Clinical manifestations and diagnosis of Shigella infection in children

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INTRODUCTION — Shigella species are a common cause of bacterial diarrhea worldwide, especially in developing countries. The organism is less susceptible to acid than many other bacterial pathogens; thus, as few as 10 to 100 organisms can cause disease, in part because the organisms can survive transit through the stomach [1]. Thus, ingested bacteria pass into the small intestine where they multiply, so that several logs more bacteria pass into the colon, where the organisms enter the colonic cells.

Intermediate bacterial replication in contaminated food or water is not required to achieve this low infectious dose. As a result, Shigella transmission can occur through direct person-to-person spread, as well as from contaminated food and water; the former accounts for most cases in the United States, whereas the latter is more important in the developing world.

CLINICAL MANIFESTATIONS — Shigella is a pathogen that primarily infects the lower intestinal tract. Patients with Shigella gastroenteritis typically present with high fever, abdominal cramps, and bloody, mucoid diarrhea. The approximate prevalence of these signs and symptoms is [2-5] :

Fever (30 to 40 %); abdominal pain (70 to 93%), mucoid diarrhea (70 to 85%), bloody diarrhea (35 to 55%), watery diarrhea (30 to 40%), vomiting (35%).

The incubation period ranges from one to seven days, with an average of three days [6]. The disease typically begins with constitutional symptoms such as fever, anorexia, and malaise; diarrhea initially is watery, but subsequently may contain blood and mucus. Tenesmus is a common complaint.

Frequency of stools typically is 8 to 10 per day but may increase to up to 100 per day. The stools are of small volume, so significant fluid loss typically does not occur (average approximately 30 mL/kg per day) [7]. These findings are characteristic of diarrhea caused by infection of the colon (the major site of infection with Shigella) because the colon functions as a storage organ. This is in contrast to small bowel infections in which the diarrhea typically is watery, of large volume; and associated with abdominal cramping, bloating, gas, and weight loss.

The spectrum of severity of disease varies according to the serogroup of the infecting organism. Shigella sonnei commonly causes mild disease, which may be limited to watery diarrhea, although Shigella dysenteriae 1 or Shigella flexneri commonly causes dysenteric symptoms (bloody diarrhea) [8]. The course of disease in a normal healthy host generally is self-limited, lasting no more than seven days when left untreated.

The typical course of disease varies with age group. In a review of 318 infants and children hospitalized with shigellosis in Bangladesh, infants had fewer days with diarrhea (four versus six) and were more likely to have watery (as opposed to bloody) stools, hyponatremia, abdominal distension, and acidosis than were older children [9]. Older children were more likely to have a leukemoid reaction than were infants. The mortality rate for infants was twice that of older children. Infants who were breast fed were less frequently infected and had a milder illness than infants who were not breast fed [2].

Intestinal complications:

**Rectal prolapse** - The severe inflammation of the rectum and distal colon that is induced by invasion of
the organism into the colonic mucosa may lead to proctitis or rectal prolapse.

**Toxic megacolon** - Toxic megacolon occurs primarily in the setting of S. dysenteriae 1 infection. The pathogenesis is unclear; it occurs in the setting of pancolitis and seems to be related to the intensity of inflammation rather than being mediated by Shiga toxin. The incidence of toxic megacolon in children with diarrhea is low (3%) [1].

**Intestinal obstruction** — Severe colonic disease may result in intestinal obstruction. The incidence in one series of 1211 patients with shigellosis was 2.5% [10]. The patients with obstruction were more likely to be infected with S. dysenteriae 1 and were more severely ill, as evidenced by a significantly higher white blood cell (WBC) count and lower serum sodium concentration than patients without evidence of obstruction.

**Colonic perforation** — Colonic perforation is an unusual complication of shigelllosis. It occurs principally in infants or severely malnourished patients and is associated with infection caused by S. dysenteriae 1 or S. flexneri (1.7% of fatal cases) [11].

**Systemic complications**.

**Bacteremia** — Bacteremia occurs in approximately 4% of patients with Shigella gastroenteritis and is associated with an increase in mortality [12]. Young, malnourished children are at greatest risk. Bacteremia with another gram-negative organism is seen in approximately 5% of patients who have a stool culture positive for Shigella.

