Clinical Practice: Exercises in Clinical Reasoning

Complementary Medicine

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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 (*italics*) is integrated throughout the discussion.

An 86-year-old man presented to the emergency room after he tripped and fell down the stairs at home. he was found to have a temperature of 39.2 °C.

While there are multiple reasons for patients to fall, including muscular weakness, the most concerning feature is the fever. In a febrile, elderly patient, I would initially consider infection as the most likely cause, but rheumatologic disorders and malignancy are also possible. As the differential diagnosis is very broad, it is reasonable to prioritize common infectious causes of fever, such as pneumonia and urinary tract infection. Infections in the elderly may cause fatigue, weakness, and volume depletion with orthostatic hypotension, leading to falls.

The discussant's first step is to define the problem. The initial framing of a patient's presentation, or problem representation, will have a significant impact on hypothesis generation. As demonstrated by the discussant, framing the problem as "a fall in a febrile elderly person" leads to three broad etiologic hypotheses, ranked by probability. These hypotheses subsequently serve as the templates upon which he looks for additional information in an attempt to explain the patient's clinical presentation.

The patient had no complaints, but reported decreased appetite over the past week. He denied fevers, chills, sweats, and weight loss. Review of systems was otherwise negative.

The lack of specific symptoms such as cough, sputum production or abnormal urination makes pneumonia and urinary tract infection less likely. However, elderly patients often have atypical presentations of infection. They are also more likely to have certain rheumatologic disorders and malignancy. At this point, I would like to know more about his past medical history, medications, and social history.

One year earlier, the patient underwent coronary artery bypass grafting and aortic valve replacement with a bioprosthetic valve. There was no recent history of travel or dental work. He had a remote history of alcohol abuse, mild chronic kidney disease, and a remote history of a malignant melanoma removal without adjunctive therapy. The patient did not smoke or use injection drugs. Medications included metoprolol, furosemide, and aspirin.

This history offers additional clues as to the etiology for fever. The prosthetic aortic valve puts him at higher risk for endocarditis. The lack of symptoms, such as rigors or presyncope, makes acute infective endocarditis (most often due to *Staphylococcus aureus*) less likely than a more indolent or subacute bacterial endocarditis. It would be important to confirm that the alcohol abuse is in fact remote, since active alcohol use can cause immunosuppression. Without a history of diabetes mellitus or hypertension, the renal insufficiency may be linked to fever by a malignancy such as multiple myeloma with a secondary infection due to the accompanying immunosuppression. Although melanoma does not commonly cause fever, tumor recurrence must always be considered in any patient with a history of malignancy. While the lack of tobacco use puts the patient at lower risk for lung cancer, it does not necessarily lower malignancy overall on the differential. While dental procedures may cause transient bacteremia, the overall association with endocarditis is not as great as once thought. None of his medications are particularly concerning for drug fever.

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The discussant uses new epidemiological data to further characterize the problem. Details of the past medical history trigger recall (often unconscious) of diseases that fit the problem representation of the febrile patient. Still operating within the three categorical hypotheses for fever, he considers the prior cardiac valve surgery as the most important historical finding, as it raises the probability of endocarditis, a “can’t miss” diagnosis. The discussant’s consideration of multiple myeloma demonstrates the complex organization of knowledge that develops with expertise. He considers immunosuppression as a risk factor for fever and then connects the pattern of chronic kidney disease, advanced age, and immunosuppression to multiple myeloma. Clinical reasoning is a complex, iterative process in which the discussant attempts to shape the patient’s past medical history and emerging clinical findings into a coherent narrative, or problem representation, which matches the story of a specific disease (i.e. “illness script”).

On physical examination, the patient was in no acute distress. The patient’s vital signs were: temperature 39.2 °C, heart rate 92 beats per minute, blood pressure 112/36 mmHg without orthostatic hypotension. The cardiac examination was notable for a 2/6 systolic ejection murmur along the left sternal border. The lungs were clear. The abdomen was soft, non-tender, and non-distended. There was no lymphadenopathy, skin lesions, edema or joint abnormalities. The remainder of the exam was normal.

