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 20 – RECURRENT FEVERS

A 33 year old woman presents with her third bout of high fever and intense muscle pains in the past 5 weeks, and sudden paralysis of her face. She's a refugee mother of six fleeing war in the Congo, living now in a tent in the refugee camp near Kisoro with 3 of her surviving children and 6 others. She arrived at the camp last week after travelling through the Congo taking shelter in abandoned huts. Her life is broken now: her husband was killed, her oldest child has had a similar illness, and her youngest died of fever/malaria 3 weeks ago, despite quinine.

Each of her 3 episodes of fever started abruptly with intense headache and diffuse pain in her back, belly and joints. Malaria is common in her home village, and the first episode was cured with 3 days of chloroquine provided by a friend, begun on day 2 of illness. However, it came back abruptly with headache about a week later, this time also associated with cough, red eyes, and (according to her friend accompanying her now) mild confusion. She received quinine from a passing U.N. convoy, as did her child, and although her child died, she recovered. She has been mourning, fatigued and depressed but otherwise physically well this past week until 2 days ago, when she developed a high fever and headache again, with nosebleeds and a facial droop, and was brought to the hospital. There's been no rash, diarrhea, or change in urinary frequency or amount (although the urine has seemed "darker"); and no history of unexpected weight loss, prior pneumonia or frequent infections.

PE: Confused, coughing without sputum, complaining of body pain and headache

T 103 axillary HR 126, with ectopic beats; RR 24, shallow; BP 92/66

skin: 3-4 non-blanching, non-palpable purpuric areas 0.5-1 cm, on feet, palms, buttocks; no other rash seen;

conjunctiva: moderate suffusion; R eye subconjunctival hemorrhage; mild icterus

mouth: buccal petechiae, no thrush

neck: supple, no LAD; JVP 5 cm above angle Louis, sitting; + HJR elicited;

lungs: scant crackles at bases bilaterally

cor: PMI 1 cm. lateral to mid-clavicle; S3 in left lateral decubitus; 5-6 PCs/minute;

abd: hepatomegaly, 13 cm to span, 3 cm below cm and tender to percussion;

spleen, soft, 2 cm below costal margin, non tender

neuro: oriented to name and place, not time, intermittently inappropriate affect, grossly non-focal except for peripheral 7th CN palsy (forehead and lower face paralysis);

1. What is the "frame" (i.e. key clinical features) of this case?

- *recurrent febrile illness with nearly weekly periodicity*
- *abrupt high fever with diffuse myalgias and conjunctival suffusion*
- *multi-system involvement: purpura (vessels or platelets), lungs (cough/rales); heart (ectopy, S3), liver (icterus, tender hepatomegaly), CNS (headache, confusion, Bell's palsy)*
- *refugee, whose illness began while fleeing; other family members affected by febrile syndrome;*

2. Why should the following tests be performed if available, and how should their results be interpreted? Urinalysis, Rapid Diagnostic Test for Malaria (RDT); EKG

- *Urinalysis (U/A): with a multi-system disease, the spectrum of organ involvement is a clue to diagnosis the U/A is a potential indicator of renal involvement. In this case, the "darker urine" could be blood, bilirubin or very concentrated urine. [It's actually very unusual that women can give a history of a change in color of their urine, since toilet facilities aren't found in poor areas of rural Africa and latrines or soil can't reveal the urine's color.]*

  U/A results:

  Specific gravity 1.025; protein (-); heme (-), bilirubin +3, urobilinogen +2, leukocyte esterase (-), nitrites (-).

  Interpretation: The kidneys are (probably) not involved pathologically, and the "darker urine" is bilirubin, consistent with the conjunctival icterus on exam.

- *Rapid Diagnostic Test (RDT) for Malaria: microscopy or RDT (see below) can diagnose malaria with sensitivities of ~90%. With any severe febrile episode in rural Africa malaria must be a consideration, especially in refugee settings, although many of the findings in this case are not characteristic of the disease.*

- *An EKG (if available) may indicate cardiac involvement in the systemic process, and substantiate the cardiac abnormalities on exam.*

  EKG results: voltage normal; QRS interval prolonged .10 with intraventricular conduction delay; PR interval prolonged .24; 2 PVCs noted out of 20 beats.

