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.

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CASE 27 –DIARRHEA x 2 Vignettes

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

A. A 20 year old woman is carried to the hospital by her husband, too weak to walk. Last night she had the sudden onset of loose stool followed by watery diarrhea and an hour later, profuse vomiting. The diarrhea soon became watery grey with flecks of mucous in it without blood, and over a few hours it increased in frequency to 2-3 times an hour and to a volume estimated at "half a liter bottle of Coke" each time. Over the night, the vomiting began to subside although the diarrhea continued. She experienced neither fever nor abdominal pain apart from intermittent abdominal cramps.

Physical Exam: Clothing slightly stool-soiled with a vague fishy smell.
Extremely weak and listless;
Afebrile; HR 160, BP barely detectable at 60/palp;
, RR 22 and deep;
Eyes shrunken/deep and dry; mouth dry; turgur poor,
Abdomen:slightly distended; bowel sounds decreased with intermittent long "gushes"; no tenderness;

1. **From which section of bowel does the diarrhea originate? Explain. What are clinical clues to the location and pathophysiologic mechanism of diarrhea?**

- *The diarrhea originates in the small intestines.*
- *The small bowel absorbs fluid and nutrients and handles around 20 liters a day of oral intake and digestive secretions from the mouth, stomach, liver, pancreas and gut.*

  The large bowel acts to absorb the last 1-2 liters of fluid it receives, to store feces and to control the timing of defecation.

  Dysfunction of the small bowel thus results in high volume diarrhea, but since the control and storage mechanisms of the colon are intact, defecation is infrequent - less than 6-8 times a day usually. Bloating, cramping and gas frequently accompany diarrhea of the small bowel.

  Large bowel diarrhea on the other hand is frequent, often more than 10 times/day, associated with the continual urge to defecate (tenesmus) but producing small volumes of stool.

  Viruses and toxins usually affect the small bowel, and fever and abdominal pain (other than cramps) are infrequent.

  Bacteria and parasites affect the colon, and many are invasive. Thus "colitis" is associated with fever, tenesmus and small-volume diarrhea with

blood, pus and/or mucous, often with pain and tenderness in the lower abdomen.

This patient's diarrhea is non-inflammatory/non-invasive, extremely voluminous and has resulted in rapid dehydration. Thus it's small-bowel diarrhea. Its explosiveness and the marked stool frequency (without tenesmus) is a sign of its severity – too much for a viral etiology but fitting the toxin-mediated mechanism of cholera.

2. a) What is the likely diagnosis and relevant epidemiology of this infection?
b) What is the differential diagnosis?
Why in this patient, now?

a) This patient's diarrhea is very likely cholera causing hypovolemic shock. Cholera is endemic in Africa and must be strongly suspected in any case of <u>adult</u> diarrhea that causes marked clinical volume depletion (many other infectious etiologies can cause severe clinical volume loss in children).

Cholera is a gram negative vibrio that produces an enterotoxin which binds to the intestinal mucosal cells and activates adenylate cyclase leading to increases in intracellular c-AMP and inducing secretion of large amounts of water and electrolytes.

Serotypes 01 Tor and 0139 are the cholera species that cause epidemic cholera in humans. Others, some in East Africa, cause sporadic cases that can be quite virulent.
The vast majority of El Tor cases are asymptomatic with 1 clinical case per 30-100 infections, with 90% of clinical cases producing self-limited mild-moderate diarrhea that can't be differentiated from other small bowel etiologies of non-inflammatory diarrhea.
Cholera is vastly underreported. Estimates range from 3-5 million cases a year worldwide, with >120,000 deaths annually, a 4% mortality.
90% of current cases come from Africa.

b) Since most cases of clinical cholera produce moderate self-limited diarrhea, the differential includes entero-toxigenic E. coli, food-borne exotoxins (e.g. C.perfringens, Staph exotoxin), viral gastroenteritis (norovirus, rotavirus, adenovirus, etc) and the parasites, cryptosporidium and cyclospora (in normal hosts without HIV).

This woman has a <u>severe</u> case of cholera, probably due to sporadically occurring non-01 subspecies that she acquired from fecally-contaminated water.

3. How should this patient be treated?

This is severe cholera and the patient is in shock and near death. She requires immediate IV hydration with Ringer's lactate (which will supply potassium and calcium as well as sodium, chloride and lactate) at 3 liters an hour through the subclavian and/or femoral veins until hemodynamically stable. Subsequent hydration should replace losses every 4 hours. Since potassium losses are high and Ringer's contains only 4meq/L of potassium, ORS should supplement IV hydration as soon as possible (or if available, potassium added to the IV solution). If an IV can't be inserted initially, an NG tube should be inserted.