The exam is notable for several pertinent negative findings. The normal pulmonary exam makes pneumonia less likely. The systolic murmur along the left sternal border likely represents a flow murmur or possibly calcific aortic stenosis in an elderly patient, although the latter is typically best heard at the right upper sternal border. I would also consider the possibility of tricuspid regurgitation secondary to endocarditis, although this murmur is usually holosystolic. The lack of a diastolic murmur does not reduce the likelihood of endocarditis, but if a diastolic murmur suggesting aortic insufficiency were present, the suspicion for endocarditis would be higher. Nevertheless, the systolic murmur in the presence of fever keeps the suspicion for endocarditis high.

The discussant describes how negative physical exam findings can refine the problem representation, leading to reprioritization of the differential diagnosis. He uses pathophysiological, or causal, reasoning to explain how the presence of the murmur could support the diagnostic hypothesis of endocarditis, but notes that this patient’s findings are not classic for this disease. This is an effort to avoid premature closure.

A complete blood count revealed a white blood cell count of 11,800 cells/mm³ with a normal differential and a hematocrit of 35 %. Chemistry was notable for a creatinine level of 2.2 mg/dl (1.8 mg/dl 3 months prior). Glucose, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase were within normal limits. A chest x-ray was normal. An electrocardiogram revealed an old first-degree atrioventricular block (AV) block, but no other abnormalities.

The mildly elevated white blood cell count is nonspecific. The mild anemia may represent the anemia of chronic inflammation, which is associated with various malignancies. The elevated creatinine again makes me think of multiple myeloma, which can cause renal insufficiency and predispose the patient to infection. The normal chest x-ray excludes pneumonia. In light of the elevated creatinine, I would like to see the patient’s urinalysis.

Thus far, this case has been characterized by its nonspecific nature. The discussant has used a combination of nonanalytic reasoning (e.g. pattern recognition) and analytic reasoning (e.g. hypothesis testing), which has been described as the dual process theory of reasoning.¹ The pattern of anemia, renal insufficiency, and fever in an elderly person triggered consideration of multiple myeloma. Attempting to square the patient’s presentation with this hypothesis, he now views the elevated creatinine as a potential pivotal finding. In challenging cases, discussants often seek and utilize key findings to attempt to make the diagnosis.

A urinalysis was notable for 2+ protein, 1+ blood, and no white blood cells. Microscopic evaluation of urinary sediment revealed two red blood cell casts per high power field.

This is the first piece of information that significantly narrows the differential diagnosis. Red blood cell casts are very specific for glomerulonephritis (GN) and will guide my diagnostic approach. GN can generally be classified as resulting from systemic diseases with renal manifestations, or from primary renal diseases. I would consider vasculitides, including granulomatosis with polyangiitis (formerly Wegener’s granulomatosis), microscopic polyangiitis, and Goodpasture’s Disease. Systemic lupus erythematosus is a common autoimmune disease that can present with fever and GN. However, we would expect accompanying skin or pulmonary findings with most of these diseases. Post-infectious GN should also be considered, but the patient reports no antecedent upper respiratory tract infection. Membranoproliferative GN is

another possibility, although he does not appear to have typical risk factors such as hepatitis C infection. Often the mechanism for glomerular injury is immune complex deposition, which can also be seen in endocarditis-associated GN. Therefore, endocarditis is still the leading diagnosis, particularly because it has potentially fatal consequences if untreated. Serum complement levels may help distinguish between the various etiologies of GN. I would also obtain serial blood cultures and an echocardiogram to evaluate for endocarditis.

The specificity of the RBC casts leads to a profound shift in the diagnostic problem representation. The discussant now discards broad categorical hypotheses and focuses on specific diagnoses. His reasoning again demonstrates the iterative nature of diagnosis as new data trigger further hypothesis generation and refinement. The process reveals high-level knowledge organization. Rather than rambling off causes of glomerulonephritis, the discussant organizes the diseases via schemas (e.g. systemic versus primary renal diseases). These schemas distill large amounts of knowledge into categories, enhancing one's ability to recall key diagnostic information. The discussant now actively compares and contrasts several GN illness scripts with his problem representation to establish a diagnosis.