  Interpretation: the heart and its conduction system is likely involved in the pathologic process.

3. What is the significance of the findings (positive and negative) on physical exam?

- *Non-palpable purpura, buccal petechiae, and subconjunctival hemorrhage: when acute (and red) these superficial signs of bleeding into the skin can be differentiated from punctate areas of inflammation by <u>not blanching</u> when viewed beneath a coverslip with pressure applied. Along with a history of recent nosebleeds, they suggest thrombocytopenia. Purpura, either petechiae (<1 - 4 mm) or ecchymoses (>1 - 4 mm), (N.B. note variability in definition in the literature), are usually due to either thrombocytopenia or vascular fragility/rupture from inflammation/vasculitis. If the purpura is "palpable" (with the examiner's eyes closed), it suggests underlying inflammation; if not, thrombocytopenia. In this case, lack of palpability suggests platelet deficiency as the cause of the dermal bleeding…*

- *Conjunctival suffusion: means red, injected conjunctiva without pus, seen commonly in certain types of infections such as viral, rickettsial and spirochetal diseases. Suffusion implies dysfunction of local endothelial tone or integrity which characterizes these blood-borne, diffuse systemic infections.*

- *No thrush, rash or LAD: along no weight loss, prior infections, herpes zoster scar, or rash of "papular prurigo", there's no clinical suggestion of underlying HIV disease, always a relevant consideration in African patients with fever.*

- *Supple neck: in community-acquired bacterial meningitis, especially in younger patients, the sensitivity of the finding of meningismus (neck stiffness on flexion) is ~90% and the LR (-) is 0.4. Thus a supple neck lessens the likelihood of meningitis.*

- *JVP 5 cm above angle Louis sitting; HJR (+); PMI 1 cm. lateral to MCL; +S3; PCs (premature contractions): Many of these cardiac findings can be seen in normal hyper-dynamic young hearts under stress – the JVP detected just above the clavicle and the PMI slightly displaced can both due to extra-vigorous contractions; the PCs can be precipitated by catecholamines, fever and respiratory alkalosis; the S3 produced by the easy diastolic expansion of a young compliant heart tapping the chest wall (up to ~ 40 years old). However the HJR is abnormal and, as a constellation, these findings suggest myocardial involvement in the systemic inflammatory process, probable acute myocarditis. (The HJR is one of the most valuable signs of elevated filling pressures: with excellent agreement (kappa ~.90), specificity ~90, and a reported LR (+) of 8.)*

- *Lungs: Crackles at bases bilaterally can be consistent with either diffuse inflammation involving the lungs, or high cardiac filling pressures (CHF) from acute myocarditis.*

- *Hepato-splenomegaly: In the context of a young patient with icterus and acute infection, hepato-splenomegaly probably reflects involvement of the liver and spleen in the systemic inflammatory process. The liver is tender to percussion and there's jaundice, suggesting "hepatitis", and the spleen is enlarged and soft. The soft consistency of the spleen suggests an acute process.*

- *Neurologic exam: Facial nerve palsy is a key finding, significantly narrowing the differential in this case. It suggests that the infecting agent has tropism for peripheral nerves. The patient's mental confusion is less specific: it can mean either involvement of the CNS directly as in "encephalitis", or indirectly through cytokine release as in the sepsis syndrome.*

4. What is the differential diagnosis in this case and the most likely diagnosis clinically? What are the clinical pros and cons for each of the possibilities?