**Metabolic disturbances** — Substantial volume depletion is uncommon in shigellosis because the stool volume usually is low. In a review of 412 patients with shigellosis, 36% had mild, 12% had moderate, and 2% had severe dehydration [2]. In another series, hyponatremia (defined as serum sodium below 120 meq/L) was noted in 29% of patients hospitalized with diarrhea caused by S. dysenteriae 1 [13]. Generally, hyponatremia is caused by the syndrome of inappropriate ADH secretion, not by volume depletion [1,13]. Several consequences of shigellosis contribute to malnutrition, such as: Increased catabolism secondary to fever, stool protein loss, decreased intake caused by anorexia, Malabsorption.

**Leukemoid reaction** — A leukemoid reaction (defined as a white blood cell count of 50,000/mm3 or more) has been noted in approximately 4% of patients, most commonly in children between 2 and 10 years of age and not at all in children younger than 1 year of age [15]. The WBC count in these patients ranged from 50,000 to 195,000/mm3 and was accompanied by an increased number of immature forms. The mortality rate also was increased (21 versus 7.4% in those without a leukemoid reaction). In contrast, an earlier study conducted in the United States found no association between disease severity and a high WBC count [3].

**Neurologic disease** — Seizures, the most common neurologic complication associated with Shigella infection, are always associated with fever (usually greater than 39ºC), are generalized, uncomplicated, nonrecurring, and not associated with neurologic deficits [16] . Seizures can be seen with all serotypes of Shigella infection, but are least common with S. dysenteriae 1. The reported prevalence of seizures in children with shigellosis has ranged from 12 to 45% [16] and, in patients of all ages hospitalized with shigellosis, is approximately 10% [1]. In hospitalized children, the most common age group in which seizures occur is that between 6 months and 4 years, the same group most likely to have simple febrile seizures [17]. Analysis of cerebrospinal fluid obtained by lumbar puncture typically is normal, although as many as 15% of these patients may have mild lymphocytic pleocytosis with as many as 12 cells [16].
In the past, neurologic complications of Shigella infection were thought to be induced by circulating Shiga toxin, which is produced by S. dysenteriae 1 [18]. Shiga toxin was not detected in serum or spinal fluid and was present in stool at levels that were 1000-fold below that of cultured S. dysenteriae 1 in children with seizures[19]. However, there are no conclusive studies demonstrating relationship between Shiga toxin and seizures. Furthermore, the majority of patients who have seizures are infected with S. flexneri or S. sonnei, neither of which expresses Shiga toxin. Taken together, these data suggest that other Shigella enterotoxins might contribute to the induction of seizures, although this possibility has not as yet been proved [22].

Encephalopathy with lethargy, confusion, and headache has been noted in as many as 40 percent of children hospitalized with Shigella infection [23]. Obtundation or coma and abnormal neurologic signs, including posturing, are rare. In cases of encephalopathy that were fatal, cerebral edema was found at autopsy.

**Hemolytic-uremic syndrome** — Although relatively uncommon, the hemolytic-uremic syndrome (HUS) can occur as a complication of infection caused by Shigella dysenteriae. Because HUS is mediated by Shiga toxin, which is present in S. dysenteriae type 1, but not other species of Shigella, only S. dysenteriae type 1 can cause HUS. HUS is a potentially life-threatening illness that is characterized by a microangiopathic hemolytic anemia, thrombocytopenia, and acute renal failure. Enterohemorrhagic Escherichia coli (EHEC) infection accounts for about 70 percent of cases in the United States [28].

**Other manifestations:** In young girls, Shigella can cause vulvovaginitis with or without diarrhea [30].

**DIAGNOSIS** — Shigella should be suspected in any patient with frequent, small volume, bloody stools, abdominal cramps, and tenesmus, particularly if accompanied by fever. Nausea and vomiting are notably absent in most patients. The presence or absence of leukocytes in the stool can be determined rapidly and simply by microscopic examination. The constellation of the above symptoms and increased numbers of fecal leukocytes is strongly suggestive of infection with Shigella, Salmonella, Campylobacter, Yersinia, enteroinvasive E. coli, or Clostridium difficile, or of noninfectious inflammatory bowel disease [33].

