Introduction:

Welcome to CUGH's bi-weekly clinical case-series, "Reasoning without Resources," by Prof. Gerald Paccione of the Albert Einstein College of Medicine. These teaching cases are based on Prof. Paccione's decades of teaching experience on the medical wards of Kisoro District Hospital in Uganda. They are designed for those practicing in low resource settings, Medicine and Family Medicine residents, and senior medical students interested in clinical global health. Each case is presented in two parts. First comes a case vignette (presenting symptoms, history, basic lab and physical exam findings) along with 6-10 discussion questions that direct clinical reasoning and/or highlight diagnostic issues. Two weeks later CUGH will post detailed instructors notes for the case along with a new case vignette. For a more detailed overview to this case-series and the teaching philosophy behind it, see Introduction to "Reasoning without Resources". Comments or question may be sent to Prof. Paccione at: gpaccion@montefiore.org

Note: If you would like to be notified when a new case is posted (along with instructor notes for the previous one), send your e-mail to Jillian Morgan at jmorgan@CUGH.org.

About the Author:

Dr. Gerald Paccione is a Professor of Clinical Medicine at the Albert Einstein College of Medicine in the Bronx, New York. His career has centered on medical education for the past 35 years – as a residency Program Director in Primary Care and Social Internal Medicine at Montefiore Hospital, and director of the Global Health Education Alliance at the school. He has served on the Boards of Directors of Doctors for Global Health, Doctors of the World USA, and the Global Health Education Consortium. Dr. Paccione spends about 3 months a year in Uganda working on the Medicine wards of Kisoro District Hospital where he draws examples for the case studies.

Gerald Paccione, MD

Professor of Clinical Medicine

Albert Einstein College of Medicine

110 East 210 St., Bronx, NY 10467

Tel: 718-920-6738

Email: gpaccion@montefiore.org

Case 37 – Farmer with Fever and Back Pain

A 31 year old male farmer who grows corn and potatoes and tends cattle presents with fevers for 2 weeks with back pain. His wife and 2 of his 3 kids have remained well over this period, but his 12 year old son recently had a "bad fever" that caused him to miss a lot of school followed by pain and loss of vision in his right eye.

Over the past 5 months, he has been treated for "malaria" 3 times, more frequently than in the past. The fever comes on especially at night, accompanied by chills, sweats, headache and fatigue which usually last 1-2 weeks. He takes various anti-malarials which sometimes work, but at other times the fever persists for days after the treatment finishes and then improves when he takes other antibiotics he gets in town. Between episodes of malaria he feels generally well, but more fatigued than usual and he's lost weight. The last episode was associated with dry cough, abdominal pain and diarrhea. Two weeks ago the fever began again, and 4 days later was associated for the first time with lower back pain that gradually progressed, eventually stopped him from working, and was worse when lying down, affecting his sleep. Last night he couldn't sleep at all, was wet with sweat, and with assistance from his brothers, came to the hospital today. He has had intermittent headache, but no cough, abdominal pain or diarrhea in the past 2 weeks of illness. An HIV test was negative 2 months ago.

PE: In no acute distress, but uncomfortable, holding his back
BP 110/82 HR 100 T 101 p.o. RR 22
conjunctiva: normal, without icterus or petechiae; fundi : benign, no Roth spots or papilledema
skin/nails: no petechiae (including axilla) or splinter hemorrhages; mouth: no thrush
neck: supple; diffuse 1-2 cm lymphadenopathy in neck, axilla, groin
lungs: clear
abdomen: liver ↓ 2 cm non-tender, span 12 cm to percussion; spleen ↓3 cm soft, non-tender
heart: PMI 5TH ICS/MCL; S1, S2 split; Gr 2/6, early SEM upper left sternal border without radiation
musculo-skeletal: all peripheral joints normal with full range of motion;
spine: cannot bend lower spine without pain but nearly full ROM;
percussion tenderness with reflex hammer, L3-L4
palpation/pressure over SI joints, normal
straight-leg raising causes back pain at 60 degrees, no leg pain
neurologic: mental status, motor, sensory, cerebellar, reflexes intact;
gait slow but evenly distributed, holding lower back.

1. **What is the "frame" in this case (i.e. key clinical features the final diagnosis must be consistent with)?**

   - *recurrent fevers, without focality for months*
   - *chronic, over 5 months, with weight loss*
   - *young male, farmer/herder*
   - *diffuse LAD, splenomegaly-soft*
   - *lower back pain with lumbar tenderness recently*
   - *(? son with febrile illness with loss of vision?)*

   (Parentheses indicate clinical features that the final diagnosis <u>may</u> be consistent with or related to, but not necessarily.)

