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 Katherine Unger at kunger@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.

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CASE 48 – Coughing Blood... Again

A 28 year old male is admitted to Kisoro District Hospital after coughing up blood for 2 days.

He was in good health until 2 years ago when he developed a cough, dry at first, then productive of yellow sputum and associated with fevers and weight loss. After 2 months of progressive symptoms, he noted blood in the sputum and he went to Kisoro District Hospital where TB was diagnosed (+AFB smears, no X-ray done), and an HIV test was negative. He was successfully treated for TB (4 drugs (Rifampin, INH, PZA, ethambutol – "RIPE") for 2 months, and INH/RIF thereafter for an intended 4 more months) and responded quickly by defervescing and gaining energy and weight. His sputum smear was negative at 2 month follow-up. He had documented adherence to DOT for 5 months, but discontinued all drugs a month earlier than anticipated when he went to Kampala for work.

He was fine for 6 months in Kampala and returned to Kisoro. Three months later he began coughing blood and came to KDH. He had not had any preceding symptoms of loss of energy, fevers, sweats or weight loss, and had a good appetite. An x-ray showed "fibrosis, ? infiltrate" in the right upper lobe. Despite 3 negative AFB smears, which were repeated as negative 2 months later, he was retreated with RIPE - DOT (with INH-RIF throughout) to which he adhered for the full 6 months, completing treatment 4 months ago. Intermittently he has had a mild cough in the morning with white-yellow sputum produced most mornings (and two days ago it was blood-streaked). He hasn't brought it to medical attention. He has remained without fatigue, weight loss, anorexia, fevers or night sweats.

Yesterday, again while feeling well without any other symptoms, digging in his fields, he began coughing blood. When it continued through the night he came to the hospital.

Physical Exam:

Well-appearing but anxious, coughing blood intermittently

B/P 110/80, no orthostatic changes; HR 90; T 36; R 18; pulse Ox 95%

Mouth: no thrush;
Neck: normal, no nodes; thyroid normal; no JVP
Lungs: right posterior lung field crackle, ronchi-wheeze which change with cough, otherwise clear
Heart: PMI normal, 5th ICS, MCL; S_1 S_2, normal without murmurs/gallups/rubs
Abdomen: normal, no hepato-splenomegaly or masses
Neurologic: normal

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

   - *prior TB - presented initially with hemoptysis, smear (+)*
   - *rapid clinical response to RIPE treatment*
   - *treated twice with RIPE for 5 and then 6 months, with documented adherence during each period*
   - *recurrent episodes of gross hemoptysis, almost a year after each treatment, with intermittent blood streaked sputum in between*
   - *no AFB on smear three times with the first recurrence*
   - *no cavity seen on CXR (done with first recurrence of hemoptysis)*
   - *no constitutional symptoms with last recurrence or at present (i.e. fever, weight loss, anorexia, fatigue or sweats)*
   - *HIV negative*

2. **What are the *central diagnostic questions* dominating this presentation?**

   - *Is this yet another recurrence of TB, or is it something else?*
   - *If TB, why so recurrent? If not TB, what else could it be?*

3. **What is the clinical significance of each of the features of your "frame"?**

   - *The patient had a prior episode of Tuberculosis which presented initially with hemoptysis, and was smear (+).*
     Hemoptysis is almost never an early but rather a <u>late</u> manifestation of TB, caused by erosion of the inflammatory reaction into the bronchial wall or sloughing of caseous necrotic tissue into the airways.
     Smear (+) TB implies a) the initial disease was indeed TB; b) the bacillary load was significant enough for AFB to be seen under the microscope. Only 60-70% of TB is smear (+) (and ~80% culture (+)).
   - *The rapid clinical response to RIPE treatment, and smear (-) status at 2 months infers that the organisms were sensitive to the therapy.*
     Smear (-) status at 2 months also weakly predicts a lower risk for relapse (see below).
   - *Treatment twice first for 5 and then for 6 months with a rifampin/INH regimen, with documented adherence both times, makes it highly likely that the patient was cured of TB. The first treatment was probably sufficient, and the second possibly overkill (but appropriate in the absence of culture facilities). (See below).*
   - *Recurrent episodes of gross hemoptysis almost a year after each treatment, with only intermittent sputum in between, augers against relapsing TB and suggests another cause of hemoptysis (see below).*

- *No AFB were seen on three smears with the first recurrence, lowering the probability of active TB (but not eliminating it. Microscopy is only ~70% sensitive for active disease, and blood can lower that performance even further).*
- *A cavity on CXR is a significant risk factor for TB relapse with 6 month "short-course" therapy and its absence on CXR (with the first hemoptysis recurrence) lowers the probability of relapsing TB. It also affects the likelihood of other diagnostic possibilities.*
- *The absence of constitutional symptoms (i.e. fever, weight loss, anorexia, fatigue, sweats) with both the last recurrence of hemoptysis and on presentation now, lower the probability of relapsing TB as the cause of the hemoptysis, a late symptom of TB.*
- *HIV negative status, although not conferring a significant advantage vis-à-vis response to therapy or probability of relapse after regimens that contain 6 months of rifampin, does lower the likelihood of re-infection with TB. (However, of note, prior TB does confer an increased susceptibility to re-infection with TB after initial eradication.)*

4. How should patients with TB be monitored in Uganda? Were any monitoring mistakes made during his prior episodes of treatment?

