Salmonella, Shigella, and Campylobacter: Common Bacterial Causes of Infectious Diarrhea

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The most common bacterial causes of infectious diarrhea in children are Salmonella, Shigella, and Campylobacter species. In 1992, pediatric cases represented 45% and 62% of cases of Salmonella and Shigella-related diarrhea, respectively. Although this article reviews in some detail the differences among the clinical and epidemiologic presentations of infections caused by these organisms, there are as many, if not more, similarities (Table 1). Each of these infections is spread most commonly by the fecal-oral route, although contaminated water and food products are implicated occasionally. In addition, animals are an occasional mode of spread for both Campylobacter and Salmonella, the latter often by reptiles (turtles). The incubation period in each case is relatively brief, commonly 48 hours or less. With each pathogen, the duration of diarrhea and other abdominal symptoms, when untreated, is between 2 and 7 days. Dissemination beyond the intestinal tract is unusual, with exceptions noted.

The pediatrician should suspect bacterial etiologies of acute infectious diarrhea when the onset is sudden, especially when it is associated with signs of intraluminal inflammation, such as blood or mucous in stools. However, each of these pathogens, including Shigella, can be associated with a watery, presumably osmotic diarrhea, and the absence of blood or mucous should not rule out this diagnosis if it is otherwise suggested epidemiologically or clinically. A useful screening test for the presence of inflammatory diarrhea is the Giemsa or Wright's stain. The presence of white blood cells on a fecal smear so stained suggests the presence of one of these pathogens. However, the sensitivity of this test is 60% to 70% at best, and as noted, the absence of white blood cells in the stool does not definitively rule out these pathogens.

The economic implications of infections caused by these organisms is significant. In 1992, there were more than 28,000 documented cases of infectious diarrhea in
US children due to Salmonella and Shigella species. Even with likely significant underreporting, it is estimated that Salmonella- and Campylobacter-related infectious diarrhea are each associated with more than $1 billion in economic losses each year in the United States alone. Although a specific figure for shigella has not been developed, its potential for spread in the day-care setting are particularly ominous, and it is likely that the economic costs of infection caused by this organism are of the same magnitude.

Each of these organisms is cultured fairly simply on routine laboratory media. A full description is included in a separate article of this issue (Hoshiko M. "Laboratory Diagnosis of Infectious Diarrhea," pages 570-574). Salmonella and Shigella species are typically cultured on Salmonella-Shigella (SS) agar. Other agars, including MacConkey, xylose-lysine-deoxycholate (XLD), and eosin-methylene blue (EMB) agars, are used sometimes. Salmonella and Shigella grow on routine MacConkey agar as clear (lactose-negative) colonies. Because stool cultures typically contain an abundance of lactose-positive organisms (Escherichia coli, Klebsiella, and Proteus), the absence of lactose-negative colonies on screening agar helps the clinician to rapidly exclude the possibility of salmonella and shigella infection even before the final laboratory report. Campylobacter species require special laboratory processing, which is available in most laboratories. Selective enrichment agars, such as campy-blood agar and similar media, enhance the growth of this organism. Furthermore, because Campylobacter species are commonly microaerophilic and grow better at 42°C, the media used for growth of this organism are cultured in enhanced carbon dioxide at 42°C.

Physicians should know the specific meaning of a "negative" stool culture report. Most laboratories provide a clear report on stool cultures, such as "Negative for Salmonella, Shigella, and Campylobacter species." Other bacterial causes of infectious diarrhea, such as Aeromonas, Yersinia, and others, typically require special media processing, and the clinician must discuss his or her suspicions with the laboratory for best results.

**SALMONELLA**

Although there has been much confusion about the speciation and serology of salmonella infections, the most straightforward classification is between typhoidal and nontyphoidal species. The latter is commonly referred to as *Salmonella enteritidis* and possesses numerous serotypes that are probably not separate species. *Salmonella typhi* is discussed separately. Salmonella gastroenteritis is typically spread by the fecal-oral route with outbreaks commonly associated with contaminated eggs, dairy products, and meats. Turtles have been shown to be common excreters of this organism, hence their commercial sale in the United States has been terminated. Immunity to salmonella infections unfortunately is short-lived, and susceptibility to identical serotypes has been documented. Susceptibility to infection is increased with alterations in gastrointestinal motility, antibiotic use, malnutrition, and achlorhydria. Enhanced severity of disease has been associated with a variety of hemolytic anemias (especially sickle cell disease in the United States), immunosuppression, malaria, and human immunodeficiency virus infection.