2. **What is the diagnostic significance of the various features of the history and physical exam of the <u>back pain</u> in this patient?**

   - *History:*
     - *insidious onset of back pain with preceding fever: the <u>insidious onset</u> is most consistent with a mass or infection, the <u>fever</u> suggests an infection, and the discrete <u>location</u> of the pain, a bacterial etiology;*
     - *pain worse when lying down: the common causes of back pain such as disc herniation or osteoarthritis are related to nerve impingement or arthritis, and are relieved by rest. However, rest often exacerbates pain originating in <u>bone</u> due to relaxation of the paraspinal muscles which splint and support the spine, putting more pressure on the diseased bone when they're relaxed. Thus patients with bone pain from infection or cancer often complain of inability to sleep due to pain.*

   - *Physical Exam: point tenderness to percussion over L3-4 confirms the suspicion of infection (osteomyelitis) or mass lesion of the spine as the cause of the pain.*

3. **What is the differential diagnosis of the prolonged fever in this patient and what are the clinical "pros and cons" for each disease suggested?**
   What is the *most likely* diagnosis?

   - *Subacute bacterial endocarditis (SBE), partially treated. Silent rheumatic heart disease, without cardiac symptoms but with scarred heart valves that can serve as the nidus of infection, is very common in Africa (~2% of school-age children by echo), and dental hygiene is poor. SBE must be considered in every chronic febrile illness. SBE would explain the chronicity of the illness, past transient responses to antibiotics, splenomegaly and present spinal pain (from septic emboli). However, the apparent responses (for weeks) after only short courses of oral therapy would be unexpected, the 5 month illness is long*

(but possible) for inadequately treated disease, and after 5 months there are no cardiac murmurs of valvular regurgitation or peripheral stigmata of endocarditis.

- *Tuberculosis: TB, an intracellular granuloma-inducing pathogen must be considered in every chronic febrile illness in Africa – miliary in this case without cough or focal symptoms until very recently. Miliary TB would explain the weight loss, fever, splenomegaly, lymphadenopathy, and conceivably the (more recent) spinal focality. BUT, the asymptomatic remissions are inconsistent with this diagnosis, there's no overt evidence of HIV disease (commonly found in miliary or extrapulmonary TB), and the marked back pain as the sole focal manifestation of miliary disease, and then its progression over 10 days, would be most unusual.*

- *Typhoid Fever: Another prominent treatable cause of chronic fever in the tropics due to an intracellular organism, Salmonella typhi is a gram (-) rod that resides in the reticulo-endothelial system. Typhoid can cause chronic fever, weight loss, lymphadenopathy, splenomegaly, and (rarely) spinal abscesses. However, the fever course is usually persistent, not spiking and relapsing, the disease runs its course in 3-4 weeks, and is usually more severe than described here. Although relapses occur in 10%, they are milder, usually single, and non-focal.*

- *Relapsing Fever (RF), a disease caused by the spirochete borrelia, carried and transmitted by either lice or ticks (in this non-epidemic situation, it would be ticks) comes to mind because of the cycling recurrent fevers. BUT, in this patient the episodes of fever and the intervals between them last too long (in RF, fevers last only 2-4 days, and come at less than 2 week intervals); they're too insidious and mild (without petechiae, conjunctival suffusion, or severe myalgia), and borrelia do not cause focal spinal disease.*

- *Malaria: Multiple discrete bouts of malaria might explain the febrile picture here and the splenomegaly, but cannot explain the focal spinal symptoms, lymphadenopathy, the erratic response to past treatments, or the unusual susceptibility at his age to this common (immunity-associated) parasitic disease, especially while his family is unaffected.*

- *Spinal osteomyelitis, Staph aureus: The physical exam is consistent with an osteomyelitis of the spine (see answer to question 2), and Staph aureus is a common cause of spinal osteomyelitis. However, since treatment must be organism specific and prolonged, and there are no cultures available in district hospitals, clinical diagnosis must be more precise – not only the pathologic process but the likely organism causing it.*
  S. aureus usually occurs in older, often-debilitated hosts, and would not explain the long course of repeated febrile episodes nor the chronic weight loss, splenomegaly, or lymphadenopathy. Attempting to explain these latter phenomena by "Staph endocarditis" which then seeded the spine ignores the 5 month duration of illness, too long for an aggressive infection like Staph Aureus endocarditis.

