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# Diarrhea, Pediatric

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**acute diarrhea** A diarrheal illness of less than 14 days duration. Acute diarrheal disease in children is most often the result of self-limited viral infections. Management includes prompt assessment and repletion of hydration status. Evaluation for an etiologic process is generally not warranted unless there is an associated finding such as blood in the stool or systemic symptoms.

**chronic diarrhea** A diarrheal illness of greater than 14 days duration. Chronic diarrhea in children can be due to either infectious or noninfectious processes. Evaluation for a specific etiology is indicated. Management of comorbid conditions such as poor growth or malnutrition is essential.

**colitis** Any inflammatory process affecting the colon. Colitis usually presents clinically as bloody diarrhea, abdominal cramping, and tenesmus.

**congenital diarrhea** A group of diarrheal illnesses that are present from birth. Congenital diarrhea can be the result of either a specific genetic defect in a secretory or absorptive pathway or abnormal intestinal development.

**gastroenteritis** A diarrheal process that affects the upper gastrointestinal tract and presents most typically as an acute watery diarrhea. Gastroenteritis usually denotes an acute diarrhea that is infectious and self-limiting.

**hemolytic uremic syndrome** A sequela of *Escherichia coli* O157:H7 colitis. This toxin-mediated microangiopathy results in a triad of hemolytic anemia, thrombocytopenia, and renal failure. The occurrence of the syndrome is generally limited to children under 10 years of age.

**inflammatory diarrhea** A diarrheal illness in which the predominant pathologic finding is an invasion of the intestinal epithelium by immunocytes. This type of diarrhea can be the result of either a normal immune response to an abnormal environment, as in infection, or an abnormal immune response to a normal environment, as in inflammatory bowel disease.

**IPEX syndrome (immunodysregulation, polyendocrinopathy, and enteropathy: X-linked)** An inherited X-linked syndrome that results from a mutation in the FOXP3 gene in humans. It is characterized by autoimmune enteropathy and multiple endocrinological abnormalities including diabetes mellitus, hypothyroidism, and hemolytic anemia.

**osmotic diarrhea** A diarrheal illness that is driven by osmotic forces that promote a net flux of water out of the interstitium and into the intestinal lumen. A stool

sodium level of mEq/liter and an osmotic gap of greater than 100 mosm/liter suggest an osmotic diarrhea.

**secretory diarrhea** A diarrheal illness that is driven by the active secretion of salt and water by intestinal epithelial cells. A stool sodium level of >70 mEq/liter, an osmotic gap of less than 100 mosm/liter, and a failure of the diarrhea to respond to a controlled fast suggest a secretory diarrhea.

Diarrheal diseases continue to contribute significant morbidity and mortality to pediatric populations in developed and developing countries around the world. The prevalence of diarrheal illness across cultures is inversely proportional to the availability of public sanitation, clean water supply, and adequate medical care. As such, it is not surprising that the incidence of diarrheal disease is much higher in developing societies and can approach 10 episodes per child per year in children under 5 years of age. In these areas, aggregate mortality can reach 3 to 5 million deaths per year. In the United States and other developed nations, both the incidence (1–2 episodes per year) and mortality (approximately 400–500 deaths annually) are considerably decreased. Nonetheless, the burdens placed on Western health care systems by pediatric diarrheal disease are considerable and approximately 20% of all pediatric ambulatory visits and 10% of all inpatient hospital admissions in children under 3 years of age are for the evaluation and treatment of these disorders and their complications.

The frequency and consistency of stool can vary considerably from individual to individual, as well as in the same individual over time. There has therefore remained a lack of a consensus as to how diarrheal illness should be defined. Investigators have employed a number of qualitative and quantitative dimensions of stool output to address this issue in the past. For the most part, children pass between one and three stools, or approximately 5–10 ml of stool per kilogram of body weight, per day. As such, investigators have begun to use these benchmarks as the upper limits of normal in their identification of subjects in studies addressing acute or chronic diarrheal disease.

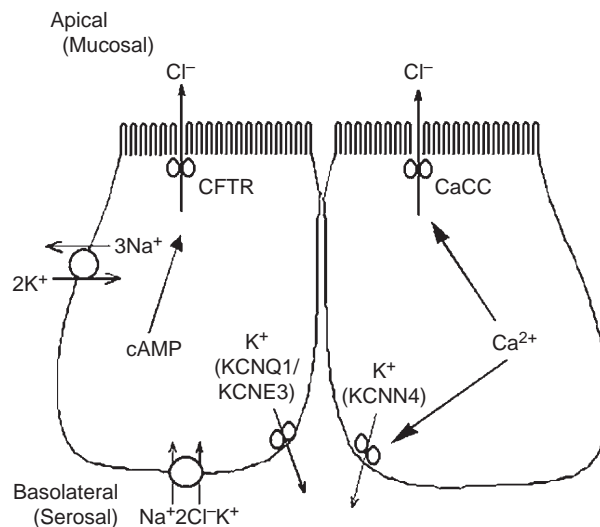
## REGULATION OF INTESTINAL FLUID SECRETION AND ABSORPTION

The mucosa lining the gastrointestinal tract must reconcile daily a seemingly contradictory array of physiologic tasks. These conflicting responsibilities include the maintenance of a tight barrier against potentially virulent bacterial and viral pathogens in the intestinal lumen, while at the same time presenting a selectively permeable interface through which to carry out immune surveillance and nutrient absorption. In this context, intestinal fluid secretion can serve both defensive (flushing away pathogens and toxins) and homeostatic (maintenance of mucosal hydration necessary to facilitate enzymatic digestion) purposes.

