CLINICAL PRACTICE
Clinical Reasoning

Mind the Base Rate: an Exercise in Clinical Reasoning

Paul B. Aronowitz, MD[1], Donna M. Williams, MD[2], Mark C. Henderson, MD[1], and Lisa G. Winston, MD[3]

[1]Department of Internal Medicine, University of California, Davis School of Medicine, Sacramento, CA, USA; [2]Department of Medicine, Wake Forest School of Medicine, Winston-Salem, NC, USA; [3]Division of Infectious Diseases, University of California, San Francisco School of Medicine, San Francisco, CA, USA.

KEY WORDS: base rate; typhoid fever; pulse fever dissociation; AIDS; chronic diarrhea.

J Gen Intern Med 34(9):1941–5
DOI: 10.1007/s11606-019-05053-z

In this series a clinician extemporaneously discusses the diagnostic approach (regular text) to sequentially presented clinical information (**bold**). Additional commentary on the diagnostic reasoning process (*italic*) is interspersed throughout the discussion.

A 37-year-old man presented to the Emergency Department with 1 month of generalized abdominal pain, fever, chills, and diarrhea. He also noted poor oral intake, anorexia, and an unintentional 20-pound weight loss. He reported four watery bowel movements per day without blood, up until 1 day prior to presentation. For the past 24 h, he had not had any bowel movements or flatus.

This middle-aged man presents with non-bloody diarrhea that is classified as "chronic," based on duration longer than 30 days. Acute diarrhea (less than 7 days) typically resolves without intervention and does not require extensive evaluation in immunocompetent individuals unless the presentation is severe. Since both fever and weight loss are alarm symptoms for chronic diarrhea, a workup is indicated to determine the etiology.

A thorough history should be obtained including stool characteristics, travel history, sexual history, history of animal exposures, employment, and recreational activities. This information, along with results of the physical examination, will guide further diagnostic testing.

Chronic diarrhea can be caused by infectious, inflammatory, malabsorptive, and functional disorders. The concomitant fevers are suggestive of infectious etiologies. An HIV test is recommended by the Centers for Disease Control and Prevention (CDC) for all persons aged 15–65 years; if positive, this would influence the diagnostic considerations in conjunction with the CD4 count. Viruses would be unlikely to cause chronic diarrhea in the absence of immunosuppression. In developed countries, bacteria are less common causes of chronic diarrhea, although *Clostridium difficile* infection occasionally presents in this fashion. Parasitic infections, including *Giardia lamblia*, *Cryptosporidium* species, *Cyclospora cayetanensis*, and *Cystoisospora belli*, commonly present with chronic diarrhea. *Entamoeba histolytica* should be considered given the patient's fever. Inflammatory bowel disease can also present with fever and diarrhea; Crohn's disease is more likely than ulcerative colitis to present with watery diarrhea. Following 1 month of diarrhea, the patient has not passed flatus for the last 24 h, indicating that he may have developed an ileus or bowel obstruction.

The discussant begins by generating a problem representation—a one-sentence description of the patient's case in abstract terms[1]—a middle-aged man with abdominal pain, chronic diarrhea, fever, and weight loss. She focuses on the diarrhea, particularly its duration, and refines the problem representation to include fever and weight loss, creating a preliminary differential diagnosis of mostly infectious etiologies common in younger patients. To avoid premature closure, she includes other important, easily overlooked diagnoses including HIV, *Clostridium difficile*, and inflammatory bowel disease—all which may present with fever, weight loss, and diarrhea.

The patient had not had nausea, vomiting, or contact with sick individuals. He had subjective fevers and chills, but did not own a thermometer so was unable to measure his temperature. He immigrated to the USA from Liberia 1 month earlier and was residing in California's Central Valley.

Since the patient immigrated from Liberia at about the time his symptoms began, several additional infections should be considered. Patients with malaria may present with diarrhea, cyclical fevers, and chills, although persistent abdominal pain and diarrhea would be unusual. Typhoid fever, caused by *Salmonella* Typhi or Paratyphi, classically causes fever, abdominal pain, and constipation, although diarrhea may also occur. Gastrointestinal tuberculosis may cause similar, chronic symptoms. Recent arrival from Liberia is a risk factor for *Entamoeba histolytica*, which can cause prolonged diarrhea and fever. Though the number of new HIV diagnoses in Liberia has fallen, HIV testing is still indicated.