- ***Brucella**: This patient vignette describes a classic case of Brucellosis, a disease with protean manifestations, both acute and chronic presentations, and potentially, focal involvement of every organ system.*

  Brucella is a gram Θ coccobacillus that lives in the reticuloendothelial system of domesticated animals, survives up to 2 months in soft cheeses made from goat's or sheep's

milk and 6 months in damp cool soil, and is stable as an aerosol. Transmission occurs through consumption of unpasteurized milk or contact with infected animals: thus farmers, herders, slaughterhouse employees, etc. are at risk. The true global prevalence is unknown due to inadequate diagnostic capacity and reporting of a non-specific illness that often remits without therapy. The true incidence is probably over 10-20 times that reported in most countries. It's a major public health problem in the mid-East, North Africa, western, central and southern Asia, in Mediterranean countries, and in pockets of Latin America and sub-Saharan Africa. Some cultures, like the Bedoin in the mid-East where boiling camel's milk is thought to destroy its vitality, have a very high prevalence of disease.

There are over 4 strains of Brucella, the most common being B. Melitensis (sheep and goats) and B. Abortus (cattle), but the clinical manifestations overlap. Most human cases in the developing world are B. Melitensis, but in Africa both are seen.

As an intracellular, reticuloendothelial pathogen that stimulates a granulomatous response in the human host, the time course of clinical disease can be acute, relapsing ("undulant"), or chronic. As in some studies, especially of populations with large families who share exposures and eating habits, for every index case there's a yet-undiagnosed case in the family with more indolent disease.

Even the "acute" form is more insidious and less severe than many other acute febrile illnesses, and patients don't usually present until the end of the first week of illness or later. Evening fevers, headache, and notable weight loss within 1-2 weeks are common; half have arthralgias or back pain, a third arthritis.
If untreated, the disease may progress to the "relapsing" form (the "classical pattern of "undulating fever" described by Bruce) which characterized 75% of patients in the pre-antibiotic era. Nowadays, the relapsing form represents ~25-30% of cases in endemic areas, usually reflecting incomplete treatment with relapse, or misdiagnosis. Focal symptoms of hepatitis, arthritis, uveitis or orchi-epididymitis in young males are common, as is a non-focal "fever of unknown origin" (FUO).
Some cases become "chronic", lasting for more than a year, presenting either as a "chronic fatigue syndrome" or as localized illness (e.g. spondylitis, uveitis), often without fever or systemic symptoms.

On exam, ~30% have splenomegaly and/or hepatomegaly; 10-20% lymphadenopathy; 50% develop bone or joint disease with corresponding symptoms - osteomyelitis, usually spondylitis, more common in adults >40 years old; or peripheral arthritis, usually knee or hip (either via reactive or infectious mechanisms) or sacroileitis (unilateral) predominantly in young adults.

This male farmer who owns livestock has the relapsing form of Brucella, presenting initially as a recurrent fever of unknown origin. Remissions are due to spontaneous immunity or incomplete responses to antibiotics. The time course of disease and symptoms (evening fevers, weight loss, fatigue, and even cough and diarrhea in symptomatic periods) are very compatible with Brucella, and so is the physical exam suggesting reticuloendothelial involvement (spleen and nodes, borderline liver size). The clinical "clincher" in this case, which both points to a bacterial pathogen and provides a more specific focus for the previously nonspecific illness, is the later development of focal spinal disease, ***brucellar spondylitis.***

4. Which other diseases are the <u>main sources of diagnostic confusion</u>, and how do you distinguish between them?

Extrapulmonary tuberculosis and typhoid are the main sources of diagnostic confusion. Like Brucella, both are intracellular, reticuloendothelial pathogens that cause chronic febrile illnesses. Both are more prevalent in Africa than is Brucellosis.

Typhoid after the 2nd week is symptomatically "more GI", and usually not musculo-skeletal; and, while tending to be more severe, runs its course in 3-4 weeks without becoming chronic or undulating.

Extra-pulmonary tuberculosis is a major confounder. Both TB and Brucella can induce granulomatous inflammation in potentially every organ in the body and the symptoms they cause overlap. The major diagnostic dilemma lies with the bone and joint disease they each cause, most commonly spondylitis.

