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:

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CASE 28 – CHRONIC DIARRHEA x 2 Vignettes

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

A) A 65 year old woman presents with abdominal pain and bloody stools for 3 years. She was well, working as a farmer, until about 3 years ago when she began to have crampy, intermittent pain in the left lower abdomen relieved by defecation. Shortly thereafter, she noticed blood in her stools - which were watery, mixed with blood, appearing "red and white". The pain and blood persisted, waxing and waning in intensity over the next 2 years, sometimes seeming to respond to treatment with antibiotics she received at the health center. During the past 6 months the left-sided pain has gotten worse, becoming constant, and associated with diarrhea more than 12 times a day. She constantly feels the urge to defecate, but passes little. She's lost weight, has felt "hot" for years on and off, and has had a cough for the past month which hasn't been bothersome.

Physical Exam:

Elderly, talkative, thin woman, pointing to her lower abdomen, in no distress
BP 97/56 without orthostasis; HR 88 (92 on standing), RR 14, T: 97.2 p.o.

Eyes: conjunctiva: mild pallor; fundi: benign;
ENT: normal Neck: no lymphadenopathy or goiter; no JVP/HJR
Lungs: clear to auscultation and percussion
Cardiac: PMI normal, 5th ICS, MCL; S1, S2 normal without murmurs, rubs, gallups
Abdomen: non-distended, normal bowel sounds; no hepato-splenomegaly;
Left-lower quadrant soft lumps and loops of ?matted bowel, mobile, non-tender with underlying discrete round lumps firm but not hard, non-tender, non-fixed, felt on deep palpation; no tenderness elicited
Rectal: no masses, stool guaiac +
Extremities: normal without edema

1. What is the frame of this case (the key clinical features the final diagnosis must be consistent with)?
What does the frame suggest about the location and pathology of the underlying disease process?

- *3 years of symptoms*
- *Left lower abdominal pain constant progressive*
- *Diarrhea with blood, frequent, small volume with tenesmus*
- *Weight loss*

- *Exam with soft and firm, non-fixed lumps ("doughy")*
- *No hepatomegaly*

The clinical features of the "frame" suggest an indolent process, gradually progressive, involving both the bowel wall (thickened loops of bowel) and the mucosa (blood), located in the distal colon-rectum (tenesmus, small volume, frequent bloody diarrhea).

Weight loss signifies a catabolic process consistent with either inflammation or neoplasm, and the history and exam do not suggest neoplasm: the left quadrant masses are mobile and firm, not fixed and hard as they'd likely be with cancer, and there's no hepatomegaly from metastatic disease (which would be expected if colon cancer caused weight loss, especially after 3 years of local symptoms).
The underlying process is most consistent with chronic inflammation involving the colon-rectum.

2. What is the differential diagnosis and the most likely diagnosis?

Differential:
- *Colo-rectal carcinoma*
- *Crohn's disease*
- *TB of the colon-rectum*
- *Amebiasis with ameboma*
- *Chronic bacterial infections with Campylobacter, yersinia, salmonella, etc.*
- *Diverticulitis/abscess*

For the reasons mentioned (see #1 above), it's unlikely to be cancer. Furthermore, 3 years would be too long for symptomatic cancer – i.e. from the onset of symptoms to this still-localized, unobstructed presentation without overt metastatic disease.

Ameboma due to chronic amebiasis is possible, but rectal bleeding in amebiasis would be due to dysentery - mucosal bleeding from undermining ulcers, a more acute and unstable process than this presentation.

Chronic presentations of usually-acute bacterial infections have been reported as mimics of inflammatory bowel disease. Nevertheless, their presentations are more acute, measured in weeks to a few months - not years; start with diarrhea and not pain/bleeding; and usually are associated with overt fever, not mobile masses/lumps (especially non-tender masses).

Diverticulitis-abscess would be tender, more discrete, and not as chronic.

The presentation is most suggestive of "inflammatory bowel disease" – either Crohn's disease or Tuberculosis of the intestines (the "African IBD") - specifically in this case colo-rectal TB.

Crohn's disease and intestinal TB are very hard to differentiate clinically: both are chronic inflammatory processes of the gut, involve the entire bowel wall, present with fever, weight loss, diarrhea (Crohn's more than TB), hematochezia, and preferentially involve the ileo-cecal region.
Tuberculosis of the bowel is the most likely diagnosis with this presentation in Uganda where TB is endemic and Crohn's disease rare.