Received October 5, 2018
Revised February 11, 2019
Accepted April 10, 2019
Published online July 3, 2019

The patient's residence in California's Central Valley raises the possibility of coccidioidomycosis, although this infection typically causes respiratory symptoms. Furthermore, this patient was apparently symptomatic at the time of immigration, suggesting he acquired the infection elsewhere. While inflammatory and malignant conditions are possible, infectious causes are more common and should be investigated first.

The discussant considers *diseases with higher base rates*[2] *in two particular regions in which the patient has recently resided—Liberia and California's Central Valley. Base rate refers to the prevalence of a given disease in a given population. In this case, malaria, tuberculosis, E. histolytica, typhoid fever, and HIV are all considered because of their high prevalence or base rate in Sub-Saharan Africa. None of these diagnoses are rejected outright because each could cause fever, diarrhea, and abdominal pain; ignoring these possibilities could lead to base rate error. This type of diagnostic error occurs when a diagnostician fails to consider the actual prevalence of a disease or base rate in a given population. While coccidioidomycosis has a substantial base rate in California, it was abandoned as a possibility because the clinical features (time course and lack of respiratory symptoms) were inconsistent with the diagnosis.*

The patient did not have significant medical, surgical, or family history. He was not taking any medications and did not use alcohol, tobacco, or other drugs. While living in Liberia, he had multiple female sexual partners and did not use condoms.

The patient's high-risk sexual behavior indicates a need for HIV testing. In patients with HIV, the risk of opportunistic infections and some cancers increases as the degree of immunosuppression worsens and CD4 count falls. In patients with HIV or AIDS, disseminated infections such as tuberculosis or histoplasmosis become more likely. Disseminated *Mycobacterium avium* complex infection may cause chronic diarrhea and fever in patients with HIV and advanced immunosuppression (CD4 cell counts less than 50/mm^3); cryptosporidiosis and microsporidiosis are additional opportunistic pathogens which can cause similar symptoms.

Noting the history of multiple sexual partners, the discussant broadens her differential diagnosis to include complications of AIDS. Although it is unknown whether the patient has HIV infection, the base rate in Sub-Saharan Africa is high enough to make it a serious consideration. Though not explicitly stated, the discussant has now generated a differential diagnosis for patients with fevers and chronic diarrhea upon arrival from Africa and a separate list of possible infections in HIV-infected persons. She sets up these lists knowing that additional information may emerge to determine which list is more relevant.

Physical examination revealed a temperature of 39.4 °C, blood pressure of 90/55 mmHg, and pulse rate of 80/min. He was cachectic but in no acute distress. Oropharyngeal exam revealed white plaques on the posterior tongue and hard palate that could be scraped off with a tongue depressor. Cardiac and pulmonary examinations were normal. His abdomen was distended with hypoactive bowel sounds, but nontender to palpation.

The physical examination reveals fever and oropharyngeal candidiasis which, along with cachexia, further raises concern for HIV infection. Thrush is more commonly observed in persons with HIV and CD4 counts below 200 cells/mm^3. Cachexia is also more frequent in advanced HIV infection. The laboratory HIV testing algorithm recommended by the CDC includes testing for both HIV-1 and HIV-2 antibodies. Although HIV-1 accounts for most cases of HIV infection worldwide, HIV-2 is a consideration in patients from West Africa.

The findings of diminished bowel sounds and abdominal distension may herald a bowel obstruction, which is also consistent with cessation of bowel movements and flatus following a prolonged bout of diarrhea. Abdominal imaging is indicated.

The discussant scrutinizes the physical exam to confirm or refute key elements of the history, such as subjective fevers in a recent immigrant who does not own a thermometer. She also continues to consider HIV infection. There are other conditions associated with oral candidiasis (steroid therapy, other immunocompromised states), but, because this patient has risk factors for HIV infection, the presence of oral candidiasis and cachexia keep her focused on that diagnosis.