Stool output in humans is a composite of ingested, secreted, and absorbed fluid intermixed with residual dietary matter and cellular debris. Adults typically ingest approximately 2 liters of fluid per day and produce an additional 9 liters in the form of salivary, gastric, small intestinal, and pancreato-biliary secretions, to complete the process of digestion. The small intestine and colon have evolved highly efficient intercellular and transcellular pathways for the reabsorption of the vast majority (approximately 99%) of this intestinal fluid, and the average adult will pass only approximately 200 g of stool per day. This balance between fluid secretion and absorption is therefore quite tight. Any microbiologic, dietary, pharmacologic, or hormonal input that affects cell membrane transporters and/or the intercellular tight junctions responsible for fluid absorption can tip this net fluid balance in favor of secretion (or reduced absorption) and thereby trigger the increased stool output observed in patients with diarrheal illnesses.

The cellular basis for salt and water secretion in the intestine, as well as in other hydrated mucosal surfaces in the body, depends upon a vectorial transport of  $\text{Cl}^-$  ions by specialized epithelial cells. Intestinal crypt epithelial cells use basolateral membrane  $\text{Na}^+/\text{K}^+$ -ATPase pumps as well as the  $\text{Na}^+$ - and  $\text{K}^+$ -coupled cotransporter NKCC1 to accumulate  $\text{Cl}^-$  ions above their electrochemical gradient (Fig. 1). The subsequent opening of  $\text{Cl}^-$  channels located in the apical membrane of enterocytes permits sequestered  $\text{Cl}^-$  ions to move down their electrochemical gradient and into the intestinal lumen. The parallel activation of plasma membrane  $\text{K}^+$  channels conducts  $\text{K}^+$  outside, thereby sustaining the inside-negative cell membrane potential that is necessary to initiate and maintain a  $\text{Cl}^-$  secretory response.

Fluid secretion in the intestine is tightly regulated by endocrine as well as neuroenteric mechanisms that utilize either cyclic nucleotides [3',5'-monophosphate (cAMP) or cyclic GMP (cGMP)] or  $\text{Ca}^{2+}$  as second



**FIGURE 1** Intestinal crypt epithelial cells use basolateral membrane  $\text{Na}^+/\text{K}^+$ -ATPase pumps as well as the  $\text{Na}^+$ - and  $\text{K}^+$ -coupled cotransporter NKCC1 to accumulate  $\text{Cl}^-$  ions above their electrochemical gradient. The subsequent opening of  $\text{Cl}^-$  channels located in the apical membrane of enterocytes permits sequestered  $\text{Cl}^-$  ions to move down their electrochemical gradient and into the intestinal lumen. The parallel activation of plasma membrane  $\text{K}^+$  channels conducts  $\text{K}^+$  outside, thereby sustaining the inside-negative cell membrane potential that is necessary to initiate and maintain a  $\text{Cl}^-$  secretory response.

messengers. Cyclic nucleotide-dependent agonists initiate  $\text{Cl}^-$  secretion through the parallel activation of the apical membrane  $\text{Cl}^-$  channel CFTR (the cystic fibrosis transmembrane receptor) as well as the basolateral membrane  $\text{K}^+$  channel KCNQ1/KCNE3. In contrast, agonists utilizing  $\text{Ca}^{2+}$  as a second messenger activate the apical membrane  $\text{Cl}^-$  conductance CaCC in concert with the basolateral membrane  $\text{K}^+$  channel IK1 (KCNN4). The net movement of  $\text{Cl}^-$  ions into the intestinal lumen imparts a transiently negative charge to this extracellular compartment and positively charged  $\text{Na}^+$  ions move via paracellular pathways in response. The osmotic force generated by transported  $\text{Cl}^-$  and  $\text{Na}^+$  ions pulls water molecules along to effect net fluid secretion. The activity of CFTR is regulated primarily by cAMP- and cGMP-dependent protein kinases. In contrast,  $\text{Ca}^{2+}$ -dependent  $\text{Cl}^-$  secretion in the intestine conducted by CLCA appears to be limited by the generation of the intracellular down-regulatory intermediates inositol-3, 4,5,6-tetrakisphosphate, and phosphorylated extracellular signal-regulated kinase.

