



## **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](mailto: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](mailto: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.

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## CASE 25 – PERSISTENT DIARRHEA

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Please read the following brief vignettes and answer the questions that follow:

- A. A 10 year old girl presents with 3 months of fluctuating diarrhea and loose stools which began abruptly with cramps and flatulence, and has waxed and waned in intensity over that time. She has 3-8 bowel movements (BM) per day, accompanied by malaise, nausea, and belching; her stools (to the best of her knowledge) are non-bloody and feel watery, but she usually uses a latrine and rarely sees them. She's lost weight, has only occasional pain with cramps, and hasn't had fever.

PE: afebrile, abdomen benign, without tenderness or hepato-splenomegaly

- **What is the “frame” of this case (i.e. the key clinical features the final diagnosis must be consistent with), and the clinical implications of the features selected?**
  - *Diarrhea - chronic, non-bloody, no fever: The lack of blood in the stool or fever suggests a “non-invasive” process.*
  - *3-8x/day: The colon controls defecation and when the colon is affected by disease urgency and tenesmus (feeling of having to defecate) are accompanied by frequent BMs, usually >8-10/day of small volume stools. The frequency in this patient suggests small bowel rather than colonic diarrhea.*
  - *weight loss: In this context weight loss could mean a catabolic illness, poor intake, or malabsorption. The diarrheal symptoms without fever or abdominal pain suggest malabsorption.*
  
- **What is the differential diagnosis?**
  - *Chronic giardiasis is the most likely diagnosis. Giardia is a water-borne protozoan passed in the stool as cysts which ex-cyst in the duodenum and jejunum forming trophozoites. Trophozoites then attach to the intestinal mucosa, colonize the surface, interfere with digestive enzymes and stimulate cytokines. About 2/3 of infections are asymptomatic; 50% clear spontaneously; 10% become asymptomatic cyst-passers. Symptomatic infections are usually*

*heralded by abrupt onset of watery diarrhea with cramps, nausea, flatulence and last 2-4 weeks. Chronic diarrhea ensues in about half of symptomatic cases resulting in weight loss and malabsorption (which may even occur in the absence of overt symptoms). Fever is rare and bloody diarrhea is not seen. In endemic areas most symptomatic infections occur in children less than 10 years old, particularly less than 5, and cause stunting.*

- *Cryptosporidia, an intracellular water-borne protozoan, is endemic in developing countries particularly in the rainy season, and responsible for 10-15% of acute diarrhea in immunocompetent hosts. Clinically it causes a non-invasive, small-intestinal diarrhea indistinguishable clinically from Giardia, lasts 1-2 weeks, and resolves spontaneously. In HIV (+) patients, cryptosporidiosis often persists indefinitely, waxing and waning, is untreatable and, in the severely immune-compromised, often fatal. The only effective therapy is HAART. Cryptosporidia wouldn't have caused this girl's illness unless she was HIV (+).*  
*Isospora and cyclospora are 2 related intracellular water-borne protozoa that can cause Giardia-like illnesses (i.e. non-invasive, non-inflammatory, small-intestinal) that are common in the developing world in areas of poor sanitation, and clinically, within the first weeks of illness, can't be distinguished from Giardia. Cyclospora, like Giardia, can be chronic even in immune-competent hosts, sometimes lasting for weeks to months with malabsorption and weight loss whereas Isospora untreated usually lasts only for 1-3 weeks. Both cause chronic diarrhea/malabsorption in the immune-compromised. Unlike cryptosporidiosis, both organisms can be successfully treated - with TMP-SMX, in both HIV (-) and HIV (+) hosts (though at higher doses for longer with isospora).*
- *Strongyloides, an intestinal nematode with protean manifestations in the intestines, lungs and skin affects over 800 million people worldwide, most of whom are asymptomatic. Symptoms, when they do occur are usually ulcer-like abdominal discomfort, bloating and heartburn (i.e. non-ulcer dyspepsia). Malabsorption has been frequently reported although causation is controversial.*
- *Tropical sprue, a disorder of unknown etiology and waning prevalence over the past 3 decades, presents with chronic malabsorption and small intestinal, non-inflammatory diarrhea. Tropical sprue is associated with upper intestinal gram negative bacterial overgrowth which produces fermentation products thought to be toxic to SI mucosa. Folate and B12 deficiencies are common. However, the disease is found in only certain regions of the tropics e.g. some Caribbean islands like Dominican Republic, Haiti and Puerto Rico (but not others like Jamaica), and India and S.E. Asia most commonly. It's virtually non-existent in Africa.*