A complete blood count revealed a white blood count of 3600/μL with 74% neutrophils, 18% lymphocytes, 7% monocytes, and 1% eosinophils and platelet count of 219,000/μL. Hemoglobin was 8.8 g/dL, hematocrit 27.8% with mean corpuscular volume 65 fL, and red cell distribution width 14.5%. Chemistry panel was notable for sodium 127 meq/L, potassium 2.5 meq/L, chloride 85 meq/L, bicarbonate 33 meq/L, alkaline phosphatase 55 μ/L, aspartate aminotransferase 72 μ/L, alanine aminotransferase 56 μ/L, total protein 6.7 g/dL, and albumin 2.7 g/dL. Chest radiography showed no infiltrates or effusions. The abdominal radiograph (below Figure 1) showed multiple dilated loops of large bowel without air-fluid levels or obvious obstruction.

The patient has a leukopenia with a low absolute lymphocyte count of 648 (3600 × 18%), which may be caused by infections, particularly HIV. He also has a microcytic anemia with a red cell distribution width in the upper range of normal. This finding is most commonly associated with thalassemia minor, particularly in someone of African descent. The chemistry panel demonstrates hyponatremia, hypokalemia, hypochloremia, and metabolic alkalosis—evidence of hypovolemia and poor oral intake.

The mildly elevated protein gap or "gamma gap" may represent a polyclonal or monoclonal gammopathy. A polyclonal gammopathy can be seen in inflammatory conditions,

Figure 1 Abdominal radiograph at time of presentation.

including chronic viral infections such as HIV or hepatitis C. Likewise, numerous conditions can cause mild elevations of aspartate aminotransferase and alanine aminotransferase, including chronic hepatitis B or C. Given the overall clinical picture, the low albumin is likely due to the underlying inflammatory response, but other causes such as protein-losing enteropathy should be considered.

The absence of free air on abdominal radiography and normal chest radiography points against a perforated viscus; however, plain radiographs are less sensitive than a CT scan for detecting perforation, bowel obstruction, and other intraabdominal pathology.

Twenty-four hours after admission, the patient's blood cultures became positive for Gram-negative rods.

The source of the Gram-negative bacteremia is likely the gastrointestinal tract. Although many Gram-negative bacilli cause diarrhea, the symptoms are typically acute and often resolve without treatment. The Gram-negative organisms causing chronic diarrhea include *Salmonella*, *Shigella*, *Campylobacter*, *Vibrio*, *Plesiomonas*, and *Aeromonas*. Enteroaggregative and enterotoxigenic *Escherichia coli* cause diarrhea in travelers but would not be expected to cause bacteremia or severe illness. Shiga toxin–producing *E. coli* can cause bloody diarrhea but bacteremia would be unusual.

Infection due to *Salmonella* is a possibility in this patient. Non-typhoidal *Salmonella* are much more likely to cause bacteremia in persons with HIV infection, and the bacteremia is often recurrent. With recent arrival from Liberia, infection due to *Salmonella* Typhi or *Salmonella* Paratyphi should also be considered. The patient's relative bradycardia with a heart rate of 80 beats per minute during a high fever—also known as pulse-temperature dissociation—is consistent with typhoid fever. Although rose spots were not described, these faint macules on the chest and abdomen may be difficult to see in dark-skinned individuals and are not present in the majority of patients.

A key piece of microbiologic data prompts the discussant to utilize a diagnostic schema,[3] a cognitive framework for approaching a symptom, physical finding, or laboratory result—in this case, Gram-negative rod bacteremia. After listing various possibilities, she tests hypotheses that would explain this bacteremia in the context of HIV infection. She returns to the physical examination to highlight the pulse rate, which is discordant with the patient's high fever—relative bradycardia[4]. This is an example of what an experienced clinician does when faced with a challenging diagnosis: she goes back to the basic clinical findings (here, the vital signs) and attempts to square them with Gram-negative rod bacteremia. While there are numerous causes such as beta-blocker therapy, which can obfuscate the normal pulse-temperature association[4], the discussant incisively applies this information to support her hypothesis of typhoid fever in the setting of HIV infection. Though relative bradycardia is neither sensitive nor

specific for typhoid fever, in this context, it is a key finding that helps the discussant narrow her diagnosis.

