CLINICAL PRACTICE

*Exercises in Clinical Reasoning***Solving Summer Fever in Early Pregnancy**

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A 37-year-old woman (G3P1) presented at 8 weeks gestation with 3 weeks of fever, cough and malaise.

Fever in early pregnancy is often due to common infections such as those due to respiratory viruses and urinary pathogens. Viral infections such as Epstein Barr Virus (EBV), Cytomegalovirus (CMV), or Human Immunodeficiency Virus (HIV) leading to mononucleosis or a mononucleosis-like illness are high on the differential diagnosis of this young patient with weeks of high fevers and nonspecific symptoms. Based on her pulmonary symptoms, bronchitis is possible, as is community-acquired pneumonia, likely with atypical pathogens such as *Mycoplasma pneumoniae* or *Chlamydia pneumoniae*.

However, in a pregnant patient, clinicians should always consider acute infections with implications for the fetus, including acute toxoplasmosis or CMV. In addition, physicians should recognize that some infections, such as Coccidiomycosis, can have a more severe course in pregnant patients.¹

Although infection is the most likely etiology, the differential diagnosis should also include malignancy and autoimmune disease.

When patients present with nonspecific symptoms such as fever and malaise, clinicians face the daunting task of narrowing a differential diagnosis from numerous possible etiologies to a more manageable list of conditions that should inform the next diagnostic and therapeutic steps. This narrowing often begins immediately through pattern recognition (i.e., non-analytic reasoning) upon hearing the chief complaint, as evidenced by the discussant's rapid enumeration of common causes of subacute fever in pregnancy. However, the discussant transitions to an analytic reasoning mode, when he

makes the metacognitive statement, “clinicians should always consider...”

Two interesting questions emerge from this shift. First, what precipitated it, and secondly, what is the specific analytic approach of the discussant? Unfortunately, the black box of the mind obscures a definitive answer to the former. However, the latter has been explored by scientific philosophers who have sought to understand scientific inquiry, otherwise known as the scientific method or hypothetico-deductive reasoning. The two most influential theories describing how scientists, including clinicians, infer the “truth,” or likelihood, of a hypothesis(es), are Bayesianism, which looks for the “likeliest” explanation, and inference to the best explanation (IBE), which seeks the “loveliest” explanation (i.e., the explanation that provides the greatest understanding).² While Bayesian reasoning focuses on pre-test odds and likelihood ratios, IBE focuses on the explanatory power of a hypothesis: “Given evidence E and candidate explanations $H_1, \dots, H_n$ of E, if H_i explains E better than any of the other hypotheses, infer that H_i is closer to the truth than any of the other hypotheses.”

In diagnosis, scientific inquiry is labeled diagnostic reasoning. From an IBE perspective, diagnostic reasoning might best be described as a search for the diagnosis(es) that best explains the “facts” of the case and then an inference that this explanation provides evidence that that diagnosis is correct, or “true.” Although the definition of IBE and this description of diagnosis might seem obvious, they beg the question: “How does a doctor decide what the best diagnostic explanation is?”, or alternatively, “What characteristics should the diagnosis that provides the ‘best explanation’ have?” Part of the answer resides in the notion that the fundamental psychological impulse of diagnosis is understanding, paired with the underlying belief that understanding of a disease process will lead to proper treatment of the patient. That is, the best explanation should maximize a clinician's understanding of the patient's problems.

The patient had initially presented to an outside hospital 2 weeks earlier, where she was noted to have a fever of 104 °F, sore throat, cervical lymphadenopathy, and mild right upper quadrant abdominal pain. While a heterophile antibody was negative, she was given a diagnosis of mononucleosis based on a positive EBV IgM, and discharged home. She presented to another clinic 1 week later with complaints of dry cough,

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fevers, and dark urine; she was diagnosed with presumed community-acquired pneumonia and began treatment with levofloxacin. She then took a pregnancy test, which was positive, so she stopped the levofloxacin after 3 days. She then presented to a clinic at this hospital with fever, chills, fatigue, weakness, and dark urine, for which she was referred to the Emergency Department.

While it is tempting to rely on diagnoses that a patient has already received, clinicians must closely examine the clinical scenario before anchoring on a diagnosis made by outside providers. Here, we will examine the evidence that led to a diagnosis of EBV.