According to WHO recommendations, AFB (+) patients starting RIPE should be monitored by microscopy at the end of the intensive 4-drug phase at 2 months. If still smear positive, microscopy should be repeated at 3 months, and if still positive culture or drug susceptibility testing obtained. If these are unavailable (as in Kisoro and most of Uganda in 2014), microscopy should be repeated at both months 5 and 6 and, if positive, the treatment deemed a "failure" and a new regimen for multi-drug resistant (MDR)-TB started. In AFB (+) cases, independent of the results at 2 months, microcopy should be undertaken again at 5-6 months. If negative, therapy can be stopped after 6 months of treatment. (N.B. The 2 month smear will be positive in ~ 20% of all smear (+) cases of TB, but is neither sensitive nor specific in predicting relapse: of those who will relapse, less than 40% will have had a (+) smear (sensitivity), and of all (+) smears at 2 months only 25% will relapse (positive predictive value).)
In patients treated for TB who were AFB (-) initially, a repeat sputum should be checked at 2 months. If still negative, no further microscopy is required.

Retreatment for suspected recurrence in those who responded clinically the first time, in areas of LOW prevalence for MDR-TB (which Uganda is), can be with the initial regimen again, but for 8 months total, with a 3 month intensive phase. In our patient without symptoms and smear (-) when re-treatment was commenced, 6 months was probably sufficient.

Monitoring in this patient by microscopy was consistent with recommendations, however his loss to follow-up after month 5 the first time he was treated prevented the final 2 sputum checks recommended in initially smear (+) patients.

5. What are the implications of the durations of treatment the patient actually received on likelihood of cure of his TB?

Despite only receiving therapy for 5 months the first time, it's likely that TB was eradicated. How likely? More than 85-90% likely. Although deemed inadequate from a public health perspective, 4 months of therapy has been shown to cure 85-90% of TB vs. 95-98% for 6 months of therapy (containing both INH and Rifampin) (Am Rev Respir Dis 1981;123:165—170). Five months is probably somewhere in the middle of those ranges.

Although 8 months is recommended for retreatment with the initial regimen, as noted above since he was without symptoms and smear (-) when re-treatment was commenced, 6 months was probably sufficient for cure.

6. What are the differences between TB treatment "failure", "relapse" and "interruption" and what are the therapeutic implications of each?

- *failure: treatment is deemed a "failure" when AFB are seen on smear after 5 or 6 months of treatment; (and "possible failure", continued symptoms (e.g. weight loss) without another cause found (e.g. HIV));*
- *relapse: relapse means recurrence of TB, documented by smear or culture, after treatment and clinical remission/microscopic cure;*
- *interruption: treatment suspended without finishing the intended course.*

Therapeutic implications:

- *"Failure" suggests either non-adherence, malabsorption, or resistance. Non-adherence is the most frequent reason overall, and is highly dependent on the quality of the local TB/DOT program; the likelihood of resistance is strongly correlated with the prevalence of MDR-TB nationally and locally which varies markedly throughout the world (i.e. from 20% to <5% for new cases of TB, and 5% to >60% for previously treated cases. Previously treated cases make up ~10-15% of TB cases worldwide.)*
- *"Relapse", in areas of low prevalence of MDR-TB, is usually caused by sensitive organisms which will respond to the initial therapy again (with fastidious attention to adherence, and a prolonged 8 month course). Globally, 65% have fully sensitive organisms, and 15% have MDR-TB but these data are very location-specific: In areas of high resistance, relapse can be associated with a 30-80% rate of MDR-TB, almost as high as the rate of MDR-TB associated with initial failure to respond. However in Africa overall, the average prevalence of MDR-TB is 1-2% for new cases and 6% for previously treated cases. As a WHO region, Africa has the lowest resistance rate in the world (but culture facilities and good data are very sparse).*
  For Africa, relapsing patients who had a good clinical response to initial treatment, recommended retreatment is with RIPE plus streptomycin for 2 months, RIPE for a 3rd month, and RI for an additional 5 months.
- *"Interruption" means stopping medications prior to the intended treatment termination. If INH/Rifampin is stopped simultaneously during the continuation phase of "RIPE" after the 4-drug intensive phase was successfully completed, and there's less than a 3 month hiatus in therapy, the course of therapy can be simply continued for the full intended course. If the therapy is interrupted during the early intensive (high-kill) phase of therapy for >2 weeks, or if the lapse during the continuation phase is longer than 3*

months before 80% of the total intended dose had been given, therapy should begin from the start. Resistance is not usually an issue with simultaneous cessation of all therapy.