Whereas  $\text{Cl}^-$  secretion drives intestinal fluid secretion, fluid absorption is mediated primarily by the vectorial transport of  $\text{Na}^+$  ions out of the intestinal lumen and into the interstitium.  $\text{Na}^+$  transport can be

electrogenic (as in the case of apical  $\text{Na}^+$  channels),  $\text{Na}^+$ -coupled, or electroneutral. The accumulation of absorbed  $\text{Na}^+$  ions in the tissue interstitium favors the subsequent movement of  $\text{Cl}^-$  ions and water molecules out of the intestinal lumen via transcellular and paracellular pathways, thereby effecting salt and water uptake.  $\text{Na}^+$  channels have been identified in the apical membrane of gut epithelium. By acting in a coupled fashion with basolateral membrane  $\text{Na}^+/\text{K}^+$ -ATPase pumps, these channels permit luminal  $\text{Na}^+$  ions to move down their electrochemical gradient and into the cell. The favorable  $\text{Na}^+$  gradient established by  $\text{Na}^+/\text{K}^+$  pumps has also been exploited by the small intestine to promote nutrient absorption. SGLT1 is the  $\text{Na}^+$ -coupled glucose transporter expressed along the apical membrane of enterocytes. Similarly,  $\text{Na}^+$  uptake in the small intestine is effected through  $\text{Na}^+$ -coupled amino acid transporters that are present along the enterocyte brush border. Finally, the  $\text{Na}^+/\text{H}^+$  exchanger NHE-3, expressed in the apical membrane of enterocytes, appears to mediate electroneutral  $\text{Na}^+$  transport in the intestine.

The tasks of intestinal fluid secretion and absorption are separated spatially along the length of the crypt–villus axis through a segregation of relevant plasma membrane channels and transporters. Cells newly differentiated at the crypt base display a primarily secretory phenotype and express high levels of CFTR. As these cells mature and migrate up the axis to take up more villous positions, they express increasing numbers of absorptive proteins including NHE-3 and  $\text{Na}^+$ -coupled glucose and amino acid transporters. Stool output is therefore the net product of intestinal fluid secretion originating in crypt cells (which occupy approximately one-third of the crypt–villus axis) and fluid absorption from villus cells (which take up the remaining two-thirds of the crypt–villus axis). Any disorder damaging surface villi, and thereby decreasing the villus/crypt ratio, will selectively decrease mucosal absorptive potential and cause increased stool output. This explains the increased stool output observed in patients with celiac disease, postviral syndromes, and giardiasis.

## APPROACH TO THE CHILD WITH DIARRHEA

Diarrhea can be classified on the basis of several descriptive factors (acute versus chronic, inflammatory versus noninflammatory, infectious versus noninfectious, secretory versus osmotic) that aid in the diagnostic approach. These include the duration of the illness, the existence of a secretory or osmotically driven mechanism, the presence or absence of a pathogen,

and the degree of mucosal inflammation. Although the pathogenesis of diarrheal disease can be explained by a discrete process in some patients, increased stool output is more often the result of a combination of factors. As such, patients with inflammatory diarrhea can present with a secretory component due to the local release of endogenous secretagogues. Clinical diagnosis rests on an understanding of the close interplay between environmental and host factors in these patients.

Central to the diagnosis of a diarrheal illness is the clinical context in which it presents. Characteristics of the individual, such as age, are often the first clue in determining an etiology. This is most apparent in the case of congenital diarrheas, which present exclusively within the first few days of life. Components of the child's overall health, such as atopy or immunodeficiency, can also suggest a particular etiology. Environmental factors, including diet, must also be taken into consideration in the diagnostic approach to the pediatric patient with diarrhea. In the setting of infectious diarrhea, an exposure history such as an ill contact at home or in daycare, a recent travel history, or contact with a pet or animal, can sometimes provide useful epidemiologic information when attempting to understand how a pathogen may have been acquired.

The character of the stool itself is often helpful when arriving at a specific diagnosis. Stool that is both watery and voluminous in nature suggests an abnormality in the absorptive or secretory function of the small intestine. In contrast, crampy abdominal pain, tenesmus, and the presence of frank blood in the stool suggest colitis or large bowel disease.

Several aspects of diarrheal disease in children merit special consideration. Children, and most especially infants, are more susceptible to dehydration than their adult counterparts. This is due both to their greater overall body surface area relative to their weight and to a dependence on caregivers, who may be less likely to offer fluids to or feed a child who is vomiting or appears ill. Poor growth and malnutrition can also become a factor in children when diarrhea is chronic in nature. During infancy and early childhood, a large proportion of caloric intake is devoted to growth. Diarrheal disease, resulting in inadequate intake or poor nutrient absorption during this critical developmental period, can alter weight gain and, in severe cases, result in stunted linear growth.

The scope of the remaining article will discuss the causes, evaluation, and treatment of diarrheal disease in infants and children. By convention, the discussion will be segregated into infectious causes and noninfectious causes with a special reference to age of onset where appropriate.

## INFECTIOUS DIARRHEA IN CHILDREN

Infectious diarrhea is usually of acute onset in a previously healthy child. Fortunately, most causes of infectious diarrhea are self-limited and require only symptomatic care. However, if left untreated, acute diarrheal illness can progress to chronic diarrhea in some patients. Fever is a common associated symptom of infectious diarrhea and vomiting is not unusual, especially if the infection occurs in the upper gastrointestinal tract (i.e., gastroenteritis). In general, infectious diarrheas are secretory or mixed secretory/osmotic in character. Toxin production, pathogen adherence, or frank tissue invasion all can contribute to increased  $\text{Cl}^-$  secretion by affected epithelial cells. When pathogenic invasion of the epithelium occurs, there is usually an inflammatory component to the diarrhea as well. Pathogens that cause diarrhea can be viral, bacterial, or parasitic.

