethoprim (Bactrim DS), and the local health department was notified of the positive stool Shiga toxin finding. In addition, close follow-up with the GI department was arranged. The patient was seen in the GI clinic 3 days following ED discharge, with initial improvement in symptoms. However, diarrhea quickly reoccurred with increased frequency and it was determined that the patient should discontinue antibiotics and undergo esophagogastroduodenoscopy and colonoscopy with random biopsy specimens to rule out eosinophilic gastroenteritis. Esophagogastroduodenoscopy was significant for erythema of the gastric antrum and biopsy specimens obtained in the antrum and duodenum were significant for eosinophilic infiltrates within the mucosa suggesting eosinophilic gastroenteritis. Biopsy specimens were negative for H. pylori, parasites, or granulomas. Colonoscopy yielded normal colon, rectum, and anal verge. Colonic biopsy specimens were insignificant for pathology or eosinophilic infiltrate.

4. What is the most likely diagnosis?
   a) Eosinophilic gastroenteritis
   b) Inflammatory bowel disease (IBD)
   c) Whipple disease
   d) Celiac disease
   e) Eosinophilic esophagitis

Gastric and duodenal biopsy supported eosinophilic infiltrate without evidence of H. pylori infection, parasitic infection, or granulomas supportive of IBD presumptively diagnosing eosinophilic gastroenteritis. Inflammatory bowel disease causes chronic relapsing inflammation of the bowel. Microscopic morphology of Crohn’s disease reflects non-caseating granulomas and lymphoid aggregates. Ulcerative colitis has continuous colonic and rectal involvement, none of which were present in this patient making IBD less likely. Whipple disease is an infectious disease caused by Tropheryma whipplei, an intracellular gram-positive bacteria. Biopsy would have reflected periodic-acid Schiff (PAS+) foamy macrophages in the intestinal lamina propria. Celiac disease is an autoimmune-mediated gliadin insensitivity. Biopsy would reflect villous atrophy and intraepithelial lymphocytosis. Eosinophilic esophagitis would reflect eosinophilic infiltrate; however, symptoms of dysphagia, odynophagia, and heartburn would be present, as opposed to the diarrhea.

Repeat complete blood count obtained before endoscopy reflected ongoing leukocytosis 13.8×10⁹ L and increased eosinophilia 45.9% (up from 36%) with an absolute eosinophil count of 6.32×10⁹ L (up from 5.73×10⁹ L).

5. What is the best initial treatment option to be considered at this point?
   a) Supportive therapy, fluid resuscitation, and as-needed analgesia
   b) Immunologic therapy, PD-1, or CTLA-4 inhibitor
   c) Loperamide
   d) Antibiotics such as ciprofloxacin and metronidazole
   e) Corticosteroid therapy
The chronicity of this patient’s symptoms without signs of improvement supports the need for more definitive treatment rather than just supportive care. However, encouraging adequate oral hydration and nutrition should be advised. Immunologic therapy, especially PD-1 and CTLA-4 inhibitors are notorious for GI side effects, with diarrhea being the most common. Antimotility medications such as loperamide would not address eosinophilic infiltrate and should be discouraged if GI infection is suspected. The patient does not meet criteria for empiric antibiotic therapy in the setting of infectious diarrhea; in addition, a positive Shiga toxin in the United States should raise concern for Shiga-toxin E. coli in which antibiotics are contraindicated. Corticosteroid therapy, specifically prednisone, is considered first-line therapy for eosinophilic gastroenteritis.

At this time, the patient was started on a 4-week course of oral prednisone with appropriate taper. Subsequent follow-up examination after treatment was significant for resolution of diarrhea, nausea, and abdominal pain. Repeat complete blood count and stool studies reflected resolution of eosinophilia, leukocytosis, and was negative for Shiga toxin or positive microbial cultures.

DISCUSSION
Diarrhea is defined as an increase in stool frequency, liquidity, or volume. Detailed patient history and physical exam can guide clinical decision-making and is imperative in diagnosis. Diarrhea is typically subdivided into two broad categories defined by duration, “acute diarrhea” and “chronic diarrhea.” Acute diarrhea is characterized as symptom duration of less than 14 days and chronic diarrhea is persistence past 4 weeks in duration. In addition to duration, diarrhea is further subcategorized by type — watery, fatty, or inflammatory — based on presentation and stool studies. Watery diarrhea is marked by increased liquidity and is either secretory (often nocturnal, osmotic gap <50 mOsm/kg) or osmotic (fecal osmotic gap >125 mOsm). Fatty diarrhea is due to malabsorption in the setting of damaged mucosa or decreased pancreatic enzymes. It is marked by steatorrhea; greasy, foul smelling stools; and weight loss. Inflammatory diarrhea is often due to infection or autoimmune disorders that may cause inflammation. It is marked by abdominal pain, tenesmus, fever, and may be bloody.