Low-osmolarity oral rehydration solution (ORS) should begin as soon as possible and except in severe cases of shock is usually the only hydration method needed. ORS has been shown to decrease mortality in severe cholera from nearly 50% to 1%, hydrating, as well as decreasing the amount of diarrhea. Zinc supplementation cuts the duration and amount of diarrhea by 10% overall.

Antibiotics are also effective and should be given in severe cases: tetracycline for 3 days has been the standard therapy, but single dose doxycycline is now preferred, ciprofloxacin works in resistant cases (also single dose) and macrolides work in areas of ciprofloxacin resistance (erythromycin for 3 days or azithromycin, single dose). East Africa has a lot of tetracycline resistant cholera, so ciprofloxacin or macrolides would be preferred.

4. Two days later, the woman's husband and her sister begin to have diarrhea, 3-4 times/day, watery, without cramps. They take no medications, and in 3 days they're fine.
What caused their illness?

Likely cholera also. As mentioned above, for every severe case of cholera, there are at least 10 others with mild or moderate clinical symptoms and many more asymptomatic infections - at least with the El Tor biotype, the most prevalent worldwide.
The reservoirs of asymptomatic human infection and brackish estuaries in our natural environment as well as the organism's ability to exist in a hibernating carrier state allows El Tor to spread effectively, something it's been doing now for over 50 years.

B. A 4 year old girl is carried to the hospital by her father. Over the past 2 days her legs felt weak and today she couldn't walk without falling.
She has been well except for an episode of fever, abdominal pain and diarrhea that started 2 weeks ago. The fevers came first for 1-2 days, followed by diarrhea

which was watery with mucous but no blood, 8-10 times a day, associated with abdominal pain but no vomiting. She was given an unknown antibiotic and the episode subsided after about 4-5 days. She recovered about a week ago and now has a good appetite and no pain anywhere. None of her older siblings or relatives had a similar illness. Her family members are farmers and raise chickens and goats.
Two days ago she couldn't run and began tripping, and today she had a difficult time walking without falling.

Physical Exam:
Anxious girl, in no distress: T: 98; HR 92; RR 20;
ENT, lungs, heart, and abdomen benign and normal
Neurologic: Cranial Nerves intact;
3/5 weakness LE below knees bilaterally, symmetric
normal sensation, normal finger to nose and dysdiadokinesis
absent knee jerk and ankle reflexes

1. **What is the "frame" of the case – the key clinical features the final diagnosis must be consistent with?**

    - *Young girl, 4 years old*
    - *Weakness involving lower legs symmetrically, reflexes absent*
    - *Diarrhea with fever and abdominal pain a week ago*

2. **What is the likely cause of the girl's inability to walk?**

The girl's inability to walk suggests an acute ascending polyneuropathy, or Guillan-Barre Syndrome (GBS, or acute demyelinating polyneuropathy, AIDP) - an auto-immune post-infectious phenomenon affecting primarily motor function. It starts distally and ascends over hours to weeks. Dysfunction peaks within 2-4 weeks and slowly remits over the next few weeks to months. (If progressive or relapsing beyond 2 months it's called "chronic demyelinating polyneuropathy" and is a distinct entity.)

3. **What are the diagnostic criteria for this neurologic entity, and what is its range of severity and clinical presentation?**

The "NINDS criteria" are widely used and are simple: progressive weakness of > 1 limb AND areflexia. The areflexia is usually total but can present with absence of ankle jerks and hyporeflexia of knees (if all else fits), and one variant (acute motor axonal GBS) can occasionally have normal reflexes. The weakness itself has a very broad range of potential severity - from mild leg weakness to total body paralysis.

Weakness usually starts in the legs (but can be arms or face in 10%), is symmetric, evolves over days to 4 weeks and begins to resolve 2-4 weeks post-peak; bilateral facial and oropharyngeal weakness are seen in ~50%; oculomotor weakness in 15%; paresthesias in hands and feet accompany weakness in >80% with few sensory abnormalities on exam; pain is frequent in the back and extremities - reported in 2/3. Dysautonomia is seen in 70% (tachycardia most frequent). Respiratory support is ultimately needed in ~10-20%.
The lab hallmark of GBS is a CSF with high protein (after week 1 of symptoms) without cells (<10 mm^3).

Clinical variants include Miller-Fisher Syndrome (non-acute evolution of a combination of ophthalmoplegia without nystagmus; ataxia; and arreflexia); acute motor axonal neuropathy (AMAN) and acute motor-sensory axonal neuropathy - both of which involve the axons rather than the Schwann cells/myelin but which are clinically similar to AIDP except for the preserved reflexes sometimes with AMAN; and a variety of other variants characterized by selective involvement of nerve function or regional groups of nerves in the GBS spectrum (i.e. pure sensory GBS, pure dysautonomia, face-arm weakness, face diplegia-distal limb paresthesia, etc.).
In all variants, areflexia is characteristic and an important clue to the diagnosis.