Viruses are the most common cause of acute infectious gastroenteritis in children (Table I, part A). There

are several reasons for the preponderance of cases of viral diarrheas. The naive immune system of an infant has not been exposed to many of the viral pathogens present in the environment. In addition, daycare provides group settings that facilitate the transmission of enteric and respiratory viral diseases.

Rotavirus is the most common viral pathogen. All children exposed to rotavirus, regardless of whether or not they manifest symptomatic diarrhea, will develop circulating antibodies to this pathogen. The decreasing incidence of rotavirus in adults is thought to be due to the protective effect of these antibodies. Rotaviruses are small, wheel-shaped viruses approximately 70 nm in diameter. Of the four major groups (A, B, C, and D), type A viruses are the most important in children. The virus invades the epithelium and promotes an inflammatory response that ultimately contributes to the destruction of the villous surface. However, the frequency and severity of stool output in these patients does not correlate closely with the degree of intestinal damage observed endoscopically or histologically. This has led to the speculation that there are other pathogenic mechanisms that contribute to the malabsorption and net fluid losses observed in these patients. Although villous destruction can be severe in rotaviral disease, recovery is rapid in most patients and symptoms typically resolve in 2 to 7 days.

Caliciviruses, including the Norwalk and Norwalk-type agents, are the second leading cause of pediatric viral diarrheas. This group of viruses presents in a similar fashion to rotavirus, with the exception that the diarrhea is usually milder. Astroviruses are similar to caliciviruses and are a common cause of diarrheal illness. Adenovirus (serotypes 40 and 41) is a well-established cause of viral diarrhea and has a slightly longer incubation period and a longer course than rotaviral disease. More recently, Torovirus has been implicated as a potential cause of diarrhea in children. However, more definitive epidemiologic data concerning this pathogen are currently lacking.

Bacterial infections can also cause diarrheal disease in infants and children (Table I, part B). As in the case of viral diarrhea, the onset of bacterial illness is usually acute and presents with fever and sometimes vomiting. Because the most common forms of bacterial diarrhea are invasive, bloody diarrhea is often reported in these patients. Specific types of bacterial illness have been reported to occur more commonly in specific age groups. *Campylobacter jejuni*, for instance, has a bimodal distribution of onset with the first peak occurring in children from 1 to 5 years old and a second peak in adolescents. Nontyphoid *Salmonella enteritidis* can cause a bacteremia in infants and in

TABLE I Etiology of Pediatric Diarrhea

Infectious diarrhea	Noninfectious diarrhea
<b>A. Viral pathogens</b>	<b>D. Inflammatory</b>
Rotavirus	Inflammatory bowel disease
Adenovirus	Celiac disease
Norwalk agent	Allergic enteropathy
Calicivirus	Autoimmune enteropathy
Astrovirus	Graft-versus-host disease
Coronavirus	<b>E. Noninflammatory</b>
<b>B. Bacterial pathogens</b>	<b>Congenital diarrheas</b>
<i>Campylobacter</i> spp.	Congenital chloride diarrhea
<i>Salmonella</i> spp.	Congenital sodium diarrhea
<i>Shigella</i> spp.	Microvillus inclusion disease
<i>Escherichia coli</i>	Tufting enteropathy
Enterotoxigenic	Carbohydrate transporter defects
Enteropathogenic	Dissaccharidase deficiency
Enterohemorrhagic (shigatoxin producing)	Amino acid transporter defects
Enteroadherent	
Enteroinvasive	
<i>Yersinia</i> spp.	
<i>Vibrio</i> spp.	
<i>Aeromonas</i> spp.	
<i>Plesiomonas</i> spp.	
<i>Clostridium difficile</i>	
<b>C. Parasitic pathogens</b>	<b>Acquired diarrheas</b>
<i>Giardia lamblia</i>	Toddler's diarrhea
Cryptosporidia	Short bowel syndrome
Cyclosporida	Small bowel overgrowth
<i>Entamoeba histolytica</i>	Antibiotic-associated diarrhea
Nematodes	Münchhausen's syndrome
Cestodes (tapeworms)	Secondary lactase deficiency
Trematodes	

immunocompromised hosts. *Shigella* species can be found in the toddler age group, but is not a commonly isolated pathogen in the United States. *Clostridium difficile*, an important cause of antibiotic-associated diarrhea in adults, is not usually a pathogen in infants. *C. difficile* toxin can be found in up to 10% of healthy newborns and is even more prevalent in neonatal intensive care units. The reason for the inability of this organism to cause diarrhea in infants remains unclear. Based on animal studies, it is thought that the receptor for this toxin is developmentally regulated and absent in early infancy. *Vibrio cholerae* causes a prototypical bacterial secretory diarrhea. It produces a toxin composed of two subunits. The B, or binding, subunit displays a pentameric form that binds selectively to the ganglioside GM<sub>1</sub>. The A, or active, subunit is internalized by intestinal epithelia, alters signal transduction, and leads to increased production of cAMP and Cl<sup>-</sup> secretion. Other forms of toxin-producing organisms include enterotoxigenic *Escherichia coli*, the pathogen responsible for traveler's diarrhea, and organisms responsible for acute food poisoning such as *Staphylococcus aureus* and *Bacillus cereus*. *E. coli* O157:H7 is an important pathogen in children. This enteropathic *E. coli* adheres to the intestinal lumen and produces a toxin that is absorbed and causes the hemolytic–uremic syndrome.

