PedsCases Podcast Scripts

This is a text version of a podcast from Pedscases.com on "**Approach to Chronic Diarrhea.**" These podcasts are designed to give medical students an overview of key topics in pediatrics. The audio versions are accessible on iTunes or at www.pedcases.com/podcasts.

Approach to Chronic Diarrhea

Developed by Katie Girgulis, Dr. Chris Novak, and Dr. Karen Forbes for PedsCases.com
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Intro

Hi everyone, welcome to Part Two of this podcast series about diarrhea. My name is Katie Girgulis and I am a medical student at the University of Alberta. This podcast was developed with the help of Dr. Chris Novak (pediatric resident at the University of Alberta) and Dr. Karen Forbes (pediatrician and medical educator at the Stollery Children's Hospital).
In the first podcast, we reviewed the pathophysiology of diarrhea and discussed a clinical approach to acute diarrhea. Now, it's time to review chronic diarrhea.

After listening to this podcast, the learner will be able to:

1) Generate a differential diagnosis for chronic diarrhea
2) Identify key features in the history and on physical exam for a child presenting with chronic diarrhea
3) List appropriate investigations that may be ordered to help determine a cause of chronic diarrhea
4) Recognize the clinical presentation, diagnosis, and management of Celiac Disease

Let's start with a case.

Clinical Case

You are a third-year medical student on your pediatrics rotation, and you are working with Dr. Jane in her out-patient pediatrics clinic. She asks you to see the first patient. Charlotte is an 8-month-old girl, and the consult letter states that she has had watery diarrhea for over one month. Hmm… you just mastered an approach to acute diarrhea, but this sounds like chronic diarrhea, which is a whole other can of worms. How will you organize your thoughts, and what is your approach when you go in to see Charlotte?

Pathophysiology

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In part 1 of the podcast we introduced the basic physiology of diarrhea. Using the same categorization of pathological processes, let's explore these a little deeper. Recall that the causes of diarrhea can be broken into 4 main categories based on pathological process: Osmotic, Secretory, Dysmotility and Inflammation.

Osmotic diarrhea occurs when there is a failure to absorb a solute from the intestinal lumen. Recall, water is absorbed from the gut via a concentration gradient. If there is an increase in solutes in the gut, then there is less of a drive to reabsorb water. A good example of osmotic diarrhea is lactose intolerance. Patients with lactose intolerance have an impaired ability to break down lactose. The gut is not able to absorb this disaccharide, and the lactose therefore remains in the lumen. The result is more solute in the lumen, reducing the concentration gradient for water reabsorption. Less water is absorbed and diarrhea results. Osmotic diarrhea typically stops overnight or. when the patient is fasting.The physiology of an osmotic load causing a gradient in the lumen is the basis for some laxatives, such as PEG3350. This osmotically active solute that draws water into the lumen of the bowel, thereby increasing the water content of the stool.
In terms of chronic diarrhea, cystic fibrosis and the resulting pancreatic insufficiency can cause an osmotic diarrhea. The lack of pancreatic enzymes leads to impaired carbohydrate digestion, and these large molecules create an osmotic load that pulls water into the lumen of the bowel.

The next type of pathologic process we will discuss is **secretory diarrhea.** A large proportion of fluid passing through the gut is from GI secretions. Anything that increases secretion leads to an increase in the total volume of water passing through the intestines, which can overwhelm the guts absorptive capacity. The classic example of secretory diarrhea is cholera. In cholera, the toxin produced by the bacteria *Vibrio cholera* attacks the cells of the intestinal epithelium, leading to increased secretion of chloride and water into the lumen. This massive activation of secretion causes huge volumes of watery diarrhea that can lead to life-threatening dehydration. It is classically very large volume and the diarrhea persists overnight despite fasting. If tested, there is a lack of stool reducing substances.

The third pathologic process is **dysmotility.** Motility refers to how quickly bowel contents are passed through the intestines. In hypermotility, GI contents are peristalsed through the intestine faster than the gut can absorb the water. This can occur in some patients with hyperthyroidism or functional diarrhea.