The diagnosis of EBV infection, manifest clinically as infectious mononucleosis, is based on clinical presentation and heterophile antibody testing. The patient's sore throat, fatigue, and lymphadenopathy are consistent with a diagnosis of mononucleosis, but are also present in a number of other infectious processes. The findings of dark urine and right upper quadrant pain, though nonspecific, may suggest hemolytic anemia, which, although documented in case reports, is an uncommon manifestation of EBV.³⁻⁵

Heterophile antibodies produced in the setting of EBV infection are so named because they react with erythrocytes from non-human animals (sheep in the classical assay), although currently ELISA testing serves as the standard. These antibodies peak 2–5 weeks after the onset of symptoms, then decline rapidly. Because the sensitivity of heterophile antibody test is 96–100 %, the patient's negative heterophile test makes the diagnosis of EBV unlikely, but does not exclude it.⁶

Specific EBV serologies are indicated when there is a clinical suspicion for EBV infection but heterophile antibody testing is negative, as in this case.⁶ Current EBV serologic testing is based on assaying for three different parameters to distinguish acute from prior infection. These include viral capsid IgM (VCAM), viral capsid IgG (VCAG) and nuclear antibody (VNAB). The typical profile for acute infection is the presence of VCAM and VCAG, since VCAG is usually present by the time the clinical syndrome develops and testing is performed, while the typical profile for past infection is the presence of VCAG and VNAB. Our patient presented with isolated VCAM positivity. While this may represent very early infection, there is the potential for confounding by other viral infections, including parvovirus (not determined in this case), CMV (IgG positive), *Toxoplasma gondii* (sero-negative), rheumatoid factor, and in case reports, babesiosis.^{6,7} EBV viral load assay can be useful to distinguish between false positive serology and early acute infection.

Because EBV is an uncommon cause of hemolytic anemia and due to the negative heterophile antibody test, I would explore alternative diagnoses.

An examination of the discussant's language illuminates diagnosis as a search for the best explanation of a patient's symptoms: "The patient's sore throat, fatigue, and lymphadenopathy are consistent with a diagnosis of infectious mononucleosis but are also present in a number of other infectious

processes." *The natural predilection of most clinicians is towards IBE; this statement is an example of that tendency. Clinicians rarely explicitly discuss pre-test odds or likelihood ratios, probably in part because of a lack of facility with these concepts, and also because of a lack of easy accessibility to such numbers (e.g., the likelihood ratio of VCAM in acute EBV infection).*

How does the discussant proceed in determining the best explanation for the patient's presentation? First, he refuses to accept the diagnosis of EBV without additional proof, thereby avoiding diagnostic momentum, a tendency to indiscriminately accept a previous diagnosis without careful confirmation. He then argues that, given the absence of heterophile antibodies, better explanations for the patient's hemolytic anemia exist.

Her past medical history was notable for a spontaneous abortion in 2012 that was treated with dilation and curettage; she was HIV-negative at that time. She had been treated for latent tuberculosis with 9 months of isoniazid in 2006. Her medications included a multivitamin and vitamin D. She took no herbal supplements and had no drug allergies. She lived in a densely wooded suburb of Boston with her husband and son and worked as a materials science engineer. She denied any alcohol, tobacco, or illicit drug use. She was originally from Xian, China and had no recent travel other than to California. Her last travel to China was over 1 year prior to her presentation.

She is at high risk of tick-borne illness, given her residence in a wooded area of Massachusetts in which these infections are endemic. Tick-borne illnesses such as babesiosis could produce a hemolytic anemia and false positive VCAM serology, and should therefore be high on the differential. Infections, such as latent tuberculosis infection, malaria, and endemic fungi, are less likely, given her lack of exposure.

The specific finding of possible tick exposure triggers a new hypothesis, tick borne-illnesses, specifically babesiosis. Without additional data, the discussant is unable to determine whether it is the "best explanation" for the patient's findings, but clearly his focus has shifted to tick-borne illnesses. Although probably obvious, it bears stating that the best explanation focuses on causality. That is, clinicians seek a diagnosis that can cause a patient's clinical findings.

In the Emergency Department, the patient was febrile to 103 °F. Her pulse was 103 beats per minute, blood pressure 106/56 mmHg, and oxygen saturation was 92 % on room air. Her exam was notable for a nontoxic appearance, tachycardia with a 2/6 systolic murmur at the left upper sternal border, lungs that were clear to auscultation, and lower extremities that were without edema. Her abdomen was soft and nontender without hepatosplenomegaly, and her skin exam was unremarkable. There was no evidence of joint swelling or neurologic abnormality. Laboratory studies (Table 1) were notable for a sodium of 129 mmol/L, total bilirubin of 1.2 mg/dL with a direct bilirubin of 0.4 mg/dL, AST 126 U/L, ALT 55 U/L, alkaline phosphatase 236 mg/dL, haptoglobin <6 mg/dL. Complete