3. What are the most feasible diagnostic tests? What is the "gold standard" of diagnosis and its limitations?

The 3 most feasible diagnostic tests are

1. Chest x-ray: looking for evidence of active pulmonary TB - seen in 25-50% of cases of intestinal TB. (Furthermore, in case series of pulmonary TB, approximately 25% have a focus of TB in the gastrointestinal tract.) The harder one looks for a pulmonary focus of TB, the more one finds: chest x-rays pick up more than history and physical, and CTs more than X-rays. In most cases, there's (at least) some evidence of old pulmonary TB in most cases of GI TB.
[Akin to looking elsewhere for clues to the existence of active TB, in many series of intestinal TB, ascites is also present in ~25%. If clinically detectable, an exudative ascites with protein >2.5, ascites/serum glucose <0.96, SAG <1.1, and/or lymphocytic cell count >150 makes accompanying peritoneal TB likely. However, AFB in the ascites yields <3% positive with peritoneal TB, and even culture has a sensitivity of only 20%.]

2. Response to empiric therapy: depending on the time course and one's clinical suspicion of disease, empiric therapy is usually the most definitive diagnostic test in Africa - especially with a chronic problem in which spontaneous resolution is unlikely over a week or 2 of observation. Symptomatic improvement is usually seen within 1-2 weeks.

3. Although non-specific, the ESR is (very) elevated in >90%, and nearly 100% have a mild anemia (~80% with Hb < 12).

The "gold standard" for diagnosis of intestinal TB is usually histo-pathologic examination of tissue via colonoscopy looking for granulomas. However, even this invasive modality (unavailable-in-rural-Africa) is only 50-80% sensitive, and AFB stains are only 30-60% sensitive. PCR has a reported sensitivity of 75-80%, and specificity of 85-95%. Examination of stool for AFB is fruitless.

4. What is the frequency of various symptoms and the complications of this disease?

Intestinal TB is usually a disease of young adulthood: 2/3 of patients are between 21-40 years old. About half of abdominal TB involves the peritoneum, presenting with

ascites, and half the intestines, presenting with bowel symptoms (see below). Intestinal TB is localized to the jejuno-ileum or ileo-cecum in >75% and the colon-rectum in ~20% of cases.

It's acquired through multiple routes: reactivation of an old focus from prior hematogenous spread; swallowing mycobacteria from an active pulmonary focus; ingestion of contaminated food or milk; spread from infected adjacent organs.

Pain is the most common symptom of intestinal TB, seen in 80-95%: Umbilical in 35%, generalized in 30%, and right iliac in 20%. (Our patient's pain in the LLQ was atypical, but consistent with the less-common localization of the process in our patient to the distal colon and rectum.)

Other symptoms include vomiting in 50%; anorexia and fever in 40-70%; weight loss in ~50%; diarrhea 20%, alternating diarrhea/constipation 5-10%. Whereas colonic TB presents with hematochezia in less than 1/3, with rectal TB 88% have bleeding.

On exam, 65% have focal abdominal tenderness; 35% a mass (usually) in the RLQ due to cecal hypertrophy/inflammation (found in 78% pathologically), lymphadenopathy in 18%, and omental masses 3%); 60% have some pallor; and ~25-50% have ascites by imaging.

Symptoms have been present for >6 months in 70% (!), and various series document <u>mean</u> durations of symptoms of 5, 10, 20, 36 and >100 months.

Complications of intestinal TB include:

- *malabsorption from ileal involvement and protein-losing enteropathy;*
- *obstruction (most common, seen in 30% of cases) – chronic and intermittent at first, progressing to complete obstruction, seen anywhere in the gut and due to fibrosis and stricture formation;*
- *hemorrhage;*
- *fistula and perforation in 2-20%.*

Follow-up:
In our patient, intestinal TB was the lead diagnosis on presentation. A chest x-ray revealed extensive bilateral pulmonary infiltrates with foci of cavitation, and sputum for AFB were positive.
She had had a cough on admission which she claimed had been present for only 1 month (we thought probably longer) - but the radiologic extent of TB was surprising given her clear lungs both on presentation and thereafter on multiple exams.