The fourth main process is **inflammation.** Inflammation of the gut lining can be caused by infectious processes such as bacteria or viruses, or by autoimmune processes like Crohn's Disease or Ulcerative colitis. Inflammation can lead to destruction of the intestinal epithelial cells, dysfunction of solute absorption, and exudation of protein and blood into the gut lumen. In addition to impaired absorption, increased inflammatory debris pulls water into the lumen leading to diarrhea.

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To review:
1) Osmotic diarrhea pulls water into the lumen with non-absorbed solutes.
2) Secretory diarrhea adds more water to the lumen than the gut can absorb.
3) Dysmotility usually means that fluids pass through the gut faster than they can be absorbed; and
4) Inflammation leads to impaired absorption and increased exudate leading to water loss.

Differential Diagnosis

If you remember from Part One of the podcast series, the first step of developing a differential for diarrhea is to determine if the diarrhea is acute (i.e. <2 weeks) or chronic (i.e. >2 weeks). The differential diagnosis for acute diarrhea can be organized into causes of watery vs. bloody diarrhea. The etiology of acute diarrhea is most commonly infectious.

For chronic diarrhea, it is a little more complicated. You can start by asking 3 main questions:

1) What pathologic process is causing the diarrhea?
2) Does the child have failure to thrive?
3) How old is the child?

We will start by discussing each of these three questions and how they can help narrow the differential diagnosis. Then we will return to the clinic to learn more about Charlotte and use this approach.

Recall, the 1st question is "what pathologic process is causing the diarrhea?" We will use the same categories as discussed in the pathophysiology section.

1) Osmotic – Think about carbohydrate malabsorption such as in lactose intolerance and excessive fruit juice consumption. Another etiology is post-infectious enteropathy. In this condition, the brush border of the intestine is damaged, impairing breakdown of disaccharides and solute absorption.
2) Secretory – several rarer conditions fall within this category. For example, congenital diarrhea syndromes caused by mutations in transporters or enzymes in the GI lining. Neuroendocrine tumors can lead to a secretory diarrhea. Graft-vs.-Host Disease can also cause diarrhea in a patient after stem cell transplant.
3) Altered motility – Think about hyperthyroidism and functional abdominal pain
4) Inflammatory – this category includes inflammatory bowel disease (IBD), Celiac disease, and non-IgE-mediated GI food-induced allergic disorders like food protein-induced allergic proctocolitis (FPIAP) and food protein-induced enterocolitis syndrome (FPIES). Note, there is a shift to use this new terminology instead of the general term "cow's milk protein allergy (or intolerance)", as we are learning that these non-IgE-mediated conditions are in fact heterogeneous. Other

inflammatory conditions include chronic infections, which are most often caused by C. difficile or parasites in immunocompetent patients. Patients with either primary or acquired immunodeficiencies can develop severe diarrhea secondary to infection. Ischemia, and radiation can also damage the GI lining leading to inflammatory diarrhea.

The next question is "does the child have failure to thrive?" It is important to think of conditions that cause diarrhea AND failure to thrive, versus conditions that cause diarrhea in an otherwise healthy and thriving child, as conditions with failure to thrive require much more urgent evaluation and treatment.

- Conditions to consider with failure to thrive include:
    - Celiac disease, IBD, food protein-induced enterocolitis syndrome or food protein-induced enteropathy, immunodeficiency states, congenital secretory diarrhea, cystic fibrosis, neuroendocrine tumors
- For patients without failure to thrive, consider:
    a. Toddler's diarrhea, functional abdominal pain, lactose intolerance, chronic infection, food protein induced allergic proctocolitis

Lastly, it's helpful to have an understanding of conditions that are more common to present in a specific age-group.