- *<u>Malaria</u>: always a major consideration in a febrile patient in Africa, malaria can cause high fever, myalgias, headache, confusion and jaundice with tender hepatomegaly. It can also cause thrombocytopenia and consequent purpura. Indeed, this patient seemed to respond to chloroquine for malaria initially, and then "relapsed" and "responded" to quinine.*
  Against this being malaria are the following observatons: the second relapse (third bout of fever) despite quinine therapy; the focal neurologic finding, Bell's palsy; conjunctival suffusion; crackles on lung exam; and multiple family members with the illness despite hailing from a hyper or holo-endemic area in the Congo and thus probably immune.

  In this patient, the paracheck (malaria RDT) was negative, but the clinical features for or against the diagnosis of malaria are always important no matter what the result of the RDT. The sensitivity of the RDT (90-95%) means that 5-10% of negatives are false negatives. And false positives in patients from endemic areas can be due to asymptomatic co-infections with malaria in which malaria parasites are present in the blood, but are not causing the acute illness. Furthermore in this case, a positive result could be from a previous successfully-treated bout of malaria: malaria antigens can be found in the blood weeks after eradication of the living parasite. A negative result thus (weakly) supports the clinical suspicion that the prior episodes of fever were actually NOT malaria.

- *<u>Typhoid fever</u>: Typhoid, which can cause cough (early), headache, nosebleeds and delirium/encephalopathy, should be considered in patients with <u>prolonged</u> fever. It is unlikely in this case because of the timing of the illness here - acute and relapsing (Although relapse can be seen in 10% of typhoid cases, the episodes of illness are longer and the onset more insidious than in this case.); the focal neurologic finding (Bell's palsy); and the conjunctival suffusion. Also, although the manifestations of typhoid are protean and almost all extra-intestinal manifestations have been described, jaundice is uncommon (<10%) and purpura early in the course, rare.*

- *<u>Bacterial meningitis</u>: Meningitis needs to be considered in febrile patients with headache, confusion, purpura (meningococcal) and fever but bacterial meningitis of any etiology would be unlikely in this patient because of the combination of relapsing episodes, supple neck, and findings of multi-system disease: jaundice, cough/crackles, and peripheral 7th cranial nerve palsy.*

- *<u>Viral infections</u>:*
  - *<u>Yellow fever</u> is possible, particularly in refugees fleeing the Congo (mosquito vector, A.Aegpti), and suggested here by the high fever, hepatic jaundice (bili in the urine), purpura and conjunctival suffusion. However, YF is rare outside of outbreaks, less frequent in East than West Africa, and, in the ~ 10% of infected victims who have the full-blown illness with jaundice, significant proteinuria is seen (U/A protein negative in this case). Also, relapses and Bell's palsy are not seen.*

  - *<u>Filoviral infection: Ebola or Marburg</u> virus is suggested by the multisystem presentation with myalgias, fevers, conjunctival suffusion, cough, purpura/nosebleed, and headache/confusion. But they usually occur in epidemics; are not relapsing; are associated with a rash appearing around day 5; abdominal pain/diarrhea are common; hypotension is common; and usually death or improvement is seen by days 7-11 due to humeral antibody response. Focal neurologic findings are not seen.*

  - *<u>Dengue</u>: Dengue is not commonly reported in Uganda, but diagnostic facilities are sparse, its vector A. Aegypti is present and disease outbreaks have been reported in nearby Kenya. Dengue is a consideration in this patient because of the severe myalgias, conjunctival suffusion, bleeding and cough; however dengue often has lymphadenopathy and rash (50%), jaundice is rare, frequent relapse and focal neurologic findings <u>not</u> seen, and usually bleeding manifestations occur later, after a week of fever when either slow recovery or (rarely) transition to a hemorrhagic phase with shock due to a capillary leak syndrome occurs.*

- *<u>Viral hepatitis</u>: (e.g. hepatitis E, Rift Valley, Crimean-Congo, etc.) Suggested by fever and jaundice with tender hepatomegaly, but not likely given the multi-system presentation, acute relapsing time course, and neurologic focality. Bleeding and confusion would be late manifestations of severe hepatic disease, not likely in a patient well a couple of days ago.*