Parasitic disease causing diarrhea is far less common in industrialized countries (Table I, part C). One notable exception is *Giardia lamblia*, which is especially prevalent in the daycare setting. *Giardia* can present as an acute diarrheal illness or as a more chronic process. The mechanism by which this organism causes diarrhea is not fully understood. There is no gross alteration in intestinal architecture or evidence of a significant immunologic response. There are multiple other parasites that can cause diarrheal disease in children. However, these occur much less commonly and will not be discussed further.

## NONINFECTIOUS DIARRHEA IN CHILDREN

Occasionally, a child will present with a diarrheal illness that is not self-limiting. Fever may or may not be present and other co-morbidities, such as growth failure and malnutrition may be prominent. Stool cultures are negative. The etiology of diarrheal disease in these patients can be broadly classified as being inflammatory or non-inflammatory in nature, based on clinical history, physical examination, and biochemical workup. Similar to patients with infectious diarrhea, the increased stool

output observed in these patients is typically the result of a combination of pathogenic mechanisms.

### Inflammatory Diarrhea

The intestine displays a tremendous capacity to generate an immune response based on the presence of numerous effector immunocytes that lie within the intestinal mucosa and submucosa. More recent data have demonstrated that intestinal epithelial cells themselves also possess the ability to process luminal antigens and present them to the underlying immune cells. The intestinal epithelium is in constant contact with the external environment. It is subsequently in a constant state of low-grade inflammation (often referred to as “physiologic inflammation”) that is the result of the epithelium playing its role in the surveillance of and response to the broad array of dietary, microbiologic, and toxigenic stimuli present within the intestinal lumen. When the degree of mucosal inflammation is severe enough to affect the absorptive and secretory function of the intestine, diarrhea ensues.

A number of immune defects or imbalances can affect the intestine (Table I, part D). Inflammatory bowel disease is example of an inflammatory diarrhea that is likely the result of a genetically driven dysregulated immune response to the luminal environment. It is also likely that genetic predisposition may leave some individuals vulnerable to an exaggerated immune response to dietary antigens that are usually not perceived to be a threat to intestinal function. This may explain the incidence of allergic enteropathies in some children. In patients with celiac disease, or gluten-sensitive enteropathy, there is an immune-mediated response to a protein present in wheat and related grain products. Although these patients can show marked diarrhea, they more commonly present with a failure to thrive precipitated by the introduction of wheat-containing solid foods between 6 and 9 months of age.

Autoimmune disease can target the intestinal epithelium itself and antibodies directed against enterocytes contribute to the severe inflammation and tissue destruction observed histologically in these patients. The IPEX syndrome is an X-linked autoimmune enteropathy that is associated with polyendocrinopathy and results in high morbidity and mortality. The gene defect is thought to lie within the FOXP3 gene and it has been shown to encode the protein scurf, a regulator of T-cell function in mice. The important role played by lymphocytes in maintaining intestinal barrier function can be appreciated in the context of bone-marrow transplant recipients. Diarrhea is a major feature of graft-versus-host disease, a clinical condition in which

donor lymphocytes recognize host intestinal epithelial cells as being foreign. Activated immunocytes subsequently initiate a destructive process that is manifest histologically as increased epithelial cell apoptosis and clinically as a secretory or inflammatory diarrhea.

### Noninflammatory Diarrheas

Children can also suffer from diarrhea that is neither infectious nor inflammatory in nature. These diarrheal illnesses can be broadly categorized into congenital or acquired forms (Table I, part E). Congenital diarrheas are most often the result of abnormal gene expression, resulting in a clinical presentation within the first week of life. Congenital chloride diarrhea is caused by a mutation in the Down-Regulated in Adenoma (DRA) gene, thought to be a colonic chloride transporter. This disease presents uniformly *in utero* with polyhydramnios. Severe diarrhea and abdominal distension appear shortly after birth and profound electrolyte disturbances can occur in these patients if not resuscitated promptly. In contrast, the cause of congenital sodium diarrhea is not known but is thought to be due to a functional uncoupling of sodium and hydrogen exchange in the intestine. No mutations have been described in the known Na<sup>+</sup>/H<sup>+</sup> exchangers in the intestine to date. The clinical presentation of congenital sodium diarrhea is similar to congenital chloride diarrhea with the exception that stool chloride levels in these patients are typically lower and the stool pH tends to be more alkaline. In addition to defects in ion transporters, there have been a number of diseases that have been described with altered transport of glucose, galactose, and amino acids. Gastrointestinal symptoms vary from defect to defect. Amino acid transport defects often have extraintestinal manifestations whose consequences far outweigh changes in bowel patterns.