Clinical clues differentiating tuberculous and brucellar spondylitis include:

- *age (TB <40, brucella >40 usually… N.B. not in this case);*
- *HIV evidence by lab or history/exam (TB usually HIV-associated; brucella no HIV association)*
- *location in spine (TB thoracic, brucella lumbar);*
- *X-ray*
  - *TB: multiple or adjacent vertebrae involved 10-30%; lytic; anterior wedge gibbus; paravertebral abscess with loss of transverse process common; diskitis late; body morphology lost early; canal compression common;*
  - *brucella: multiple vertebrae 20-30%; lytic and blastic; wedging uncommon; small circumscribed paravertebral abscess; diskitis early; body intact until late; canal compression rare;*

5. Which data, *missing from the history in the vignette above,* are important in patients with <u>chronic fever</u>?

Other epidemiologic data could be very relevant in patients with chronic fever. The vignette provides important information about occupation, animal exposure, and illness in the family. Additionally relevant would be:

- *Ingesting un-boiled (non-pasteurized) milk or cheese*
- *Exposure to sick animals*
- *Tick bites*
- *Recent travel*
- *History of prolonged febrile illness with arthritis as a child (rheumatic heart disease)*

6. What is the <u>gold standard</u> of diagnosis for this disease, and how is the disease diagnosed in Africa?

- *Culture of blood, bone marrow, CSF or joint fluid is the gold standard for diagnosis of Brucellosis, but is difficult and certainly not feasible in rural Africa: the organism takes up to 6 weeks to grow by traditional techniques, and isolation from blood occurs in only 50-70% of cases, 90% from bone marrow. Brucella is a biohazard in the lab, and if suspected, special precautions must be taken.*
- *In African district hospitals without culture facilities, the only alternative to clinical diagnosis is serology:*
  The Rose-Bengal test is an agglutination test used initially and usually confirmed by the "standard agglutination test" or SAT. In non-endemic areas an SAT titer of 1:160 or higher is considered positive; in endemic areas 1:320 or more is positive given the high background prevalence of a disease which can be minimally symptomatic and remit without treatment, and the tendency of these antibodies to persist for years. Cross reactions also occur with some types of E. coli, cholera and Salmonella, decreasing the specificity of the tests for Brucella. Although specificity is high when measured in healthy controls, it can be as low as 60-70% in sick, febrile patients without Brucella, and is not useful in following patients or in diagnosing relapse (~10% with treatment).
  Vis-à-vis sensitivity in those with Brucella, in one large study of culture proven cases any positive titer yielded a sensitivity of 85%; a titer of 1:160 or higher, 65%; and 1:320 or higher, ~50%. SAT is often (-) in the first week of illness, and titers can wane and become negative in relapsing and chronic disease.
  ELISA and PCR tests are being investigated, but are as yet unavailable in rural Africa; bedside tests such as the LFA (lateral flow assay) show promise and can be applied in areas with few laboratory resources.

7. a) What are the most common reasons for *missing* the diagnosis?

- *not thinking of the disease - most often presenting as a non-specific febrile illness, and seeming to respond to antibiotics transiently;*
- *not taking an adequate history, i.e. not probing about timing and recent past illnesses, and thereby failing to appreciate the chronic or relapsing nature of the illness;*
- *not realizing that the serologic test available has a low sensitivity early in the disease, and a sensitivity at the widely accepted cutoff point of 1:160, of only 50-65%.*

b) What are the most common reasons for *over-diagnosis* of the disease?

- *ordering Brucella serology when it's not clinically indicated: i.e. in acute febrile syndromes in which the pre-test probability of Brucella clinically is low due to the much higher prevalence of other diseases that explain the symptoms.*
- *not appreciating that serology has limited specificity due to cross-reactions and persistence of antibodies;*
- *not appreciating that the "cutoff" for a positive test is not "any" positive titer but >/=1:160 - or even higher, 1:320 - in endemic areas.*

8. When should this disease be considered clinically?

In patients:

- *with fever persisting for > 1 week;*

- *from endemic areas, or with at least one of the environmental-epidemiologic risk factors for disease (contact with livestock, ingesting un-boiled milk);*
- *with one of the following focal manifestations of disease and either fever (>1 week) or constitutional symptoms:*
  a) Musculo-skeletal disease: peripheral arthritis (usually monoarticular/large joint); sacroileitis (unilateral); spondylitis (usually lumbar);
  b) Epididymitis/orchitis or prostatits: in ~5-6% of males;
  c) Hepatitis: jaundice 5%, transaminitis 70%;
  d) Neuro-psychiatric: depression common; 1-5% with meningitis/encephalitis;
  e) Uveitis

9. a) How would you empirically treat the patient in the vignette, and why?
b) What are the therapeutic implications of the principle *alternative diagnoses* on the choice of empiric therapy?