- *Lactose intolerance is a common cause of persistent diarrhea, usually induced or unmasked by a primary infectious etiology and perpetuated by ingestion of lactose-containing foods thereafter.*
- *Pellagra is caused by niacin deficiency and is uncommon outside of refugee (or other extraordinary) settings conducive to prolonged micronutrient deficiencies. It presents with watery diarrhea; oral manifestations like cheilosis, fissures, tongue atrophy; mental changes and peripheral neuropathy; and photo-sensitive rash.  
Zinc deficiency is both a cause and a result of chronic diarrhea and presents with skin changes (e.g. acral dermatitis), alopecia, cognitive defects and stunting.*

B. A 30 year old man presents with gradual onset of lower abdominal pain and loose stools which have gradually gotten worse over the past 2 weeks to the point that he is now passing 10-15 small volume stools/day with tenesmus, mucous (“strings of sticky liquid like after a goat gives birth”) and blood. He’s had no fever or chills.

PE: afebrile, BP 110/70; HR 82; no orthostasis;

Abdomen: mild-moderate tenderness to deep palpation in lower quadrants without masses palpable;

perianal skin ulcer, tender, 1cm diameter.

- **What is the “frame” in this case (the key clinical features the final diagnosis must be consistent with)?  
What do the features of the frame imply about the *type of organism* causing the diarrhea?**
- *Chronic diarrhea (>2-3 wks);*
- *gradual onset;*
- *tenesmus with small volume stools;*
- *mucous/blood;*
- *no fever*
- *skin ulcer*

*The chronicity, gradual onset and lack of fever suggest an indolent, non-pyogenic process that incites minimal inflammatory response. The organism is unlikely to be bacterial, more likely parasitic.*

*The tenesmus and frequent small volume stools are characteristic of colonic irritation, and the mucous and blood are signs of invasive disease i.e. a colitis.*

*The perianal skin ulcer is notable, likely a clue to the same process occurring within the colon.*

*Thus we have an indolent, progressive invasive colitis with ulceration but minimal signs of inflammation.*

- **What is the most likely etiology, its epidemiology, the limitations of diagnostic tests, the complications of this disease, its differential diagnosis, and its treatment?**

*Amebic dysentery due to *E. histolytica* is the most likely diagnosis. Amebiasis is second only to malaria as the most common cause of death from protozoan infections (40-100,000 annually) with 40-50 million cases of intestinal or hepatic amebiasis occurring worldwide each year. Probably most infections are asymptomatic with 5% in a Bangladesh refugee camp found to be silently harboring the organism, and 8.4% of Mexicans sero-positive for past Amebic infection. Exactly how many with infections are truly asymptomatic is unknown: the recent discovery of the more common *E. dispar*, a non-pathogenic look-alike about 3 times as prevalent as *E. histolytica*, has led to reconsideration of this issue: many past surveys couldn't differentiate between *dispar* and *histolytica* and thus the estimates of asymptomatic infection with EH were probably inflated.*

*Once symptomatic, most amebic colitis begins insidiously and presents an average of 2-3 weeks after onset (in one study after an average illness duration of 21 days was seen with *Ameba* vs. 4 days for *Shigella*); almost half have lost weight; fever is seen in only about 20% and is usually low-grade; abdominal pain occurs in about half. Stool is heme + in ~70%, but stool examination reveals the invasive trophozoite form in only 30-50% and they can't be differentiated from *E. dispar*. Serology is positive in 70% with colitis, >90% with hepatic abscess after a couple of weeks, but it remains positive for years thus losing specificity in acute disease. Stool antigen testing is best, with both sensitivity and specificity for EH of ~90%, but is unavailable in Africa.*