- Neonatal – remember to think about congenital etiologies, such as enzyme deficiencies, pancreatic insufficiency, abnormal transport channels, and immune dysregulation.
- Infants/Toddlers – Celiac disease, food protein-induced enterocolitis syndrome or food protein-induced allergic proctocolitis, autoimmune enteropathy, and cystic fibrosis commonly present in infants and toddlers
- Older children and adolescents – inflammatory bowel disease, lactose intolerance, and functional abdominal pain are more common in this older age group

<u>Back to the case</u>

Let's practice this initial approach to chronic diarrhea with Charlotte, our 8-month old girl in the out-patient clinic. You obtain some helpful information from the initial intake with the clinic nurse.

1. Pathologic process: Charlotte's parents described the stools as "watery, greasy and smelly". They denied seeing any blood in the stool. Based on this information, osmotic, secretory, and altered motility would be more likely than inflammatory.
2. Failure to thrive: Charlotte was measured during today's visit, and her weight and height were plotted on her growth curve. She plots along the 50th percentile for height. You note that she was initially tracking along the 50th percentile for weight, but today she plots at the 10th percentile. This should clue us in to consider etiologies in the "failure to thrive" category.

3. Age: Charlotte is 8 months old, so we will frame our differential diagnosis accordingly.

Next, you enter the room to take the history. Let's quickly review some key information to obtain.

History

History of presenting illness – similar to acute diarrhea, it is important to ask about onset, duration, quality of the stools, timing during the day and night, aggravating and alleviating factors, and any associated symptoms. Ask specific questions about stool characteristics. Bloody diarrhea can occur with inflammatory bowel disease and some chronic bacterial or parasitic infections. Mucous in the stool can occur with Toddler's diarrhea. Undigested food particles can also be seen in Toddler's diarrhea. Greasy, foul-smelling stool that floats in the toilet suggests steatorrhea, which suggest either a maldigestion or malabsorption issue.

Remember to take a good dietary history, including the introduction of solid foods and cow's milk, as well as the amount of juice consumed.

Ask about travel in the past few months, particularly if there was exposure to unclean drinking water. In these cases, diarrhea could be due to a chronic infection.

Finally, remember to do a head-to-toe review of systems, inquiring about fevers, lethargy, weight loss, change in appetite, oral ulcers, abdominal pain, muscle or joint pains, and rashes or skin changes as these may suggest a multisystem disease.

Past Medical History – In this section of the history, it is crucial to ask about growth and weight gain. For example, child who was thriving until the introduction of solids, but then develops diarrhea, weight loss, and failure to thrive, could have Celiac disease. Failure to attain normal growth despite adequate caloric intake is an important clue to an underlying pathologic process. A personal history of other autoimmune conditions like type 1 diabetes or hypothyroidism can be a clue to consider Celiac disease and IBD.

Medications – Remember to ask about recent antibiotic use, as this is a risk factor for C difficile infection.

Family history – inquire if there are any relatives with conditions such as Celiac disease, inflammatory bowel disease, cystic fibrosis, atopy, or food allergies?

Back in the clinic:

Feeling more confident with your knowledge and approach to chronic diarrhea, you enter the room to meet Charlotte and her parents. You learn that Charlotte has been having frequent liquid-y stools for a few months. At first, her parents thought she could have caught a "stomach flu". However, her diarrhea just seemed to linger on and never resolve. Her parents describe the stools as "greasy and smelly", with maybe 5-6 diarrheal episodes per day. More recently, they have begun to worry that the diarrhea is giving her a tummy-ache. She tends to be more irritable and sometimes curls up into a ball after eating. In fact, she seems to be eating less and sometimes refuses food all

together. Her parents are frustrated by this, as they have been trying their best to introduce Charlotte to more and more of their family foods.
Charlotte is an otherwise healthy 8-month-old. Her mother was G1P0, and the pregnancy was uncomplicated with routine prenatal care. Charlotte was born at term via spontaneous vaginal delivery. There were no postnatal complications and she did not require stay in the NICU. She has been attaining her developmental milestones as expected. Currently, she crawls, pulls herself to stand, transfers toys between hands, says “mama”, waves goodbye, looks for dropped objects, and gets upset when separated from her parents. She has received immunizations up to 6 months. She is not taking any medications other than vitamin D. She was exclusively breast fed for 6 months, at which point they began adding baby cereal and other solids. She continues to breastfeed and drinks sips of plain water. Her parents have been avoiding juices as they are both dentists and want to protect her teeth!
Both parents are healthy with no known medical conditions, and they are not aware of any medicals conditions in their siblings, nieces, or nephews. Charlotte has never travelled outside of Alberta. No one else in the family has diarrhea.