Diagnosis is best made by stool culture, described above. Serology for salmonella infection is imprecise and often nonspecific. Its use cannot be recommended. There is little evidence that antibiotics are
useful in the management of milder manifestations of acute gastroenteritis caused by Salmonella species. This recommendation is altered for young infants, who should be treated as described separately. Bacteremia and dissemination rarely occurs in older children and adults, but can occur in 5% to 40% of infants with gastroenteritis. Localized infections occur in up to 10% of those with bacteremia with the most common sites of dissemination including the meningi, skeletal system, heart, and kidneys. Enteric fever is commonly caused by S typhi, but can be seen occasionally with several other salmonella serotypes. In this latter condition, there is rather insidious onset of malaise, progressive fever with abdominal pain or constipation, and bradycardia, relative to the height of fever. After approximately 1 week, diarrhea may develop concurrent with a rash (rose spots). Identification of the organism during the first week of illness is best accomplished by blood or bone marrow culture. During the second week, stool cultures are commonly positive and blood cultures are occasionally positive. If untreated, the disease may progress during the third week to include hepatitis, myocarditis, cholecystitis, gastrointestinal hemorrhage, and manifestations of the systemic inflammatory response syndrome. After the third week, cultures are often negative, and the diagnosis may need to be made clinically or serologically.4

Routine handwashing precautions are appropriate for the prevention of spread of salmonella infections. Food handlers are the only group for whom routine reculture is recommended because of the risk of further spreading this infection. Children in day care need to be excluded only if diarrhea is present. Individual day-care centers may have policies concerning exclusion of children who have had an episode of salmonella gastroenteritis that are overly aggressive, and the pediatrician may need to intervene with more scientific recommendations. Routine culture of contacts is not recommended unless they are symptomatic.

Asymptomatic chronic excretion of salmonella occurs in less than 1% of patients with nontyphoidal infection. It is slightly more frequent with enteric fever, with rates as high as 4% being reported. Chronic carriage seems to be more common in females and infants and those with preexisting biliary tract disease.

As noted above, antibiotics should be used only in those with typhoid (enteric) fever or an invasive infection. In these cases, ampicillin, chloramphenicol or trimethoprim-sulfamethoxazole can be used based on local susceptibility results. In our hospital, trimethoprim-sulfamethoxazole has the highest susceptibility rate, 97% in 1993 (Figure). Patients with invasive infection should be treated with a broad-spectrum cephalosporin such as cefotaxime or ceftriaxone. The infant younger than 1 year of age has been the subject of several clinical studies. A cautious approach is to culture the blood of all infants with salmonella infection and prescribe empiric systemic antimicrobial therapy until a negative blood culture can be confirmed. A reasonable consensus approach to such infants is described in Table 2.

Several salmonella vaccines are available, although none are widely used. An inactivated whole-cell vaccine has been shown to have efficacy rates of 51% to 70%, while an oral live attenuated vaccine may have slightly greater efficacy but has not been well studied in children.

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SHIGELLA

Shigella infections are associated with four species, each of a different serogroup: Shigella dysenteriae (subgroup A), Shigella flexneri (subgroup B), Shigella boydii (subgroup C), and Shigella sonnei (subgroup D). Again, the fecal-oral route is the common mode of transmission. Outbreaks have been associated with contaminated water or food, swimming pool exposures, and day-care centers. The disease is more common in the summer and fall. Virulence factors for shigellosis infections have been well studied. Briefly, the organism usually produces cytotoxins (verotoxins), which mediate systemic effects including neurotoxicity and seizures. The organism itself can penetrate intestinal epithelium wherein multiplication and inflammation can lead to mucosal and submucosal ulcerations and abscesses. Both humoral and cell-mediated immunity occurs, but prior infection confers only partial protection from subsequent exposure.

The clinical manifestations of shigellosis are somewhat stereotypic after an incubation period of 24 to 48 hours. High fever, abdominal pain, and voluminous watery diarrhea begin, followed within 24 hours by decreasing diarrheal volumes and increasing mucous and blood. Some patients present with bloody diarrhea and occasional patients have only watery diarrhea, which therefore does not exclude the possibility of shigellosis, if suggested epidemiologically. The diagnosis is made by stool culture, as described above. Serologic techniques have not been useful, mainly because of cross antigenicity between shigella and some strains of E. coli. Leukocyte counts are usually normal, but both leukopenia and significant leukocytosis (leukemoid reaction) can occur with a significant shift to immature leukocyte forms.

The duration of diarrhea, even when untreated, is seldom more than 4 to 5 days. Complications include neurotoxicity with seizures in 10% to 40% of infected children. The pathogenesis of this complication is unclear because shigella meningitis is rarely described. The cytotoxin, Shiga's toxin, had been suggested to be a direct neurotoxin, but a recent study found no molecular evidence of Shiga's toxin or its structural genes in several strains isolated from patients with shigellosis and seizures. Other rare complications include hemolytic uremic syndrome, intestinal perforation, urinary tract infection, and chronic carriage with diarrhea. This latter complication is much less frequent than with salmonella infection. A syndrome of reactive arthritis, conjunctivitis, and keratitis occasionally occurs, although this is more common with yersiniosis.

Treatment is generally supportive because most patients have begun to recover before the laboratory report confirming the presence of shigella is available. Antibiotics appear to shorten the duration of illness and the shedding of the organism and are recommended if diarrhea has persisted to the time of diagnosis. There is little or no evidence that antibiotics will prevent the occasional complications noted above. Shigella species have become increasingly resistant to commonly used antimicrobials, and less than one third of the strains are susceptible to trimethoprim-sulfamethoxazole or ampicillin (Figure). A recent study confirmed the clinical efficacy of cefixime, a broad-spectrum cephalosporin, for trimethoprim-sulfamethoxazole-resistant strains. Most shigella strains are also susceptible to quinolones, although these are uncommonly used in pediatrics. A 4- to 5-day course of antibiotics is usually sufficient.