*Complications of amebic infection include toxic megacolon (<0.5%) with perforation, hemorrhage, hepatic abscess, intestinal obstruction due to an "ameboma" which can mimic cancer, skin ulceration, and rarely CNS localization by aberrant migration of trophozoites that escape the portal circulation and end up in the spine or brain causing seizures or motor weakness.*

*The differential of amebic colitis includes schistosomiasis (in areas where it's endemic), inflammatory bowel disease, and chronic forms of bacterial colitis with salmonella, yersinia, campylobacter.*

*Treatment is with metronidazole 500-750 tid for 7-10 days, ideally followed by a luminal agent against the cyst form of the infection such as diiodohydroxychloroquine (although 10 days of metronidazole is often sufficient to eradicate infection).*

- C. A 32 year old man presents with a 6 month history of alternating small-volume diarrhea and constipation and stools occasionally with mucous. He thinks he may have lost weight but isn't sure and has had no fever. For the past 2-3 weeks he's had increasing right lower quadrant abdominal pain with a tender persistent lump felt, and last night he had the sudden onset of lower abdominal severe cramping, without passing stool or flatus.

PE: tender RLQ mass, distention and intermittent high-pitched bowel sounds.

- **What is the “frame” of this case (key clinical features the final diagnosis must be consistent with)?**
  - *chronic lower bowel symptoms (6 months) affecting mucosa (mucous);*
  - *increasing tenderness and lump in right lower quadrant;*
  - *sudden severe pain now, with tender mass*

*Thus suggesting colonic mucosal disease complicated by a progressive mass and now obstruction.*

- **What diagnosis is suggested, and what is the differential?**
  - *Chronic amebiasis is likely by history, with a complicating “ameboma” developing in the ileocecum, now with acute intussusception. Ameba can survive for long periods in a tenuous relationship with the host, causing either no symptoms or minimal colitic symptoms of intermittent diarrhea alternating with constipation over many months. (Although once thought to be much more common than its dysenteric presentation, the existence of the smouldering colitis presentation has become more controversial as one study in the tropics showed no clinical difference between those with ameba (EH)*

*in their stools and those without, and with the recognition that non-pathogenic ameba are much more commonly identified than is E. histolytica.) However, the existence of “amebomas” is not debated: a chronic often circumferential mass of granulation tissue that forms in response to chronic infection most commonly in the ileo-cecal region. It presents as a usually moderately tender palpable mass that mimics colonic neoplasm. In this case, the sudden onset of pain was an intussusception.*

- *Tuberculous enteritis is in the differential of indolent bowel symptoms and an abdominal mass. TB often affects the ileum leading to malabsorption and a non-specific change in bowel habits over months, often presenting with a RLQ mass without fever. It also can cause intestinal obstruction, perforation, enteric fistulas and bleeding. Six months is long but consistent with TB. The symptoms of colitis with small-volume diarrhea wouldn't be characteristic of TB of the ileocecum.*

D. A 42 year old woman presents with 2-3 month history of gradually worsening diarrhea and loose, non-bloody stools, 4-8x/day. She has lost weight, complains of cramping abdominal pain which often prevents sleep, feels “hot and cold”, and has little appetite. She's taken no antibiotics.

PE: notable for T<sup>0</sup> 101, normal BP and HR of 92, diffuse mild abdominal tenderness without masses or hepato-splenomegaly; no guarding. Guaiac negative, soft brown stool.