In most such cases, intestinal TB is the result of intestinal spread from an indolent tuberculous pneumonia by swallowing AFB. However, if her claim of only 1 month of cough was true, it is possible that her disease "ping-ponged" between her lungs and her bowel: a lung focus decades

ago, since quiescent, could have seeded the bowel and reactivated there - causing 3 years of symptomatic colo-rectal TB; and then, after years of catabolic abdominal illness and protein loss, her compromised state facilitated either hematogenous spread from the bowel back to the lungs or reactivation of the original pulmonary focus of TB.

Regardless of the pathogenesis of the dual sites of infection, she was treated with RIPE. Within days, her cough lessened, her anorexia improved, and her stools decreased in frequency from >12 per day, to 2.

B. A 5 year old child is brought to clinic by his mother for persistent diarrhea for 3 weeks. He is one of 5 living children (2nd youngest, 3 other siblings died in infancy) but was never healthy as long as his mother remembers. He was weaned at 4 months when his mother couldn't produce enough milk for him and his older sister. During the first couple of years of life he had a bout of watery diarrhea every month or two, similar to but worse than his siblings, and episodes of cough and fast breathing for which he was hospitalized 3 times. He grew slowly and is shorter than most of the kids his age.

Within the past year or two, his stools have been loose, usually about twice a day, with flares of watery diarrhea that persist for 2-3 weeks and occur every 2-3 months. This recent episode of diarrhea began 3 weeks ago with an abrupt worsening - from "loose" stool to frankly watery diarrhea 6-10 times a day without blood, accompanied by a low grade fever. He received ORS from the Village Health Worker and after 3 days his diarrhea improved, but 3 weeks later he still has diarrhea 3-4 times a day. His mother brought him to the clinic because he's lately been refusing to eat. His mother hasn't noted fast breathing, blood in the stool or fevers. She and her husband are poor but without known health problems. Both have been tested HIV-negative, as has the child who has received all his vaccinations.

Physical Exam reveals a restless child, short in stature and mildly cachectic; hair slightly lighter than normal and thin; normal respirations and depth, temperature axillary 97.5, HR 96; eyes and mouth moist, tongue smooth, conjunctiva mildly pale, eyes sunken, skin turgur on flank and chest normal, capillary refill time over palmer surface of distal finger 1-2 seconds; lungs clear; heart normal, no organomegaly or edema.

1. "Syndrome" definitions focus pertinent differential diagnoses and probabilities of disease.
What syndrome applies to this child, and how is it defined?
How serious a global health problem does it represent?

This child has "persistent diarrhea". "Persistent diarrhea" is defined as loose or watery stools occurring at least 3 times/day for more than 14 days.

Persistent diarrhea is a major contributor to overall child mortality and to growth stunting, which in turn is associated with performance and cognitive deficits later in life.

Diarrhea is the principle cause of child mortality world-wide, and persistent diarrhea, which represents ~10% of all cases of diarrhea, is responsible for 30-50% of the deaths. It is also thought to underpin ~25% of growth stunting worldwide.

2. What are the primary objectives of the physical exam when assessing this problem, and which particular signs are most relevant and/or useful?

The physical exam in a patient with persistent diarrhea should focus on
a) hydration/volume status;
b) signs of complicating acute or chronic bacterial infection, particularly pneumonia and TB;
c) signs of malnutrition, micronutrient deficiencies.

In an article entitled "Is this Child Dehydrated?" Steiner, et.al (JAMA 2004; 291:2746-2754) reviewed the evidence for the physical exam as a diagnostic test for volume depletion in young children. Most of the classic signs when present have relatively weak likelihood ratios (LR) between 1-2 -which raise the pretest probability of dehydration marginally, by <15%: sunken eyes, dry mucous membranes, sunken fontanelle, increased HR (>150), poor general appearance, abnormal respiratory rate/depth (sign of acidosis). The most useful are abnormal capillary refill (press pulp of finger until blanches and immediately release, normal 1-2 seconds to regain color) (LR 4.1), and poor skin turgur (LR 2.5).
Combinations of signs were most valuable (Gorelick, et al Pediatrics 1997; 99:E6), with 3 of 10 signs detecting 5% dehydration with a sensitivity of .87, specificity of 0.82 (LR 4.8); and 7 of 10 with an LR of 8.4 for severe (>10%) dehydration.