Physical Exam

Next, you are ready to move on to the physical exam. Let’s review some key elements. Always start by measuring height and weight and plotting these values on an appropriate growth curve. It is important to look at multiple points of the child’s growth parameters over time. Look for indications of failure to thrive, such as a child tracking below the 3rd percentile, crossing percentile lines, or losing weight. If there are growth concerns, determine what parameters (weight, height, or both) are affected. During the general inspection, pay attention to the child’s fat stores and muscle bulk. You should do a complete head-to-toe exam, as some etiologies of chronic diarrhea can cause extra-intestinal findings. Pay particular attention to any eye, oral mucosa, joint, or skin changes. Examine the abdomen for distention, tenderness, or masses. Inspect the peri-anal region for fissures, fistulas, and abscesses.

Investigations

After the initial history and physical exam, many cases of chronic diarrhea will require some investigations to rule in or out the etiologies on your differential diagnosis.
As always, what you choose to order will be guided by the history and physical exam. This is particularly important if there is failure to thrive, where the workup must be tailored to the symptoms. An initial workup may include a CBC to check for anemia, leukocytosis, or thrombocytosis, and an ESR or CRP to look for inflammation. If you are worried about the child’s nutritional status, consider checking serum albumin and/or protein, iron, vitamin B12, and folate levels. A stool sample should be sent for culture and sensitivity if there is blood in the stools, as well as ova and parasites, to rule out infectious causes. Especially in the context of recent antibiotics, consider testing the stool for C difficile toxin in children older than one year of age. Some labs are also able to check for fecal leukocytes or fecal calprotectin, which may suggest gastrointestinal inflammation.

If suspicious, screen for Celiac disease by checking for anti-transglutaminase (anti-TTG) antibodies. It is important to note that this test will be falsely negative if the child is IgA deficient. Thus, you should always order an IgA level along with the anti-TTG. Some labs will automatically test IgA is the anti-TTG is negative.

The role of imaging is limited in the initial assessment of chronic diarrhea. Ultrasound, CT or MRI may sometimes be helpful in showing bowel thickening (suggestive of inflammation). Endoscopy or colonoscopy is invasive but sometimes necessary to directly visualize the mucosa and to take biopsies for histological analysis, such as are required for the diagnosis of Celiac disease or IBD. This would be done based on clinical suspicion.

Back in the clinic:

You are ready for the physical exam! As we discussed earlier, Charlotte was measured, and her weight is falling off her previous growth trajectory but her height continues to track nicely. Her vitals are within normal range for her age. She does not appear dehydrated. During general inspection, you note that Charlotte is a playful and active kid. Her abdomen looks a mildly distended to you, especially since she is otherwise a fairly thin little girl. There is no guarding with percussion and palpation, and you don't palpate any masses nor organomegaly. The rest of the exam is unremarkable.

You excuse yourself from the room to review with Dr. Jane. She probes you to list a few things on your differential and whether you would like to do any further investigations for the diarrhea. You consider the possibility of a protein intolerance, allergic or autoimmune enteritis, Celiac disease, inflammatory disease, and chronic infection. However, given Charlotte's age, recent failure to thrive and introduction of solid foods, Celiac disease is highest on your differential. Therefore, you suggest ordering a CBC to check for anemia, stool cultures to rule out infection, and anti-TTG and IgA levels to screen for Celiac disease. Dr. Jane agrees! She is impressed with your clinical decision making and joins you back in the room to observe as you explain the plan to Charlotte's parents.