Table 1 Laboratory Values at Initial Presentation and on Admission

	Initial presentation	Admission
Sodium (mmol/L)	132	129
Potassium (mmol/L)	3.8	3.7
Chloride (mmol/L)	91	92
Bicarbonate (mmol/L)	22.5	26.7
Urea nitrogen (mg/dL)	10	13
Creatinine (mg/dL)	0.56	0.71
WBC count (thousands/mL)	4.7	4.9
%Neutrophils	39.0	52.0
% Bands	0	7.0
% Atypical cells	0	2.2
Hemoglobin (g/dL)	10.3	8.2
Hematocrit (%)	31.3	24.7
Platelets $\times 10^9$ /L	116	102
AST/SGOT (U/L)	153	126
ALT/SGPT (U/L)	94	55
Alkaline phosphatase (U/L)	276	236
Total bilirubin (mg/dL)	0.8	1.2
Direct bilirubin (mg/dL)	0.0	0.4
Beta-hCG (mIU/mL)	—	1224
PT-INR	—	1.1
Haptoglobin (mg/dL)	—	<6 (undetectable)
Reticulocyte count (%)	—	5.6

blood count revealed 4900 white blood cells/mL, and manual differential showed 52 % neutrophils, 7 % bands, 2 % atypical lymphocytes, and 2 % metamyelocytes, a hematocrit of 24 %, and platelets of 102×10^9 /L. Urinalysis was notable for 2+ protein and 3+ blood.

Her elevated total bilirubin with a normal direct bilirubin, low haptoglobin, and AST>ALT is diagnostic of hemolytic anemia. This constellation of thrombocytopenia, hemolytic anemia, and hepatitis, when combined with her subacute fever and dry cough, is concerning for an infectious etiology such as babesiosis, Lyme disease, Anaplasma, Ehrlichia, subacute bacterial endocarditis, atypical pneumonia, Bartonella, viral hepatitis, or malaria. Non-infectious considerations include thrombotic microangiopathy, Evans syndrome (autoimmune thrombocytopenia and hemolytic anemia), antiphospholipid antibody syndrome, and autoimmune hepatitis. The finding of hemolytic anemia in a patient from an area endemic for tick-borne illnesses should immediately raise the possibility of babesiosis.

Initial diagnostic evaluation should therefore include blood cultures, Hepatitis A and B serologies, and a chest x-ray. Peripheral blood smear should be performed urgently to evaluate for malaria, babesiosis, and thrombotic microangiopathy, all of which can be life-threatening if not recognized and treated early in the course of illness. Because there is a high suspicion for babesiosis, thin smear should also be performed.

Without conclusive data to confirm Babesiosis or exclude other potential diagnoses with adequate certainty, the discussant again considers multiple new possibilities based on the laboratory findings. IBE theory highlights the point that often the scientific or diagnostic question is relative to other hypotheses. It is not “Why X (e.g., Babesiosis)?” but rather “Why X not Y (e.g., EBV)?”² If there are no alternative hypotheses left, then the likelihood of the last diagnosis standing is even

greater. He seeks additional data/evidence to confirm or reject these hypotheses and determine the best explanation for the patient’s findings.⁸

A peripheral smear revealed intra-erythrocytic ring forms with an estimated parasite load of 3–5 %; no schistocytes were seen (Fig. 1).

Given her residence in an endemic area, the intracellular ring forms were thought to be due to infection with *Babesia microti*. It can be challenging to distinguish the ring forms of *Babesia microti* from the ring forms of *Plasmodium falciparum*; despite the superficial similarity, there are several features that can be used to differentiate between them. These include most classically the presence of the “Maltese cross,” a tetrad of intracellular merozoites, which is pathognomonic of babesia. Other features that may suggest babesia are the presence of extra-erythrocytic parasites in the setting of high parasitemia, the absence of hemozoin (a brownish pigment) in the ring forms, and the absence of schizonts and gametocytes (forms which are unique to the Plasmodium life cycle).⁹

The intra-erythrocytic ring forms and lack of a travel history, which are inconsistent with all the other diseases mentioned on his differential diagnosis, enable the discussant to reject the numerous hypotheses previously mentioned and confirm babesiosis as the best explanation. IBE suggests five characteristics that make a hypothesis or diagnosis a good explanation. These characteristics are scope, simplification, precision, mechanism, and unification. Good diagnoses simplify the myriad of clinical findings, provide more precise descriptions, illuminate mechanisms, and unify disparate elements of the presentation. The diagnosis of babesiosis fulfills many of these criteria.

Her beta-hCG was 1224 mIU/mL and a transvaginal ultrasound revealed an endometrial stripe of 7 mm, but no visualized intrauterine or ectopic pregnancy. The patient stated that while her pregnancy was unexpected, she did want to retain the pregnancy.