Acute bacterial infection, usually pneumonia or sepsis, is often found when children present with persistent diarrhea. Persistent diarrhea is a major risk factor for malnutrition, compromised immunity, and co-infection, and extra-intestinal infections are often the" final straw" that both exacerbates the diarrhea and brings the child to medical attention. In a large multi-center international WHO study of children with persistent diarrhea, 62% received antibiotics for non-intestinal infection on or shortly after admission (BullWHO 1996;74:479-489).
Cough, fever, crackles, respiratory rate are all important clues to underlying pneumonia or sepsis. A urinalysis should be done to assess urinary infection.
In areas endemic for tuberculosis, active TB often lurks in the shadow of malnutrition and persistent diarrhea. A high index of suspicion for indolent TB in chronically ill children is appropriate.

Malnutrition is both cause and effect of persistent diarrhea, and a strong risk factor for associated mortality. Measuring MUAC (mid-upper arm circumference) and weight-for-height and/or age, and examining hair, skin, mouth, bones, extremities, etc. can detect signs of

calorie (MUAC) or protein-calorie malnutrition (edema, hair lightening, "flaky paint" dermatitis) and specific vitamin and micronutrient deficiencies (e.g. glossitis, chelitis, acrodermatitis (zinc), pallor (nutritional anemia), etc.).

3. What is the "frame" of this patient's presentation (i.e. key clinical features the final diagnosis must be consistent with), and the clinical relevance of each feature?

- *Poor family, with many siblings dying in infancy [Poverty breeds overcrowding and poor hygiene and sanitation. Diarrhea and water-borne illness accounts for most child mortality in Africa.]*
- *Weaned from breast milk early [Exclusive breast feeding through 6 months and continued after other foods are introduced up to 2 years is recommended by the WHO to delay exposure to water-borne pathogens and protect against infection (a property of breast milk).. Early weaning is a risk factor for persistent diarrhea.]*
- *Multiple episodes of diarrhea in first 2 years of life, watery [Risk of stunting increases 2.5% with each episode of infantile diarrhea; 25% of stunting is reportedly due to infants having >5 diarrheal episodes before 2 years old (Int J.Epidem 2008; 37:816-0)]*
- *Chronically loose stools, now recurrent diarrhea for >3 weeks, no blood*
- *No signs of acute dehydration*
- *Light hair, atrophic glossitis [evidence of malnutrition and micronutrient deficiency]*
- *Loss of appetite, not eating [Possibly a sign of micronutrient (zinc) deficiency or underlying acute infection.]*
- *HIV (-) [HIV is common in patients with persistent diarrhea.]*

4. What is the differential diagnosis of this problem in children in rural Africa?

- *Persistent bacterial infection: i.e. one pathogen that persists (10-20% of acute gastroenteritis goes on to develop persistent diarrhea): E.Coli (enteroadherent, EAEC), enteropahogenic (EPEC, in infants <6 months), Shigella, Cryptosoporidium, Cyclospora, Giardia…*

- *Sequential bacterial infections: multiple pathogens in sequence thought to be more common than persistence of one…*

- *HIV infection: HIV can cause chronic enteropathy with villus atrophy, but more commonly persistent diarrhea is due to any one of a slew of opportunistic infections (CMV, MAI, cryptosporidium, microsporidium, isospora, TB, etc.) that are more likely to become chronic in HIV-infected hosts. Congenitally-acquired HIV can present for the first time after the age of 10, but usually will cause symptoms in the first 5-6 years of life and persistent/chronic diarrhea is common.)*

- *Non- HIV Viruses: half of serious viral gastroenteritis worldwide is due to rotavirus: watery, with fever and vomiting for which there's a vaccine now (not in SW Uganda*

however or most areas of need). Calcivirus, astrovirus, CMV are other pathogens that present similarly. Most viral GE affects children <2 years old, with bacteria and parasites becoming increasingly common as the child ages. Usually, viral GE lasts <5 days, usually ~2-3, but in malnourished hosts the duration of symptoms can be longer, and since infection is so common, viruses are common (sequential) contributors to persistent diarrhea.