Shiga toxin is a bacterial toxin produced by Shiga toxin—producing E. coli (STEC) or Shigella dysenteriae. Shiga toxin—producing E. coli is the most common cause of infectious bloody diarrhea in the United States, whereas S. dysenteriae is more common in developing countries or individuals who have recently traveled. Shiga toxin produces symptoms of fever, abdominal pain, tenesmus, and at times bloody diarrhea described as dysentery. Our patient with a positive Shiga toxin and negative stool culture may be due to insufficient bacterial yield or more likely a false positive result. Stool polymerase chain reaction, an alternative means of diagnosis, is more sensitive and specific. Treatment for infectious diarrhea is usually supportive. Antibiotics are not recommended for toxin-producing bacteria, especially STEC due to the risk of hemolytic uremic syndrome and bacterial lysis leading to worsening illness or prolongation of symptoms; however, S. dysenteriae may be treated with antibiotics. Patients with infectious diarrhea of unknown origin may be treated empirically if they are an infant younger than 3 months, immunocompromised, international travelers with sustained fever (>38.5°C), systemic signs of sepsis, severe abdominal pain, or bacillary dysentery presumptively caused by S. dysenteriae infection. Empiric antibiotics in adults are usually a fluoroquinolone such as ciprofloxacin or azithromycin. In children, azithromycin or a third-generation cephalosporin is traditionally used if indicated. Our patient did not meet criteria to be treated for antibiotics, nor should she have been treated if STEC was suspected. In addition, oral sulfamethoxazole and trimethoprim (Bactrim DS) is not first-line therapy when antimicrobial therapy is indicated. Shiga toxin—producing E. coli and Shigella infections are both reportable diseases to the local health department and providers should take the necessary steps to do so.
Our patient’s symptom history initially supported a confounding picture marked by acute inflammatory diarrhea caused by STEC infection and chronic watery diarrhea caused by eosinophilic gastroenteritis. We believe the toxin positive stool with negative culture was likely a false-positive result due to negative toxin and culture results on repeat studies and CT scan negative for signs of inflammation such as decreased enhancement, bowel wall thickening, and pericolonic stranding or edema. Upper endoscopy with eosinophilic infiltrate makes eosinophilic gastroenteritis more likely. Explanation of intermittent bleeding may be due to a mild episode of colon ischemia related to volume depletion, which may have resolved upon endoscopic assessment of the colon. There are no known cases of Shiga-toxin E.coli or Shigella causing eosinophilic gastroenteritis. Although these infections may cause leukocytosis, differential is significant for neutrophilic predominance.

Eosinophilia is diagnosed with a complete blood count and differential. The upper limit of normal in peripheral blood is 3% to 5%, with a corresponding absolute eosinophil count (AEC) of 350 to 500/mm³. Eosinophilia is subcategorized based on severity of AEC: mild (AEC from the upper limit of normal to 1500/mm³), moderate (AEC 1500 to 5000/mm³) or severe (AEC >5000/mm³). Primary eosinophilia is a hematologic disorder of the bone marrow and often neoplastic. Secondary eosinophilia is more common and is most often due to infection (especially parasitic), atopy, drug-induced eosinophilia, vasculitis, or rheumatologic diseases.

Symptomatology guides further workup and subsequent management. The first step in evaluating a patient with eosinophilia is to assess the potential of tissue infiltration and end organ damage. The most commonly affected organ systems are the integumentary, pulmonary, cardiac, and GI systems. Cardiac troponins are a sensitive, noninvasive marker in patients with hyperesinophilia and may be used to assess organ damage.

Eosinophilic gastroenteritis (EG) is a benign condition defined by GI symptoms, biopsy-proven eosinophilic infiltration into the digestive tract, and absence of reactive causes such as parasitic infection, allergies, et cetera, or infiltration into other organs. Interestingly, peripheral eosinophilia is not considered a diagnostic criteria and may be absent in 20% to 40% of patients. Eosinophilic gastroenteritis is rare, observed in 1 to 20 individuals in 100,000 with peak incidence in the third to fifth decade of life, with a small predominance in males.11

Presentation of EG varies depending on the area of digestive tract affected and patients may endorse abdominal pain, nausea, vomiting, diarrhea, melena, dysphagia, weight loss, and in advanced cases intestinal perforation or intussusception.12

Treatment of EG is centered on the use of glucocorticoids. Supportive therapies such as dietary modification in the form of low-fat, gluten-free, and diets free of known patient allergens can help alleviate symptoms as well. Immuno therapy to suppress cytokines known to mediate eosinophil release such as interleukin 4 (IL-4) and IL-5 have been applied in small clinical trials, but are not considered first-line treatment.13 In addition, there are case reports with positive response to montelukast, ketotifen, and sodium cromoglycate, but these are not well studied. Long-term prognosis and prevalence of patients with EG is limited, due to favorable response to treatment, but studies support that EG is not associated with malignancy.12

Diarrhea, especially bloody diarrhea, is a diagnosis most easily diagnosed and treated using an algorithmic approach with detailed history and physical exam. Similarly, eosinophilia is approached in the same way. Eosinophilic gastroenteritis is a rare, benign secondary cause of eosinophilia responsive to glucocorticoid treatment.

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REFERENCES


CORRECT ANSWERS 1. b. 2. c. 3. c. 4. a. 5. e.