- *<u>Typhus</u>: There are 3 forms of the rickettsial disease, "typhus", in Africa: louse-borne (epidemic), murine or flea-borne (endemic) and tick-borne. All present similarly and fit this presentation closely. High sudden fever, conjunctival suffusion, severe myalgias (with tenderness), cough, abdominal pain, and delirium are frequent symptoms, and so is rash (but in only ~40% of Africans - check the axilla - and not seen here). In this case, the refugee setting and the multiple affected family members add to the plausibility of this often-missed diagnosis which has many mimics (an epidemic in war-torn Burundi smouldered for <u>years</u> before it was recognized in Europe - in an evacuated expat who died!).*
  - Epidemic typhus is a severe disease of cold, poverty, and lice, uncommon outside of epidemics. Mild jaundice can be present (20%).

  - Murine typhus is endemic in the tropics along humid coastal areas, carried by rat fleas. In general, although less severe than louse-borne epidemic typhus, the two can't be clinically differentiated.

  - Tick-borne typhus, milder than the other two, is prevalent in rural East Africa, is characterized by skin eschars in ~75% (often multiple), diffuse rash in 15-50%, and regional lymphadenopathy (LAD) – none of which were seen in this case.

  The principal reasons that typhus would be an unlikely etiology in this patient is her relapsing time course, absence of rash, and presence of peripheral neurologic focal findings.

- *<u>Leptospirosis</u>: Leptospirosis is a ubiquitous zoonotic disease caused by spirochetes, especially common in the tropics in both rural and urban areas with heavy precipitation. The spirochete lives in the renal tubules of mammals – rodents, dogs, cattle, etc.; is excreted in the urine, and gains access to humans through skin penetration.*
  The acute presentation of leptospirosis is very similar to this patient's: of symptomatic infections, ~90% are undifferentiated anicteric febrile illnesses with symptoms of fever, chills, myalgias, headache in >90%, nausea/vomiting/diarrhea and/or abdominal pain in 30-40%, dry cough in 30-60%, and uncommonly rash (<10%). Conjunctival suffusion is common (>60%), and lymphadenopathy and/or

hepatomegaly are seen (~20-30%). Although the illness is often biphasic, it is not relapsing week(s) later. When biphasic, the first or septicemic phase (with the above symptoms) lasts 3-9 days, followed by 2-3 days of defervescence, and then the "immune phase" appears with a recrudescence of fever, headache with aseptic meningitis, and interstitial nephritis. As in this patient, it can cause jaundice in ~10% (usually associated with renal insufficiency and designated Weil's syndrome, with a 30-50% mortality), thrombocytopenia and bleeding, myocarditis, and pulmonary symptoms and findings.

However, despite peripheral neuropathy having been reported in leptospirosis, it's very rare, and in this patient the Bell's palsy, the relapsing nature of the illness, and the appearance of same (severe) illness in other members of the family all auger against leptospirosis as the diagnosis.

- ***Borrelia**: A spirochete whose vectors can be ticks or body lice (as with typhus), Borrelia causes syndromes of "relapsing fever" both in temperate and tropical environments.*
  As in typhus, louse-borne relapsing fever (LBRF) is rarely found outside of cold, damp, overcrowded environments and epidemics. Tick-borne disease (TBRF) is endemic in some rural African villages, a potential problem wherever there are soft-bodied ticks (night-feeding, long-lived, 3-6 mm of the Ornithodoros species) feeding on rodents (usually) that live in the walls and floors of thatch/mud huts. It's estimated that there is a 50% chance of acquiring disease from a single bite by an infected tick.

  This patient has "relapsing fever", probably tick-borne, acquired along with two of her children while sleeping in abandoned, infested huts while on the run. The clinical picture of TBRF is characterized by recurrent episodes, spaced about a week apart (4-14 days), of sudden onset of high fever each lasting 1-3 days and ending abruptly by "crisis": an acute rise in temperature, followed by a fall with diaphoresis and hypotension. The organism is resourceful: the body produces antibodies that kill the spirochetes, but the relapses reflect antigenic variants that escape the immune system and return full force - in LBRF 2-3 relapses, and in TBRF up to a dozen relapses.