Prevention of spread of this organism requires strict attention to handwashing and personal hygiene. Studies have shown that as few as 10 organisms can be clinically infectious. This has led to recommendations that all children in day care with documented shigella infection should receive antibiotic therapy and be excluded from the day-care until follow-up cultures are negative. Stool cultures are recommended for any symptomatic day-care contacts and for all household contacts of children not yet toilet-trained.

CAMPYLOBACTER

Campylobacter species increasingly are recognized as being as common or more so than Salmonella and Shigella as causes of infectious diarrhea in children. The organism is usually associated with infection in the warm summer months, although there is some geographic variability. Campylobacter jejuni is the species most commonly associated with acute gastroenteritis. Isolation rates in young children with diarrhea in large day-care centers have been as high as 40% to 45%. Males appear more likely to be infected than females, although this relationship is true predominantly in children. As noted, the principal mode of spread is by fecal-oral transmission. Outbreaks have been described associated with undercooked poultry or meat, unpasteurized dairy products, or animal contact, especially with young dogs and cats.
The organism is intermediate in infective dose between *Salmonella* and *Shigella* with approximately $10^4$ organisms required for clinical infection. Once present in the small intestine, campylobacters commonly adhere and then multiply in a fashion similar to the mechanism of shigella infection. *Campylobacter fetus* is an exception in that it is much more likely to cause systemic illness by unknown mechanisms.

Symptomatic campylobacter infection appears to protect against subsequent reinfection. Asymptomatic infection, which occasionally occurs, does not seem to result in the same degree of protection. Interestingly, for a gastrointestinal pathogen, an inverse correlation between serum antibody levels and the incidence of symptomatic disease also has been described.

The clinical presentation is quite similar to that described for shigella infection, with a slightly longer incubation of 2 to 4 days, followed by fever, abdominal pain, and a secretory diarrhea progressing over 1 to 2 days to a dysenteric picture. Temperature is variable, but can be as high as 40°C. Complications of *C. jejuni* infection are uncommon but occasionally include nonspecific colitis or pseudomembranous. Unusual syndromes, including chronic diarrhea, asymptomatic bloody stools in neonates, and abdominal pain without diarrhea have been described. Most infections are mild and self-limited, and diarrhea resolves within 5 to 7 days. Relapses apparently occur in less than 10% of untreated children, but prolonged carriage appears uncommon. Younger children may shed the organism for as long as 2 to 3 weeks.

Most bacteremic or extraintestinal infections are caused by *C. fetus*, which is an uncommon cause of infectious diarrhea. *Campylobacter jejuni*, the cause of 95% of intestinal campylobacter infections, has not been commonly associated with bacteremia, meningitis, colicystis, urinary tract infection, or pancreatitis. As is true with salmonella and shigella infections, a reactive arthritis with manifestations of Reiter's syndrome has been described with campylobacter infection. This is more common in males between 15 and 30 years of age and is typically self-limited.

The diagnosis of campylobacter infection usually is made by culture, but the characteristic curved rods occasionally can be seen on direct smear of fresh stool specimen, stained with Gram's stain or carbol-fuchsia stain. This is one of the few situations where direct Gram's stain of stool can be diagnostic because the mononuclear microscopic picture of rapidly motile curved rods strongly suggests campylobacter infection. The treatment of intestinal campylobacter infection remains unclear. The American Academy of Pediatrics Committee on Infectious Disease recommends erythromycin to shorten the duration of excretion. Most strains also are susceptible to tetracycline, chloramphenicol, quinolones, and aminoglycosides, but their role in shortening the clinical course is uncertain. Therapy is delayed beyond 4 days after presentation, there appears to be no significant clinical benefit, although shortening the duration of shedding may still suggest the use of antibiotics. Antimotility agents have been associated with prolonged symptomatic disease, including intestinal perforation, and should be avoided. The overall prognosis is good, and relapsing infection is unusual. Preventative strategies are limited to careful handwashing and attention to personal hygiene.

**SUMMARY**

*Salmonella*, *Shigella*, and *Campylobacter* species are the most common causes of acute bacterial enteritis in the United States. These pathogens should be considered seriously in children who progress rapidly from secretory to inflammatory diarrhea syndrome or in whom diarrhea persists beyond 5 to 6 days. Furthermore, children who appear more toxic than their state of dehydration would suggest should be suspected of having an acute bacterial etiology for their diarrhea. Systemic, extraintestinal dissemination of these organisms is uncommon, with the exception of salmonella infection during the first year of life and in immunocompromised hosts. In this latter situation, culture of blood and other appropriate body fluids should be considered, along with empiric systemic antibiotic therapy. When antibiotics are warranted in patients with shigella or campylobacter infection, oral therapy is usually sufficient. Careful attention to handwashing and personal hygiene is always appropriate to prevent further spread of these organisms. The very low infectious dose of shigella infection mandates an even more compulsive attention to these latter recommendations when this organism is implicated.

**REFERENCES**