Empiric therapy in this patient would be for "bacterial spondylitis in the context of a chronic (relapsing) febrile illness in an African farmer".

The 3 most likely causes of bacterial spondylitis in Africa are Brucella, Tuberculosis, and Staph spondylitis. The ultimate diagnosis would (ideally) be informed by radiography of the spine and serology for Brucellosis. However, these additional tests (both serology and radiography) are often unavailable in district hospitals.
As discussed, the clinical probability of Brucellosis in this patient is high, and if supported by either radiographic or serologic testing (as described above), therapy <u>only</u> for brucellosis would be rationale. However, as mentioned the tests are not very sensitive, and could be falsely negative. Thus if negative, given the high clinical suspicion of Brucellosis in this patient, the post-test probability of Brucellosis would probably still be high enough to warrant treatment for the disease.

However, treatment of Brucellosis should NEVER be taken lightly. Even non-focal disease in adults warrants <u>6 weeks of therapy with at least 2 antibiotics.</u>

Treatment for Brucella with focal complications like spondylitis is even longer: 3-6 months of therapy with doxycycline 100 mg twice daily, combined with either IM streptomycin 0.75-1g daily for 14-21 days OR rifamipin 600-900 mg daily for 3-6 months. (Streptomycin results in fewer relapses, perhaps due to rifampin's effect of lowering doxycycline's blood levels.) Brucella spondylitis is often difficult to treat, and some recommend the more effective streptomycin regimen supplemented by rifampin for 3-6 months. Note that rifampin and streptomycin are both antibiotics for tuberculosis as well, and that the treatment courses of both TB and focal Brucellosis are prolonged. (N.B. Instead of Streptomycin, Gentamycin has shown equivalent efficacy with a shorter, but nevertheless parenteral course of therapy of 5-14 days.)

Thus depending on the post-test probabilities of each disease after the results of HIV testing, X-ray and brucella serology (if available), and the national policies about the use of rifampin for non-mycobacterial disease, a rational strategy could be full course therapy for extra-pulmonary TB of the spine supplemented by doxycycline for 3-6 months. (N.B. In an effort to limit the development and spread of resistant TB, in rural Uganda rifampin is unavailable as monotherapy, and only as part of a combination pill (RIPE) for TB.

N.B. RIPE and doxycycline would cover both TB and Brucellosis without running any risk of inducing resistance to rifampin with incomplete TB therapy (if the diagnosis were TB).

(The initial clinical response should be carefully monitored. Progression of symptoms despite therapy should call for reevaluation of the diagnosis with particular attention to the possibility of Staph aureus spondylitis. Although not a likely initial consideration in the case presented here for reasons discussed above, since the implication of missing the diagnosis could be paralysis or death, progression or lack of any response to weeks of empiric therapy for Brucella and TB becomes a very important added variable in clinical reasoning, mandating diagnostic and therapeutic reevaluation.)

Suggested Reading:

Gotuzzo, E. Brucellosis *in Principles, Pathogens and Practice* (2nd Ed). Guerrant, R.L., Walker, D.H., Weller, P.F. Churchill/Livingstone/Elsevier 2006

McDermott, JJ, Arimi S.M, Brucellosis in sub-Saharan Africa: epidemiology, control and impact Veterinary Microbiology 90 (2002) 111–134

Pappas, G, et.al; Brucellosis N Engl J Med 2005;352:2325-36.

Pappas, G, et al; The new global map of human brucellosis Lancet Infect Dis 2006; 6: 91–99

Franco, M.P, et.al, Human brucellosis Lancet Infect Dis 2007; 7: 775–86

Ismail, T.F. et. al, Evaluation of Dipstick Serologic Tests for Diagnosis of Brucellosis and Typhoid Fever in Egypt J Clin Microbiol Sept. 2002, p. 3509–3511

Alp, E, et.al Doxycycline plus streptomycin versus ciprofloxacin plus rifampicin in spinal brucellosis BMC Infectious Diseases 2006, **6**:72

Hasanjani Roushan MR, Mohraz M, Hajiahmadi M, et al. Efficacy of gentamicin plus doxycycline versus streptomycin plus doxycycline in the treatment of brucellosis in humans. Clin Infect Dis 2006; 42:1075