  Although LBRF is generally more severe than TBRF, most symptoms can be seen in both forms of disease: myalgia, headache, cough, nausea, delirium, and (more commonly in LBRF than TBRF) hepatitis and bleeding with thrombocytopenia. Both can cause myocarditis (with the prolonged QT interval and exam findings in this patient) which can lead to death. More common in TBRF is direct involvement

with the nervous system, commonly causing cranial neuritis of the 7^{th} or 8^{th} nerves. Other complications include radiculopathy, myelitis and/or meningo-encephalitis.

The propensity for borrelia to involve the nervous system and the heart characterizes both Lyme disease (Borrelia burgdorferi) and relapsing fever.

In this patient, the Bell's palsy and the relapsing time course are two powerful clues to the diagnosis of this disease, an otherwise non-specific multi-system febrile syndrome. When the presentation lacks these more specific clues, the differential includes the diagnostic possibilities discussed above and heavily relies on the epidemiologic setting to estimate probabilities of disease.

5. How can this disease be more definitively diagnosed in Africa?

The most accessible and accurate test at present is microscopy: examination of a Giemsa or Wright-stained smear of blood detects $>10^5$organisms/cc (thin smear) or $>10^4$/cc (thick smear), and, possibly available in endemic areas, phase contrast or dark-field inspection of buffy coat smears can detect $>10^3$organisms/cc.

6. What constitutes rational empiric therapy in this case?

Doxycycline 100 mg or tetracycline 500 mg: a single dose effectively treats LBRF (!) while TBRF takes more - 10 days of multi-dose therapy. This is due to TBRF's CNS location and the blood-brain barrier.

Unless highly specific clinical, epidemiologic or lab evidence for Borrelia infection is available, doxycycline therapy at 100 mg bid for 10 days can be used to treat the possibility of borrelia infections, typhus, and leptospirosis.

7. The patient is treated with antibiotics, and one hour later develops rigors and intense anxiety with hyperventilation, a rise in BP, HR up to 150 beats/minute,

and the temperature climbs from 101 to 104. It lasts for 2-3 hours. In hour 4, the patient's SBP is 60. What happened?

- *Jarisch-Herxheimer (J-H) Reaction: J-H reactions are seen in 80-90% of LBRF and 30-40% of TBRF. It's also seen after treatment of Lyme borreliosis, leptospirosis, and syphilis. It's fatal in 5%. Similar to the "crisis" that terminates a recurrent episode of relapsing fever, the Jarisch-Herxheimer reaction is due to the sudden lysis of spirochetes and massive antigen release which triggers a sudden overwhelming cytokine storm of vasoactive mediators (e.g. TNF).*

Suggested Reading:

Barbour, A.G. in *Principles, Pathogens and Practice* (2nd Ed). Guerrant, R.L., Walker, D.H., Weller, P.F. Churchill/Livingstone/Elsevier 2006 p.499-510

Barclay A.J.G, Coulter J.B.S; Tick-borne relapsing fever in central Tanzania TRSMH (1990) 84, 852-856

Dupont, H.T., et al; A Focus of Tick-Borne Relapsing Fever in Southern Zaire CID 1997; 25:139-144

Cadavid, D., Barbour, A.G. Neuroborreliosis During Relapsing Fever: Review of the Clinical Manifestations, Pathology, and Treatment of Infections in Humans and Experimental Animals CID 1998; 26:151-164

Cobey, F.C., et. Al; Detection of Borrelia (Relapsing Fever) in Rural Ethipia by Means of the Quantitative Buffy Coat Technique *Am. J. Trop. Med. Hyg.*, 65(2), 2001, pp. 164–165

Gasem, M.H., et al; Murine Typhus and Leptospirosis as Causes of Acute Undifferentiated Fever, Indonesia Emerging Infectious Diseases 2009 15, No. 6: 975-977