Congenital diarrheas can also be caused by genetic defects that result in the malabsorption of the products of digestion such as carbohydrates and fat. Congenital disaccharidase deficiencies are rare and result in an osmotically driven diarrhea. Much more common are the transient and secondary deficiencies in mucosal disaccharidase levels that result from small intestinal injury or inflammation. Fat malabsorption can also present with diarrhea of variable severity. Congenital fat malabsorption can be the result of pancreatic insufficiency, seen in patients with cystic fibrosis, or due to specific genetic defects such as abetalipoproteinemia. Fat malabsorption is characterized by varying degrees of greasy and malodorous stools. Finally, congenital disorders of the intestinal architecture can lead to diarrhea. Microvillus inclusion disease is a rare autosomal

recessive disease that is characterized by severe watery diarrhea at birth. Diagnosis is based on a histologic demonstration of marked or complete villous atrophy and electron microscopic evidence of intracellular microvillus inclusions and absent or rare microvilli.

There are multiple acquired forms of pediatric diarrhea that can be characterized as being noninfectious and noninflammatory in nature. Often, these diarrheas result from a predisposing insult that diminishes the ability of the intestinal mucosa to absorb nutrients, thereby contributing to an osmotic diarrhea. The most common example of this is toddler's diarrhea or chronic nonspecific diarrhea of childhood. There is no underlying inflammatory or biochemical abnormality that drives the increased stool output seen in these young children. In many cases, these patients will respond to a reduced dietary intake of fruit juices. Because many of these juices contain large amounts of sorbitol, an indigestible carbohydrate, they can induce an osmotic diarrhea. As such, the diarrhea will resolve in most patients within a few days after removal of the offending juice. Other examples of acquired and primarily noninflammatory diarrheas that fall into this category include antibiotic-associated diarrhea, short bowel syndrome, and small bowel bacterial overgrowth. Additionally, Münchhausen's syndrome-by-proxy must always be considered in children with diarrhea and no predisposing factors.

### LABORATORY EVALUATION OF DIARRHEA

Laboratory evaluation of the pediatric patient with diarrhea varies with the suspected cause and is dictated by the clinical picture. Any suspicions about potential inflammation or bacterial infection should be addressed immediately. Evaluation of acute diarrhea is usually limited to cases in which a given patient is presenting with systemic symptoms or co-morbidities. Chronic diarrhea must always be evaluated, especially in the context of poor growth or malnutrition. An evaluation that proceeds in a logical and stepwise manner generally results in the most expedient and cost-effective diagnosis.

The first step in the evaluation process is to determine whether or not the presenting patient's symptoms are most consistent with an inflammatory or noninflammatory process. This can be done by an examination of the stool for gross or occult blood or the presence of fecal leukocytes. Previous studies have also demonstrated the sensitivity and specificity of biochemical assays for fecal lactoferrin, a constituent of neutrophil granules. Patients with infectious or inflammatory diarrhea will

typically present with rectal bleeding or overt (positive fecal leukocyte smear) or biochemical evidence (lactoferrin) of fecal white blood cells. In contrast, these studies should be negative in patients with noninflammatory (viral, osmotic, or secretory) diarrheal disease. Nonetheless, although these markers may increase the yield of sending stool cultures, they do not exclude intestinal inflammation and any final decision about pursuing an infectious workup must be made on clinical grounds.

If there is clinical or biochemical evidence of an inflammatory process, then routine stool cultures remain the gold standard in the search for a bacterial cause of diarrhea. Most hospital-based laboratories have a standard panel of cultures associated with common pathogens including *Campylobacter*, *Shigella*, *Salmonella*, and *Yersinia enterocolitica*. Many hospitals also routinely screen for *E. coli* O157:H7. The identification of some pathogens relies on the detection of a particular toxin that is produced by the bacteria and released into the stool. *C. difficile* is perhaps the best recognized pathogen in this class.

The diagnosis of parasitic disease is most often made by a close microscopic evaluation of the stool for ova and parasites. The identification of *Giardia* and Cryptosporidia has been further facilitated by the development of enzyme-linked immunosorbent assay (ELISA)-based stool tests. It is imperative to know a specific laboratory's capabilities and limitations prior to interpreting the results of any stool, toxin, or parasitic studies.

Most "noninflammatory" diarrheal disease is viral in nature. However, routine evaluation of stool for viral pathogens is not often useful because of the self-limiting nature of the disease process in the vast majority of patients, the specialized nature of obtaining viral cultures, and the expense of detecting specific viral pathogens. One notable exception is the rotavirus stool antigen test. This commercially available ELISA-based test provides relatively rapid results that can assist both in patient care and in making decisions about the need for isolation of hospitalized patients. Other viral stool tests include polymerase chain reaction-based screening for viral DNA in the case of adenovirus. However, these more costly and specialized tests are typically reserved for the evaluation of immunocompromised patients, in whom targeted supportive or antiviral therapy is much more critical.

Characterization of the stool can be helpful for determining the nature of noninflammatory diarrheal illness. Stool evaluation for fat, pH, and reducing substances is important in determining whether or not there is an underlying malabsorptive process. The presence of "neutral" fat in the stool suggests some

deficiency in the production or delivery of pancreatic (lipase) or hepatic (bile acid) secretions into the intestinal lumen. An increase in "split" fat in the stool indicates a primary inability of enterocytes to perform fat absorption. Reducing substances are the result of undigested carbohydrates making their way into the large intestine. The presence of these fecal sugars can be readily assessed with commercially available colorimetric strips or test solutions. It must be remembered that sucrose is a nonreducing sugar. As such, stool must first be pretreated with an acid solution to make this nonreducing sugar detectable. Undigested carbohydrates, as well as dietary fiber, are consumed by bacteria in the large bowel and generate short-chain fatty acids. Carbohydrate malabsorption can therefore also be assessed by a fall in stool pH.