- *Nutrient deficiencies: vitamin A and zinc deficiencies are common in impoverished populations, and zinc particularly is deficient in patients with chronic diarrhea. Zinc supplements reduce the severity and duration of diarrhea.*
- *"Secondary diarrhea" due to lactose intolerance from loss of lactase on villi tips after the initial diarrheal episode; or to small intestinal bacterial overgrowth from malabsorption and decreased motility, inducing more malabsorption.*

- ***"Tropical enteropathy":** since growth in children, temporarily halted by bouts of diarrhea, can catch up between episodes, the diarrheal episodes alone explain only a few percent of the stunting seen in children with "persistent diarrhea"; furthermore, optimizing nutrition in these children can recoup at best only 30% of their growth deficit.*

  These and other observations have given birth to an entity called "tropical enteropathy" - which purports to provide an explanation for the pathogenesis and associated stunting and increased mortality of persistent diarrhea through persistent inflammation. The enteropathy is thought to be ubiquitous in the developing world, histologically affecting almost all children and adults with and without symptoms.

  Tropical enteropathy is theorized to be induced by ingestion of fecal bacteria in large amounts chronically due to poor sanitation and hygiene. These bacteria induce a T-cell-mediated immune reaction which increases gut permeability, translocates microbes, atrophies villi, hypertrophies crypts, and induces malabsorption… and often leads to persistent diarrhea. Compounded by protein loss, hypercatabolism, and marginal nutrient intake, stunting and increased mortality result.

  Toilets for the 40% of the world's population that lack them have thus been promoted as the answer to child under-development, independent of their (more direct) effect on diarrhea per se.

5. What laboratory tests could be useful in assessing the problem and what are the limitations of "gold standard" tests in this situation?

- *HIV test (negative in this patient)*
- *Urine dipstick of diarrheal fluid: a glucose of +2 or a pH<5 suggest severe villous atrophy (decreased glucose absorption and bicarbonate secretion in the atrophic gut).*

- *Gross observation of stool for blood indicates invasive pathogens; however, hemacult testing is too insensitive and non-specific to be of value*
- *Fecal leukocytes are both insensitive for invasive bacterial pathogens and non-specific (i.e. can be seen with viral or other non-dysenteric etiologies)*
- *Cultures aren't available in district hospitals in rural Africa. However even when available, they can lead to false conclusions. Many potential pathogens are cultured from the stools of asymptomatic patients in areas of poor sanitation, and in patients with diarrhea the pathogens that are cultured may not be the ones causing the diarrhea.*
- *Stool for ova and parasite microscopy is unlikely to be useful. Most ameba that look like E.histolytica are non-pathogenic (by 3-4 fold), and the yield for giardia is low.*

6. In this patient, what is the likely diagnosis and the approach to treatment?

*This 5 year old malnourished child probably has chronic **"tropical enteropathy"** - with a recent flare a few weeks ago due to a superimposed infection. He also is probably deficient in zinc and other micronutrients.*

Treatment should focus on hydration, nutrition and possibly antibiotics.

Our patient is not acutely dehydrated. In general, hydration should replete both fluids and electrolytes using a low-osmolarity oral rehydration solution as recommended by the WHO for all diarrheal states except cholera (in which a normal-osmolarity solution is recommended). The WHO solution contains 75 mMol/L of glucose, 75 mEq/L sodium, and osmolarity 245 mOsm/L. Breast feeding should be continued.

Nutritional supplementation is key, and the WHO diet using local foods (cereals, legumes, vegetable oil and milk products) but with lactose minimized to 3.7gms per 150 kcal resulted in a 65% success rate. This rose to 80% if, after a week without response, children were fed a lactose-free diet - with protein supplied by poultry and egg whites.

All children with persistent diarrhea should be assumed to be zinc and Vitamin A deficient, and these micronutrients provided.

Finally, since common bacterial and parasitic causes of gastroenteritis often persist in malnourished hosts, the recent flare diarrhea might warrant a 3 day trial of ciprofloxacin (for Shigella, Salmonella, Campylobacter and Cholera) and/or a 10-14 day course of metronidazole (for the parasites giardia and ameba).

Suggested Readings:

Horvath, K.D., Whelan, R.L.; Intestinal Tuberculosis: Return of an Old Disease Am J Gastroenterol (1998) 93: 692

Haddad FS, Ghossain A, Sawaya E, Nelson AR. Abdominal tuberculosis. Dis Colon Rectum 1987;30:724-735.
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