4. **What is the differential diagnosis of the neurologic dysfunction and what are the features that distinguish these other disorders from the likely diagnosis in this patient?**

Chronic demyelinating polyneuropathy (CIDP) is the designation for GBS-like syndromes that continue to progress or relapse for >8 weeks. In addition, CIDP usually has a slower and less defined onset, a milder course (most can walk vs. only 40% of GBS children), and less frequently involves the cranial nerves.

Spinal cord processes (e.g. transverse myelitis, impingement, infarct) manifest hyperreflexia, a sensory level and earlier bowel and bladder dysfunction. Early on however, myelopathies can have hypo-reflexia (spinal shock). Furthermore, since GBS is usually associated with back and/or extremity pain, a spinal process is often suspected.

Other acute polyneuropathies can be due to vasculitis, porphyria, sarcoid, paraneoplasia, leptomeningeal processes (malignancies, granulomas), etc. Clues to the underlying disorders are often evident in the history and/or physical exam. Vasculitic processes are often broadly systemic but can involve the peripheral nerves and their vasa vasorum early on and dominate the initial presentation. Systemic signs and motor-sensory asymmetry are potential clues.

Neuromuscular junction disorders (myasthenia gravis, botulinism, Eaton-Lambert) or muscle diseases don't have sensory symptoms or findings on exam.

5. What is the relationship of the child's neurologic dysfunction to her preceding diarrhea, if any?

The preceding diarrhea is undoubtedly the clinical event that precipitated GBS. 70% of patients with GBS had an identifiable preceding illness within the past 1-4 weeks. Furthermore, the most common precipitant (up to 30% of all cases of GBS in the West and more in the developing world) is Campylobacter infection, which in this patient is thus the most likely cause of the diarrhea. GBS follows about 1 in 2000 Campylobacter infections.

The GBS that is usually seen post-diarrhea is the acute motor axonal neuropathy (AMAN) variant - due to cross-reacting antibodies to GM1 ganglioside formed in response to epitopes on the infecting Campylobacter strain.

6. a) What are the usual clinical characteristics of this cause of diarrhea?
b) How does its clinical presentation differ between patients in developed and developing countries?

Campylobacter in the West presents with the abrupt onset of abdominal pain and diarrhea in ~2/3. ~1/3 have high fevers for 1-2 days prior to the diarrhea. The infection starts in the jejunum and ileum and then involves the colon. About 50% have more than 10 stools/day. Campylobacter diarrhea in developed countries has more abdominal pain than other causes of diarrhea and can mimic appendicitis. Nausea is common but vomiting infrequent, ~15-20%. The diarrhea lasts a mean of 7 days, is accompanied by bloody stools in ~50%, the pain is slower to resolve and weight loss is common.

In the developing world, the disease is ubiquitous and thus more a disease of children than adults with multiple infections annually in infants and under-5's. Most infections are asymptomatic after the age of 5. Indeed immunity is acquired and symptomatic disease in adults is uncommon - unlike disease in developed countries.

The character of the diarrhea in the tropics is also different: whereas in the developed world Campylobacter infections are usually inflammatory and can't be differentiated from Salmonella or Shigella clinically, diarrhea caused by Campylobacter in the tropics is less frequently inflammatory – watery or mucoid (only 30% with blood) with less abdominal cramping and pain. Its differential often includes toxigenic and viral causes of diarrhea. The diarrhea resolves in 1-2 weeks, but 20% have relapsing infections lasting weeks. Particularly in HIV-infected (or malnourished) patients infections can be recurrent, prolonged and severe.

7. What spectrum of complications of this infection can be seen?

Campylobacters cause both pyogenic complications such as cholecystitis, myopericarditis and septic arthritis - mostly seen in malnourished and debilitated hosts, and auto-immune complications such as GBS. Besides provoking the AMAN variant of GBS, Campylobacter

is a common precipitant of the Miller-Fisher variant (ataxia and diplopia), and a common cause of post-infectious reactive arthritis.

Suggested Readings:

Zuckerman, J.N., et.al; The true burden and risk of cholera: implications for prevention and control *Lancet Infect Dis* 2007; 7:521–30

Levine, M.M., et.al; Cholera Infections in *Tropical Infectious Diseases: Principles, Pathogens and Practice* Guerrant, R., Walker, D., and Weller, P. Elsevier, 2006, p. 273

Allos, B.M.; Blaser, M.J. Campylobacter Infections in Tropical Infectious Diseases: Principles, Pathogens and Practice Guerrant, R., Walker, D., and Weller, P. Elsevier, 2006, p. 265

Van Doorn, P.A., et. al. Clinical features, pathogenesis, and treatment of Guillain-Barré syndrome Lancet Neurol 2008; 7: 939–50