- **What is the clinical “frame” of this case?**

- *37 years old*
- *chronic diarrhea over months*
- *fever, pain*
- *no blood seen in stool;*
- *weight loss*

*The clinical features suggest an indolent (months), inflammatory process (fever/pain) involving the bowel wall and not just the mucosa (tenderness/weight loss/no blood seen).*

- **What is the most important initial diagnostic test?**

*An HIV test - which would “orient” the approach to both diagnosis and therapy.*

*If positive, the next most informative test, now available in many district hospitals in rural Africa, is a CD4 count: the degree of immune suppression is closely correlated with the likelihood of a particular pathogen causing the illness.*

▪ **What is the differential diagnosis?**

- *If HIV positive with a CD4 count <200: the organisms that cause chronic diarrhea can be grouped into 3 general categories based on virulence and host immune status:*

*- organisms that commonly cause chronic diarrhea in non-immune-suppressed hosts such as giardia, ameba, schistosomiasis or C. difficile (especially post-antibiotics);*

*- organisms that can cause disease in both normal and immune-suppressed hosts but in the immune-suppressed are either far more common such as TB, or more likely to become chronic – such as non-salmonella typhi or campylobacter; or*

*- organisms that (almost) only cause chronic diarrhea in severely immunosuppressed hosts, such as cryptosporidia, microsporidia, isospora belli, CMV (colitis), HSV, MAI, lymphoma, Kaposi’s sarcoma, or “HIV enteropathy”.*

*The lack of bloody stools or colitic symptoms after 2-3 months leans away from HSV, Kaposi’s, or CMV (which can be watery at first); the gradual progression, fever, and mild-moderate degree of diarrhea auger against the more severe but less inflammatory presentations of cryptosporidia/microsporidia or isospora; fever is uncommon with giardia.*

*The fever, crampy pain, lack of blood and diffuse tenderness suggest a process extending beyond the mucosa into the bowel wall - such as TB enteritis, MAI (less common than TB in Africa), chronic infections with non-typhi salmonella or campylobacter. Of course, these can also come with bloody stools. “HIV enteropathy” is possible, but alone doesn’t usually cause fever.*



- *If HIV negative, or HIV + with a CD4 count of >200, the differential is more limited. TB enteritis, inflammatory bowel disease like Crohn's disease (IBD) presentations in Africa are more likely due to TB causing the "inflammation", or unusual presentations of infections that have become chronic such as Ameba, salmonella or campylobacter.*
  
- **What diagnostic approach is available in most district hospitals?**  
*Beyond HIV and CD4 counts few worthwhile diagnostic tests are available. Stool for ova and parasites is low yield and insensitive, mostly irrelevant to the differential at hand, and in Africa non-specific – potential pathogens are often found in asymptomatic hosts. Stool cultures for bacteria and endoscopy/biopsy/histo-pathology for cryptosporidia or microsporidia are unavailable.*

*If TB enteritis is a strong consideration, a chest X-ray may suggest concomitant pulmonary disease in up to 50% of patients, and a high WBC with left shift suggests a bacterial pathogen or gut perforation.*

*The most useful diagnostic test for prolonged diarrhea in rural Africa is an intelligent sequence of empiric therapy – treating sick patients broadly and less sick patients more selectively, and holding in reserve treatments that commit the patient to many months of therapy until shorter term trials have proven ineffective.*

- **What therapy is reasonable?**

*The empiric therapy sequence depends on the most likely pathogens which in turn depend on HIV status, CD4 count, and the clinical characteristics that are clues to site of disease, inflammation, malabsorption and invasion.*

*The primary drugs to consider using are ciprofloxacin, TMP-SMX DS, metronidazole, albendazole, RIPE, and ART therapy.*

*Ciprofloxacin is active against most bacteria: salmonella, shigella, campylobacter (and will partially treat MAI and TB); metronidazole against giardia, ameba and C. difficile; TMP-SMX against isospora belli and cyclospora (and some Salmonella); albendazole has some activity against microsporidia.*

*RIPE is treatment for TB enteritis, but shouldn't be used early in the sequence unless the patient is deathly ill or the pre-treatment probability is very high (e.g active disease in the lung); ART is the best treatment for HIV enteropathy or cryptosporidia/microsporidia; and ART with ganciclovir or foscarnet for CMV (for which the patient usually needs referral).*

**Suggested Readings:**

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