Stool electrolytes can help to determine whether or not a diarrheal process is secretory in nature. In general, a stool  $\text{Na}^+$  concentration of greater than 70 mEq/liter is indicative of a secretory process. The stool osmotic gap, calculated by

$$([\text{Na}^+] + [\text{K}^+]) \times 2 - \text{stool osmolarity}$$

$$[\text{Na}^+] = \text{concentration of Na}$$

$$[\text{K}^+] = \text{concentration of K}$$

is useful in distinguishing between osmotic and secretory diarrheal disease. An osmotic gap greater than 100 mosm/liter suggests an underlying osmotic process. Similarly, whereas osmotic diarrhea will typically respond to a dietary fast, secretory diarrheal diseases are driven by processes that are independent of exogenous (dietary or pharmaceutical) factors.

The ability to study the large and small intestine of patients using videoscopic endoscopy has greatly advanced the ability to diagnose and treat diarrheal disease in pediatric and adult patients. Clinicians are now able to assess the gross appearance of the lining of the small and large intestine, obtain biopsy samples for histologic examination, measure directly mucosal disaccharidase levels, collect pancreatic and biliary secretions, and sample fluid from the small intestine for quantitative culture.

Blood tests can often prove to be useful adjuncts to stool studies. Peripheral eosinophilia may point to an underlying allergic disease. Decreased serum albumin levels can suggest malnutrition or a protein-losing enteropathy. Specialized serum tests such as the detection of antibodies directed against tissue transglutaminase are highly predictive of celiac disease. However, for most patients, blood work plays a



supportive role in the workup of diarrheal disease. Results from serologic studies most often suggest an etiology that will need to be confirmed by more definite stool or endoscopic studies.

## TREATMENT OF DIARRHEAL DISEASE

The treatment of pediatric diarrheal disease can be divided into symptomatic and curative therapies. First and foremost in the treatment of any child with diarrhea is a prompt assessment of hydration status. For most cases of mild to moderate diarrhea, oral rehydration solutions are the first line of therapy. When oral intake is limited secondary to an altered mental status or when severe dehydration or shock is present, intravenous replacement of fluid and electrolytes can be lifesaving. Once the patient is adequately hydrated, the diet may be readily advanced. The provision of adequate calories is critical to maintain an anabolic state that will provide the metabolic fuel necessary to promote epithelial restitution. The advantages of enteral supplementation should not be overlooked as luminal contents have been shown to be trophic to the intestinal epithelium. A transient lactose intolerance may occur in either acute or chronic diarrhea. This can be addressed using soy, rice-based, or lactose-free milk products. High-fructose and sorbitol-containing drinks are palatable, but should be avoided due to the increased osmotic load they place on an already compromised epithelial lining. Other supportive measures that have been used include anti-secretory agents, anti-motility agents, and resin binders. These agents decrease overall stool output by slowing intestinal transit. Although clinically beneficial in most cases, clinicians must be wary of the possibility that these agents can contribute to third-spacing of body fluid in distended and pharmacologically atonic intestinal loops.

Specific therapies that are designed to treat the underlying cause of diarrhea can be employed. This includes antibiotic use in certain forms of infectious diarrheas. In general, however, antibiotics should be avoided in patients with diarrheal disease unless there are systemic consequences of the diarrhea, such as that observed with *Salmonella* infections in infants and the elderly. Inappropriate antibiotic use can lead to resistant organisms or prolong the carrier state. Notable exceptions include infectious diarrheas that may become chronic if left untreated, such as diarrhea caused by *C. difficile* and *G. lamblia*.

Other specific therapies for diarrheal disease in pediatric patients include the following: immunosuppression in the immunologically mediated diarrheas such as inflammatory bowel disease or autoimmune

enteropathy; specific replacement of electrolytes in the case of the congenital chloride and sodium diarrheas; or enzyme replacement therapy in patients with pancreatic insufficiency or lactose intolerance. Removal of an offending agent, such as gluten-containing foods in celiac disease, lactose in lactase deficiency, or specific dietary antigens in congenital or acquired protein intolerances, can be critical in certain diarrheal illnesses.

## SUMMARY

The intestine is a site of competing physiologic processes including salt and water secretion, nutrient absorption, and immune surveillance. Stool output is subsequently the net product of opposing secretory and absorptive capacities that are separated geographically along the length of the intestine as well as along the length of the crypt–villus axis. Any disruption of these tightly regulated homeostatic processes can lead to altered stool formation and the development of pathologic diarrhea. In most cases, these illnesses are self-limited in nature and respond favorably to supportive measures. Nonetheless, pediatric diarrheal diseases remain a significant cause of morbidity and mortality worldwide.

The diagnostic approach to diarrheal disease in children differs substantially from that pursued in other age groups. Consideration must be given to congenital or developmental etiologies not seen in adult populations. Moreover, because children are still growing, the impact of chronic diarrheal processes on linear growth and physical development must also be addressed. Evaluation of diarrheal disease in pediatric patients should proceed in a stepwise fashion that begins with an in-depth clinical history and includes a limited number of microbiologic and biochemical tests. Physicians with a firm grasp of the epidemiology and pathogenesis of diarrheal illness in children will be better positioned to pursue a rational approach to the diagnosis and management of their pediatric patients with these common and potentially debilitating illnesses.