The treatment of babesiosis, especially the initial choice of antibiotics, must account for the finding of a beta-hCG of 1224 mIU/mL. First we must consider whether the absence of intrauterine pregnancy on transvaginal ultrasound can exclude the possibility of an intrauterine pregnancy in a patient with beta-HCG of 1224 mIU/mL. In a woman with no intrauterine fluid collection and normal adnexa on ultrasound, if the beta-hCG is >2000 mIU/mL, the likelihood of a viable intrauterine pregnancy is 2 %; if the beta-hCG is >3000 mIU/mL, this likelihood decreases to 0.5 %.¹⁰ This data suggests that a viable intrauterine pregnancy cannot be excluded on the basis of a beta-hCG <3000 in a patient in whom transvaginal ultrasound does not visualize an intrauterine pregnancy. For this reason, we must treat our patient as if she is pregnant in order to avoid harming a viable fetus.

Next, we must address the severity of the patient’s illness in order to choose an appropriate therapy. This patient with an intact spleen appears to have mild to moderate degree of illness, based on a lack of heart failure symptoms, diffuse

Figure 1 Peripheral blood smear showing intra-erythrocyte ring forms consistent with the diagnosis of *Babesia microti* infection (a 100× magnification, b 400× magnification).

intravascular coagulation, or adult respiratory distress syndrome and parasitemia <10 %. Studies reveal that a combination of atovaquone and azithromycin is equivalent to and has fewer side effects than treatment with clindamycin and quinine in patients with mild to moderate babesiosis.¹¹ However, because this patient may be pregnant, we must balance the risks of each treatment regimen's teratogenicity with its ability to cross the placenta and treat babesiosis that may be present in the fetus. Each treatment regimen carries a risk of teratogenicity. Atovaquone is pregnancy category C, and azithromycin is category B; neither drug is thought to cross the placenta. Clindamycin and quinine are both category C, but cross the placenta.¹² In one case report, a patient in the third trimester of pregnancy was successfully treated for babesiosis with clindamycin and quinine, because both drugs cross the placenta and because quinine has been used worldwide to treat malaria in pregnancy.¹²

In the majority of patients infected with babesiosis, we also treat with doxycycline while awaiting the results of the remainder of their tick-borne illness studies in order to treat possible co-infection with *Borellia*, *Ehrlichia*, or *Anaplasma*. Doxycycline, however, is pregnancy category D. Such patients can be given amoxicillin to empirically treat Lyme disease if suspicion is high.

She should receive a 10-day course of oral clindamycin and quinine and should be empirically started on amoxicillin while awaiting the results of her Lyme serology.

Using the analogy of diagnostic reasoning, therapeutic reasoning might be called, "inference to the best treatment." The "best treatment" is one that minimizes harms while maximizing benefits within the context of patient preferences. The discussant applies this approach by choosing an antibiotic regimen that does the least harm possible to both mother and fetus while maximizing the benefit.

The patient was started on oral clindamycin and quinine. Her beta-HCG continued to rise, but did so more slowly than would be expected for a normal intrauterine pregnancy. She underwent a repeat transvaginal ultrasound several days after admission which revealed a gestational sac in the right Fallopian tube. She then underwent an uncomplicated right salpingectomy.

Following the diagnosis of ectopic pregnancy, the babesiosis regimen should be changed to the less toxic regimen of azithromycin and atovaquone to complete a 10-day course and her Lyme disease regimen should be changed to 21 days of doxycycline.

DISCUSSION

Philosophers have struggled for millennia to explain how human beings "know" something to be true. Physicians are no different in their quest to prove that a diagnosis is "true" or accurate. Bayesianism and IBE have emerged as two theories

that try to describe the process of the scientific method. Studies have shown that physicians do not naturally use Bayesian reasoning, even when provided necessary data. Where Bayesianism fails, IBE provides a powerful description of scientific inquiry generally, and diagnostic reasoning specifically. Physicians seek to understand a patient's clinical findings by finding a disease(s) that best explains the findings, including predicting the results of additional testing.¹³

The explicit recognition of the diagnostic reasoning process as a search for understanding may have implications on learning and teaching medicine. Studies have highlighted that basic science plays an important role in diagnosis even for experienced clinicians. As biomedical knowledge continues to grow exponentially and external factors drive the shortening of the pre-clinical years and even medical school training as a whole, the pressure builds to short change mechanisms of disease and pathophysiology that allow clinicians to explain disease manifestations. Medical educators would be prudent to consider these potential, unforeseen costs as they contemplate the ideal philosophy and means of training the 21st century physician.

CLINICAL TEACHING POINTS

- Babesiosis produces hemolytic anemia, thrombocytopenia, and mild hepatitis, constitutional symptoms and a dry cough.
- A definitive diagnosis of babesiosis can be made with a simple peripheral blood smear, but thin smears should be done for confirmation.
- Clindamycin and quinine cross the placenta and may prevent fetal complications of babesiosis without a substantially increased risk of teratogenicity.

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