Case Resolution

Charlotte returns to clinic for her follow-up visit two weeks later. According to her parents, the symptoms have persisted in this time interval. You are not surprised, as you reviewed the results of the initial investigations prior to entering the room. You noted that Charlotte has a microcytic anemia and an elevated anti-TTG. Her stool cultures were negative. Together with Dr. Jane, you disclose these results to the family and discuss the probable diagnosis of Celiac disease. Charlotte's parents inquire about the next steps, and you explain that you will refer them to a pediatric gastroenterologist for endoscopy and biopsy to confirm the diagnosis. Charlotte should continue her current diet until the endoscopy.

Six months later, while on a pediatrics elective, you run into Dr. Jane. She remembers your role with Charlotte and updates you about how she is doing. The biopsy confirmed

the diagnosis of Celiac disease, and the family met with a dietician to learn about a proper gluten-free diet. Now without gluten, Charlotte is a much happier kid with more formed and less frequent stools. At her most recent visit, she was gaining weight and looking well!

Horary, we were able to reason through Charlotte's diarrhea and manage her Celiac disease appropriately. We will wrap things up with a few key points about Celiac disease.

Celiac disease

Celiac disease is an immune-mediated enteropathy. Gluten triggers the production of autoimmune antibodies that subsequently damage the small bowel mucosa. The classic presentation of Celiac disease is a child 6-24 months old with failure to thrive, abdominal pain and distention, and diarrhea. In more severe cases, children can develop nutritional deficiencies, leading to iron deficiency anemia, Rickets, and dental enamel hypoplasia. Older children with Celiac disease may present with short stature, delayed puberty, and/or dermatitis herpetiformis (which is a pruritic vesicular rash on the extensor surfaces of the arms and legs).

There is often a personal or family history of other auto-immune conditions such as type 1 diabetes mellitus and autoimmune thyroiditis. There is also a higher prevalence in children with Down syndrome. If you suspect Celiac disease, you can order transglutaminase antibody (anti-TTG) and IgA levels. Please note that the anti-TTG can be falsely negative if the child has already eliminated or limited gluten in their diet. The child must be eating gluten consistently for a minimum of 3 months before re-testing.

The standard of care is to confirm the diagnosis with endoscopy and duodenal biopsies. Hallmark histologic findings include villous atrophy, elongated crypts, and intra-epithelial lymphocytes. There is emerging evidence that Celiac disease can be diagnosed based on serologic markers, such as if the anti-TTG level is >10x the normal value, although this is not universally accepted as standard of care.

As with Charlotte's case, treatment involves adhering to a strict gluten-free diet. Families will often benefit from working with a dietician. Some patients will develop a secondary lactose intolerance. As such, they may also need to limit lactose in their diet.

Conclusion

That's it for chronic diarrhea! Before we leave, lets finish with some take home points from this podcast:

1) In pediatrics, chronic diarrhea is defined as diarrhea persisting for >2 weeks.
2) The differential diagnosis can be organized by physiological process causing the diarrhea. These are: osmotic, secretory, abnormal motility, and inflammatory. It is also important to differentiate chronic diarrhea in a healthy, thriving child versus diarrhea in a child with weight loss or failure to thrive.
3) Remember to include a review of systems during the history, and complete a thorough physical exam to look for extra-abdominal findings that may point towards a specific diagnosis.

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4) Initial investigations may include basic blood work to check electrolyte and nutrition status, as well as check for markers of inflammation. Stool samples should also be sent to the lab to rule out infectious etiologies.
5) Referral to a pediatric gastroenterologist may be required for further workup, including endoscopy.

You should now be able to:

1) Generate a differential diagnosis for chronic diarrhea
2) Identify key features in the history and physical exam for a child presenting with chronic diarrhea
3) List appropriate investigations that may be ordered to help determine a cause of chronic diarrhea
4) Recognize the clinical presentation, diagnosis, and management of Celiac Disease

That concludes our presentation. Thanks for listening to PedsCases podcasts. Remember to refer to the website where you can find practices cases and questions to help solidify your diarrhea knowledge.

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