## See Also the Following Articles

Anti-Diarrheal Drugs • Bacterial Toxins • Carbohydrate and Lactose Malabsorption • Colitis, Ulcerative (Pediatric) • Diarrhea • Diarrhea, Infectious • Gastroenteritis • Malabsorption • Malnutrition

## Further Reading

American Academy of Pediatrics. Provisional Committee on Quality Improvement, Sub-committee on Acute Gastroenteritis (1996). Practice parameter: The management of acute gastroenteritis in young children. *Pediatrics* 97, 424–435.

- Corrigan, J. J., and Boineau, F. G. (2001). Hemolytic-uremic syndrome. *Pediatr. Rev.* **22**, 365–369.
- Fuller, C. M., Ji, H. L., Tousson, A., Elble, R. C., Pauli, B. U., and Benos, D. J. (2001). Ca<sup>2+</sup>-activated Cl<sup>-</sup> channels: A newly emerging anion transport family. *Pflug. Arch.* **443**, S107–S110.
- Guandalini, S. (2000). Acute diarrhea. In "Pediatric Gastrointestinal Disease" (W. A. Walker, P. R. Drurie, J. R. Hamilton, and J. B. Watkins, eds.), pp. 28–38. B. C. Decker, Lewiston, NY.
- Jensen, B. S., Strobaek, D., Olesen, S. P., and Christophersen, P. (2001). The Ca<sup>2+</sup>-activated K<sup>+</sup> channel of intermediate conductance: A molecular target for novel treatments? *Curr. Drug Targets* **2**, 401–422.
- Keely, S. J., and Barrett, K. E. (2000). Regulation of chloride secretion: Novel pathways and messengers. *Ann. N. Y. Acad. Sci.* **915**, 67–76.
- Ramaswamy, K., and Jacobson, K. (2001). Infectious diarrhea in children. *Gastroenterol. Clin. North Am.* **30**, 611–624.
- Rudolph, J. A., and Cohen, M. B. (1999). New causes and treatments for infectious diarrhea in children. *Curr. Gastroenterol. Rep.* **1**, 238–244.
- Sandhu, B. K. (2001). Practical guidelines for the management of gastroenteritis in children. *J. Pediatr. Gastroenterol. Nutr.* **33**, S36–S39.
- Schroeder, B. C., Waldegger, S., Fehr, S., Bleich, M., Warth, R., Greger, R., and Jentsch, T. J. (2000). A constitutively open potassium channel formed by KCNQ1 and KCNE3. *Nature* **403**, 196–199.
- Sellin, J. H. (1993). Intestinal electrolyte absorption and secretion. In "Gastrointestinal and Liver Disease" (M. Feldman, B. F. Sharshmidt, and M. H. Sleisenger, eds.), pp. 1451–1471. W. B. Saunders, Philadelphia, PA.
- Sicherer, S. H. (2002). Food allergy. *Lancet* **360**, 701–710.
- Vanderhoof, J. A. (1998). Chronic diarrhea. *Pediatr. Rev.* **19**, 418–422.
- Velázquez, F. R., Matson, D. O., Guerrero, M. L., Shults, J., et al. (2000). Serum antibody as a marker of protection against natural rotavirus infection and disease. *J. Infect. Dis.* **182**, 1602–1609.
- Wildin, R. S., Smyk-Pearson, S., and Filipovich, A. H. (2002). Clinical and molecular features of the immunodysregulation, polyendocrinopathy, enteropathy, X linked (IPEX) syndrome. *J. Med. Genet.* **39**, 537–545.



## Diet and Environment, Role in Colon Cancer

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**colorectal adenocarcinoma** A malignant neoplasm of the colon or rectum.

**colorectal adenoma** A benign neoplasm of the colon or rectum with malignant potential.

**colorectal polyp** A growth protruding from the mucosal surface into the bowel lumen.

**dietary fiber** The components of plant material that are resistant to digestive secretions produced by humans.

Significant progress has been made over the past decade in identifying factors that modify the risk of colorectal cancer. Large international variation in colorectal cancer incidence and mortality rates, and the prominent increases in the incidence of colorectal cancer in groups that migrated from low to high incidence areas, provided important evidence that lifestyle factors influence the development of this malignancy. These observations formed the basis for various hypotheses of lifestyle factors in the etiology of colorectal neoplasia.

The focus of this article is on the role of diet in relation to colorectal cancer.

### FAT AND RED MEAT

Rates of colon cancer are strongly correlated with national per capita disappearance of animal fat and meat, with correlation coefficients ranging between 0.8 and 0.9. A sharp increase in colon cancer incidence rates in Japan in the decades following World War II coincided with a 2.5-fold increase in fat intake. Intake of animal or saturated fat or red meat has been shown to be associated with colon cancer risk; however, some studies do not support these associations. Data from earlier epidemiologic studies provided some evidence for a positive association between dietary fat and increased risk of several cancers, including the colorectum. However, an overall review of studies