7. What are the major risk factors for *relapse* of TB after initial cure*?*

Significant risk factors for relapse include:
- cavitary disease, implying a large burden of organisms
- sputum smear positivity at 2 and 3 months
- patient very ill at initial presentation, with considerable cachexia/weight loss, extensive pulmonary disease, etc. [N.B. In Uganda, most diagnoses are made by smear without an x-ray, and these clinical indicators reflect the overall mycobacterial burden of disease].
- treatment regimens that didn't include rifampin for a full 6 months (8% vs 3% relapse rate with pan-sensitive organisms, and 38 vs 6% for those with INH mono-resistant organisms for those who had only 2 months of rifampin (in the intensive phase) vs. 6 months of rifampin (throughout the entire course). Also, 6 months of rifampin cuts the failure rate by more than half, and acquired resistance more than a third.)

8. Summarize the most important clinical issues regarding the likelihood of recurrent TB as the etiology of the first bout of recurrent hemoptysis in this patient, and the second.

- *The patient was very likely cured even with only 5 months of treatment: even 4 months of therapy cures 85-90% of active TB (6 months, 95%) with sensitive organisms.*
- *The rate of MDR-TB is Uganda is low, and he responded clinically to treatment for TB the first time with weight gain, etc.*
- *He received rifampin throughout both courses of therapy.*
- *He was asymptomatic with the initial bout of recurrent hemoptysis, and the second – now having been treated for TB twice;*
- *He was sputum smear negative at 2 months initially*
- *The CXR done with the first bout of recurrent hemoptysis did not show evidence of cavitary disease.*
- *The bouts of hemoptysis occurred 9-10 months post-therapy both times. Most relapses of TB occur in the first 6 months post-therapy.*
- *It is very improbable that two times the initial presentation of recurrent disease would be <u>only</u> gross hemoptysis without other progressive symptoms(unlikely even once);*
- *studies have shown that the most common cause of recurrent hemoptysis post-TB treatment is NOT recurrent TB (see below).*

9. Besides relapse of active TB, what is the differential diagnosis of hemoptysis post-treatment for TB, and what is the *most likely diagnosis* in this patient?

Besides relapsing active TB, TB-associated causes of hemoptysis include:
- *mycetoma or endo-cavitary fungal infection with either aspergillus or actinomyces organisms*
- *erosion of a calcified broncholith or lymph node into a large airway*

- *rupture of a "Rasmussen aneurysm": a small-to-medium pulmonary artery branch distorted by inflammation in the wall of a tuberculous cavity and/or transversing and suspended in it. Its rupture can cause exsanguination or asphyxia, and death.*
- *Bronchiectasis: TB heals by fibrosis, which deforms and deepitheliazes airways causing areas of poor drainage where bacteria can reside. Chronic bacterial colonization/infection induces inflammation that stimulates new vessels fed by both bronchial and non-bronchial arteries. Post-TB bronchiectasis is the most common cause of recurrent hemoptysis post-treatment.*

*The most likely diagnosis in this patient is **bronchiectasis.** The prior CXR did not show a cavity and so both a Rasmussen artery rupture and an erosive mycetoma, which often appears as an opaque crescent within a pre-existing cavity, are both unlikely; the recurrences of bleeding make erosion of a broncholith or rupture of a Rasmussen artery, both more likely to be one-time events, less likely; the intermittent morning cough with occasional sputum, the recurrences and the sudden copious hemoptysis in a previously healthy patient, all suggest post-TB bronchiectasis as the cause in this patient.*

10. What tests should be done, and what treatment offered?

- *The only test should be sputum for AFB, not because TB is likely, but because a negative sputum would be added evidence against TB. A third course of TB treatment is not indicated for the reasons outlined above.*
- *If available, a CXR could be repeated, largely to verify that there's no cavity nor mycetoma evident. The danger in ordering the test is over-interpretation of shadows of aspirated blood as areas of new infection.*
- *First "treatment" is to lay the patient on his right side so the bleeding doesn't spill into the other lung, and instead tamponades itself.*
- *Treatment should then be with broad-spectrum antibiotics that would not cross-cover TB (e.g. quinolones) – with the goal of suppressing smoldering bacterial inflammation within the bronchiectatic airways that probably precipitated the bleed.*

Suggested Readings:

Pasteur, M et al., An Investigation into Causative Factors in Patients with Bronchiectasis Am J Respir Crit Care Med Vol 162. pp 1277–1284, 2000

Marostical PJC, Fischer GB Non-cystic-fibrosis bronchiectasis: A perspective from South America PAEDIATRIC RESPIRATORY REVIEWS (2006) 7, 275–280

Barker AF Bronchiectasis N Engl J Med 2002; Vol. 346, No. 18: 1384

Haemoptysis due to chronic tuberculosis vs. bronchiectasis: comparison of long-term outcome of arterial embolization INT J TUBERC LUNG DIS 2007 11(7):781–787

Treatment of Tuberculosis Guidelines, WHO 4th Edition, 2010