**Fecal leukocytes** — In a study that examined the usefulness of fecal leukocytes in predicting the etiology of diarrhea, the presence of fecal leukocytes was associated with a bacterial cause of acute diarrhea in 89% of cases [34]. Patients infected with Shigella had fecal polymorphonuclear leukocytes in 70 to 100% of samples tested, with at least 10 to 25 cells/hpf in the majority of patients [2,34]. In comparison, healthy controls and patients with cholera or viral diarrhea had no fecal leukocytes. In volunteers infected experimentally, the presence of fecal leukocytes was a more sensitive means of diagnosing infection with S. dysenteriae 1 than was stool culture [34].

**Stool culture** — Confirmation of the infecting organism can be made only by culture of the stool. Shigella is a fastidious organism; as a result, it requires prompt handling and optimally should be inoculated onto agar at the bedside. Culture from a stool sample may give a better yield than culture from a rectal swab [35]. If transport of the sample is required, the best medium is buffered glycerol saline (BGS) [36]. The best yield is from a mucoid part of stool.
REFERENCES

Treatment and prevention of Shigella infections in children

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SUPPORTIVE THERAPY — The mainstay of the treatment of acute gastroenteritis in children, irrespective of the cause, which usually is not known at the time of presentation, is correction of fluid and electrolyte losses [4]. Oral rehydration is preferred, when feasible [10], but intravenous fluids may be necessary. (Ver texto inserido como apêndice ao final).

The use of intestinal antimotility drugs, such as diphenoxylate (Lomotil), should be avoided in children with suspected shigellosis. These drugs may prolong duration of fever, diarrhea, and excretion of the organism [11].

Early restoration of oral intake, especially protein, is important, particularly in developing countries, to prevent the exacerbation of malnutrition [12-14].

Patients with severe toxemia or suspected bacteremia, underlying immune deficiency, and who are unable to take oral medications should be hospitalized.

ANTIBIOTIC RESISTANCE — The increasing antimicrobial resistance of Shigella species is a major problem in treating shigellosis. The major route for dissemination of multiple resistance is by horizontal transfer of plasmids carrying antibiotic resistance (R-plasmids). A commonly isolated plasmid carries resistance against ampicillin, chloramphenicol, tetracycline, sulfonamides, streptomycin, and trimethoprim [17]. Ampicillin resistance also is mediated by beta-lactamases.

High rates of antimicrobial resistance were first reported in Asia, Africa, and South America, but antimicrobial resistance has rapidly spread to developed countries [18-20]. In India and Bangladesh, 20 percent or more of isolates are resistant to nalidixic acid [21-23]. Resistance to nalidixic acid also been reported in England [24] and the United States [20].

Antimicrobial resistance is an increasing problem in the United States. Between 1999 and 2002, the following results were reported:

- All isolated Shigella were susceptible to ceftriaxone and ciprofloxacin.
- 78% of isolates were resistant to ampicillin, 46% to TMP-SMX, 38% to both ampicillin and TMP-SMX, and 1 percent to nalidixic acid.

ANTIBIOTIC THERAPY

Rationale — The goals of antibiotic therapy for Shigella include improvement in symptoms and decreased spread of infection to contacts. Appropriate antimicrobial treatment of Shigella gastroenteritis reduces the duration of fever, diarrhea, and fecal excretion [28-31]. It also may reduce the risk of developing complications [32].

In randomized, placebo-controlled trials during the 1960s and early 1970s (before the widespread development of resistance to ampicillin), children with shigella infection who were treated with ampicillin had decreased duration of diarrhea, fever, and fecal shedding than those who received placebo [28-31].

The findings of the largest two studies are presented below:

- In Children hospitalized with Shigella gastroenteritis, those who received ampicillin (compared to placebo) had shorter duration of diarrhea (3.3 versus 6 days), fever (1.3 versus 2.6 days), and fecal shedding (positive stool culture for 2 versus 5 days) [28].
In another randomized study of 373 children with acute diarrhea who were treated as outpatients, 101 children had stool cultures positive for Shigella [29]. Compared with those who received placebo, fewer children with Shigella who were treated with ampicillin had positive stool cultures after 48 hours (8 versus 70 %) and fewer continued to have diarrhea after five days (5 versus 50 percent). None of the patients who were treated with ampicillin required hospital admission or treatment with another antibiotic after completion of therapy (compared with one and five children in the placebo group, respectively).