Blood cultures were drawn and vancomycin and gentamicin were started for presumed endocarditis. A transthoracic echocardiogram (TTE) showed mild aortic stenosis with no evidence of valvular vegetations. Serum complement levels were: C3 95.7 mg/dL (nl 71–184 mg/dL) and C4 20.8 (9.4–51.4 mg/dL).

I agree with empiric antibiotics for possible endocarditis, even though we don't yet have a definitive diagnosis. Typically, serum complement levels are low in cases of GN associated with endocarditis, as one mechanism of glomerular injury is immune complex deposition and activation of the complement cascade. The sensitivity of TTE for endocarditis is approximately 50 % compared to the 95 % sensitivity of TEE. Therefore, a normal TTE does not rule out endocarditis. However, the combination of normal complements and absence of a vegetation by TTE certainly raises questions about the diagnosis of endocarditis.

The discussant once again combines pattern recognition (e.g. "complement levels are low...") and analytic reasoning by implicitly invoking the concepts of pre-test and post-test probability, sensitivity, specificity, and threshold to treat. Citing the limited sensitivity of TTE, he implies that the

post-test probability is not low enough to withhold treatment, because of the high pre-test probability and risk for morbidity or mortality without treatment.

As concern for endocarditis remained, a transesophageal echocardiogram (TEE) was performed, showing no vegetations. On the third hospital day, blood cultures grew Gram-negative rods, possibly an anaerobic species. Gentamicin and vancomycin were stopped; ceftriaxone and metronidazole were begun.

Because clinical suspicion for bacterial endocarditis remained, the appropriate action was to pursue a more sensitive test, one with potential to lower the probability of disease below the threshold to treat. Bacterial endocarditis is usually caused by *Staphylococcus* or *Streptococcus* species, and atypical organisms include the HACEK bacteria. A negative TEE (a highly sensitive test for endocarditis) and bacteremia with an organism not usually found in endocarditis effectively rules out that diagnosis. The differential diagnosis must be broadened to search for other causes of Gram-negative bacteremia and normal complement GN.

The discussant concludes that a negative TEE and unusual blood culture results lower the likelihood for endocarditis below his threshold for treatment or further testing. He has restated the problem representation with great precision as: a patient with Gram-negative bacteremia and normal complement glomerulonephritis. Redefining the problem representation as accurately and specifically as possible allows the clinician to readily search for conditions that explain both findings even if s/he does not recall the complete differential diagnosis.

The next day, *Bacteroides fragilis* was identified from the blood cultures.

Bacteroides fragilis is a very rare cause of endocarditis. At this point, the series of negative testing in conjunction with this organism growing in culture eliminates this diagnosis. Now we need to explain why this patient has *Bacteroides* bacteremia. Anaerobic bacteria such as *Bacteroides* are commonly found in the lower gastrointestinal tract, so abdominal imaging would be the next step to identify a possible source.

The discussant now considers an abdominal source of bacteremia as a unifying diagnosis for the patient's fever and GN based on the principle of Occam's Razor—a single, parsimonious explanation for a patient's clinical syndrome is preferred over multiple different explanations.

An abdominal computed tomography (CT) scan showed a 5 cm mass in the right lobe of the liver concerning for abscess. Aspiration revealed purulent material and cultures subsequently grew *E. Coli*. A percutaneous drain was placed, antibiotics were continued, and the patient recovered.

Three weeks later, a colonoscopy revealed left-sided diverticulosis. Source of the hepatic abscess was believed to be a polymicrobial bacteremia associated with an inflamed diverticulum. The broad spectrum antibiotics were felt to be the explanation for the discrepant blood and abscess cultures.