The Gram-negative rods were identified as *Salmonella* Typhi. The patient's HIV test returned positive and his CD4 cell count was 44/μL. He was treated with ceftriaxone and his symptoms resolved. He was started on antiretroviral HIV therapy and was discharged in good condition to follow-up in HIV Clinic.

COMMENTARY: CLINICAL REASONING

Clinical reasoning is a complex process that involves processing and sorting of numerous, sometimes conflicting details, driven by what the clinician believes to be their relative importance in making a diagnosis. An accurate diagnosis requires consideration of the patient's unique presentation or story, along with the likelihood of a disease based upon its base rate in a given population.[2] Failure to attend to the base rate of a disease in a given population, also known as "base rate neglect" or "base rate error", can lead even the most seasoned diagnostician to make a diagnostic error. For example, in considering the possible origins of shortness of breath in a middle-aged woman seeking care in a western country, the clinician may fail to consider the base rate of coronary artery disease in this population and miss the diagnosis of myocardial ischemia. As the clinician processes information, testing various hypotheses for the origins of a patient's problem, she assesses the prior likelihood of disease based upon the base rate of that disease in the population.

Early on in the discussion, with limited information about the patient, our discussant considered diseases with higher base rates in regions where the patient had recently lived (Sub-Saharan Africa and California's Central Valley). She began to consider HIV infection and typhoid fever, as both diseases have relatively high base rates in Sub-Saharan Africa and could cause these symptoms. Approximately 70% of the global burden of HIV disease is in Sub-Saharan Africa and two-thirds of new infections worldwide occur there each year.[5] Using an apparently simple construct, the discussant carefully contemplates the base rate of diseases of faraway places to construct her differential diagnosis, subsequently comparing and contrasting evidence for those illness scripts as more information becomes available. Utilizing her knowledge of base rates, she builds a solid initial foundation, upon which the remainder of the patient's story and diagnostic information rests.

COMMENTARY: TYPHOID FEVER

Typhoid fever is caused by the Gram-negative bacterium, *Salmonella* Typhi, and is usually contracted by fecal-oral ingestion of contaminated food or water in areas with poor sanitation. In the nineteenth century, typhoid fever was an important cause of morbidity and mortality in the USA and Europe due to overcrowded and unsanitary conditions. Today, there are a few hundred cases each year in the USA with 90% occurring in returned travelers.[6] Worldwide, there are approximately 21 million cases of typhoid fever with roughly 200,000 deaths.[7] The majority of cases occur in the developing world with the highest prevalence in southern Asia.

Once ingested, the bacterium invades the mucosal cells of the small intestine, then translocates to intestinal lymphoid follicles and into the reticuloendothelial system. The incubation period is 7 to 14 days and secondary sites of infection include the liver, spleen, bone marrow, gall bladder, and Peyer's patches of the terminal ileum.[8] Patients typically present with systemic symptoms including fever, chills, headache, malaise, diffuse abdominal pain, dry cough, and myalgia. In adults, constipation is more common than diarrhea, but not universally present. In HIV-infected patients, diarrhea is more common[8] than constipation (as was the case in this patient).

Physical examination may reveal relative bradycardia or pulse-temperature dissociation, but this is not a consistent finding. Other findings include hepatomegaly, splenomegaly, or diffuse abdominal tenderness. Rose spots, erythematous blanching macular lesions less than 5 mm in diameter on the trunk and occasionally extremities, occur in 5–30% of patients.[8] Complications typically occur in patients who have been ill for greater than 2 weeks, although HIV may have a protective effect against *Salmonella* Typhi bacteremia, thus leading to less severe disease.[9] Complications include intestinal perforation (1–3% of hospitalized patients), shock, and gastrointestinal bleeding (10% of patients). Case fatality rates vary from 2 to 30–50% in areas of Indonesia and New Guinea. Most deaths occur in children less than 1 year of age and in the elderly. Relapse occurs in 5–10% of patients, usually within a few weeks of completing antimicrobial therapy.[8]

Diagnosis of typhoid (enteric) fever can be challenging. High-volume (15 cc) blood cultures are reportedly positive in 60–80% of patients,[8] but the overall sensitivity of blood cultures is as low as 40%.[10] Stool cultures are positive in only 30% of patients with acute typhoid fever.[8] If there is high clinical suspicion, treatment with antibiotics while awaiting culture results is warranted.