Visceral abscess is the unifying diagnosis for this elderly man with fever, anorexia, and Gram-negative bacteremia. Although it is unlikely that the discussant suspected hepatic abscess, he recognized the positive blood cultures as a key finding or leverage point and sought to discover its source with further testing.

DISCUSSION

Clinicians face a significant biological constraint when solving complex cases: working memory has a limited capacity.² The discussant’s approach to the differential diagnosis of fever and GN provides a case study of how clinicians circumvent this obstacle. In considering the differential diagnosis for fever, the discussant chose three broad etiologic categories rather than specific diseases. In doing so, only three “slots” of working memory were occupied, leaving room for additional processing, a process similar to that of a computer’s random access memory or RAM. In considering the differential diagnosis for GN, the discussant used schemas such as systemic versus primary renal disease and normal versus low serum complements. Studies of clinical reasoning suggest that expertise derives from both knowledge and knowledge organization.³ Experts learn via experience and study how to minimize the burdens on working memory by organizing their knowledge into meaningful “chunks”, enhancing their ability to make accurate diagnoses.

This case also illustrates two essential elements of clinical reasoning: 1) the characterization of the diagnostic problem representation, and 2) the combined use of analytic and nonanalytic reasoning.⁴ The discussant’s definition of the problem evolves from an initially broad statement (i.e. elderly patient with a fever) to a very specific one (normal complement glomerulonephritis and *B. fragilis* bacteremia). This problem context and refinement of the differential diagnosis can change rapidly as new information emerges and different illness scripts shift from the forefront to the background (and vice-versa).⁵ Certain key findings trigger diagnostic considerations through nonanalytic reasoning or

pattern recognition (i.e. *B. fragilis* is a gastrointestinal organism), and serve as leverage points in the iterative process of clinical diagnosis. However, in complex cases, analytic approaches (e.g. diagnostic hypothesis testing) often supplement nonanalytic reasoning. In this case, the discussant continued to pursue the possibility of endocarditis, recognizing that a negative TTE did not rule out the disease given the initially high pre-test probability. However, serial Bayesian analysis (normal complements, normal TTE and TEE, Gram-negative bacteremia) lowered the post-test probability below the threshold to test. This dynamic interchange between analytic and nonanalytic cognitive processes is termed the dual process theory of reasoning.¹ The complementary relationship between analytic and nonanalytic reasoning enhances our ability to solve challenging clinical problems.

CLINICAL TEACHING POINTS

1. The pathognomonic finding of GN is the presence of red blood cell casts or dysmorphic red blood cells on microscopy of urine sediment. GN may be classified by whether it is due to primary renal disease or a manifestation of systemic disease and by serum complement levels (Table 1).^{6–8} This classification scheme allows for probabilistic reasoning (e.g. lack of low complements makes endocarditis less likely).
2. Serum complements are low in 60–90 % of cases of endocarditis-related GN. The likelihood of hypo-complementemia depends on the acuity and diffuseness of the glomerular lesion.⁹
3. Pyogenic liver abscess is a rare cause of GN.^{10,11} Clinical findings include: chills, night sweats, vomiting, weight loss, right upper quadrant tenderness, hepatomegaly, elevated right hemidiaphragm, pleural effusion, and abnormal hepatic enzymes.¹² Complement levels in visceral abscess related GN are typically though not always normal.^{7,8,13}

Table 1. Classification of Glomerulonephritis

	Systemic disease	Primary renal disease
Normal serum complement	<ul style="list-style-type: none">• Granulomatosis with Polyangiitis• Hypersensitivity vasculitis• Henoch-Schoenlein purpura• Goodpasture’s Syndrome• Visceral abscess	<ul style="list-style-type: none">• IgA-Nephropathy• Idiopathic rapidly progressive GN
Low serum complement	<ul style="list-style-type: none">• Systemic Lupus Erythematosus (SLE)• Cryoglobulinemia• Endocarditis• “Shunt” nephritis	<ul style="list-style-type: none">• Post-infectious GN• Membranoproliferative GN

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