Antibiotic resistance is a rising problem throughout the world. Southern Asia is a high-risk area for fluoroquinolone-resistant infection and there are increasing reports of multidrug-resistant *Salmonella* Typhi. Intravenous ceftriaxone is a reasonable empiric treatment for hospitalized travelers with suspected or confirmed typhoid fever while sensitivity testing is being performed.

The patient described was at risk for numerous opportunistic infections associated with advanced HIV disease, but was ultimately found to have a highly prevalent disease in the region in which he had previously dwelled.

CLINICAL TEACHING POINTS

1. The diagnosis of typhoid fever can be challenging. While not highly sensitive or specific, a finding of relative

bradycardia in the appropriate clinical context increases the likelihood of typhoid fever.[4] Rose spots are present in only 5–30% of patients and may be harder to identify in dark-skinned individuals.

2. Resistance to fluoroquinolones is emerging in *Salmonella* Typhi infections. Therapy with a third-generation cephalosporin such as ceftriaxone is recommended in ill, hospitalized patients with suspected or proven typhoid fever. If the isolate is susceptible, a fluoroquinolone is recommended due to faster response times and lower rates of treatment failure.[8]
3. Chronic carriage of *Salmonella* Typhi may occur following infection. In the USA, people in high-risk occupations such as food preparation, health care, and childcare are typically retested after treatment to ensure stool cultures are negative before being allowed to return to work or school (http://publichealth.lacounty.gov/acd/procs/b73/DiseaseChapters/B73TyphoidFeverAcute.pdf).

Corresponding Author: *Paul B. Aronowitz, MD; Department of Internal MedicineUniversity of California, Davis School of Medicine, Sacramento, CA, USA*

Compliance with Ethical Standards:

Conflict of Interest: *The authors report that Dr. William's spouse is a co-founder and partial owner of a medical device company called Certus Critical Care, Inc. At this time, the company has no devices on the market. All remaining authors declare that they do not have a conflict of interest.*

REFERENCES

1. **Bowen JL.** Educational strategies to promote clinical diagnostic reasoning. N Engl J Med. 2006;355(21):2217–2225.
2. **Maserejian NN, Lutfey KE, McKinlay JB.** Do physicians attend to base rates? Prevalence data and statistical discrimination in the diagnosis of coronary heart disease. Health Serv Res. 2009;44(6):1933–49.
3. **Minter DJ, Manesh R, Cornett P, Geha RM.** Putting schemas to the test: An exercise in clinical reasoning. J Gen Intern Med. 2018.
4. **Cunha BA.** The clinical significance of fever patterns. Infect Dis Clin N Am. 1996;10(1):33–44.
5. **Kharsany ABM, Karim QA.** HIV infection and AIDS in Sub-Saharan Africa: Current status, challenges and opportunities. Open AIDS J. 2016;10: 34–38.
6. **Date KA, et al.** Changing patterns in enteric fever incidence and increasing antibiotic resistance of enteric fever isolates in the United States, 2008-2012. Clin Infect Dis. 2016;63:322–329.
7. **Crump JA, Luby SP, Mintz ED.** The global burden of typhoid fever. Bull of World Heal Org. 2004;82(5):346–353.
8. **Parry CM, et al.** Typhoid fever. N Engl J Med. 2002;347(22):1770–1782.
9. **Crump JA, et al.** Invasive bacterial and fungal infections among hospitalized HIV-infected and HIV-uninfected adults and adolescents in Northern Tanzania. Clin Inf Dis. 2011;52(3):341–348.
10. **Gilman RH, Terminel M, Levine MM, Hernandez-Mendoza P, Hornick RB.** Relative efficacy of blood, urine, rectal swab, bone-marrow, and rose-spot cultures for recovery of Salmonella typhi in typhoid fever. Lancet. 1975;1:1211–1213.