The decreased duration of shedding with antimicrobial therapy reduces the risk of person-to-person spread of the infection. In the absence of specific antibiotic treatment, children with Shigella gastroenteritis shed the organism for up to four weeks, and children with immune deficiency, for much longer periods, even if their symptoms have resolved [4,6,7,33].

Shigella is highly contagious; ingestion of only 10 to 100 organisms can produce disease. Therefore, treatment of an infected child at risk to transmit the disease to others (eg, a day-care attendee, hospitalized patient) is particularly compelling.

The benefits of antimicrobial therapy discussed above outweigh the potential risks of therapy, which include the possibility of favoring emergence of resistant organisms [3] and potential adverse effects.

**Indications** — Decisions regarding initiation of antimicrobial therapy must consider the appearance of the patient, the presence of host factors that predispose to more severe infection, and public health considerations.

We recommend empiric antimicrobial therapy for shigellosis in children and adolescents who present with suspected shigellosis (bloody/mucousy diarrhea, high fever) and are immunocompromised or bacteremic [33].

We recommend antimicrobial therapy for children and adolescents with culture-proven Shigella who [33]: Have bacteremia, require hospitalization, attend day care, live in institutions or are involved in food handling. Treatment of mild cases or of children who have recovered by the time the report of positive Shigella culture is available is controversial. Antimicrobial treatment of such children is unlikely to significantly affect the clinical course, but will shorten fecal excretion and thus reduce the spread of this highly contagious bacterium.

**Choice of regimen** — The medication spectrum and regimen (oral versus parenteral) are determined by severity of illness, local resistance patterns, and history of travel to an area of frequent resistance [3,35].

**REFERENCES**


REIDRATAÇÃO

Jefferson P Piva

O tratamento da desidratação inicia pela análise da história clínica, da diurese (se possível), da perda de peso e estimativas de perdas e aporte de líquidos. O exame físico deve ser acurado, procurando detectar sinais de comprometimento do intravascular. Os exames complementares devem incluir sódio, potássio, cálcio, hemograma, uréia, creatinina, glicose, pH, bicarbonato, podendo ainda ser indicados em casos selecionados a dosagem sérica de albumina e osmolaridade séricos, além de creatinúria, glicosúria, cetonúria, pH urinário, osmolaridade e dosagem de eletrólitos na urina.(1-2)

Na desidratação leve e em alguns casos moderada, a reidratação deve ser realizada por via oral, pois, não há comprometimento dos espaços intravascular e intracelular. Nestes casos administra-se 25-30 ml/kg/hora de solução de hidratação oral. A solução de hidratação oral recomendada pela OMS foi
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modificada em 2002. O conteúdo de Na foi reduzido de 90 para 75 mEq/L, o K foi mantido em 20 mEq/L e o bicarbonato mantido em 30 mEq/L, enquanto que a glicose foi reduzida de 2 para 1,3%. Com estas modificações a osmolaridade foi reduzida de 310 para 245 mOsm/L.

Nos pacientes com desidratação de III grau e naqueles de II grau com menos de 3 meses, com alteração de estado de consciência, vômitos intransáveis, distensão abdominal ou íleo adinâmico, o tratamento recomendado é a hidratação endovenosa (5,6).

Existem vários esquemas de reidratação, que levam em consideração a quantidade de líquido perdido, as possíveis perdas posteriores e a quantidade de líquidos de manutenção para cada indivíduo. Na prática, a reidratação endovenosa deve ser um procedimento simples, eficaz e com controle clínico contínuo. De forma que ao compensar o comprometimento intravascular retorna-se a hidratação pela via oral.

A reidratação endovenosa é constituída por duas etapas: a fase de reposição ou de expansão volumétrica e a fase de recuperação ou de estabilização.

A fase de expansão é rápida e agressiva, visando a restauração do volume intravascular nas primeiras horas (em média de 2 horas). Assim, quanto maior for a depleção de volume, mais agressiva e rápida deve ser a reposição volumétrica.

Em crianças desidratadas de II e III grau, preconizamos expansões com solução fisiológica (NaCl 0,9%) de 20 ml/kg a cada 20 minutos ou 30 minutos (40 a 60 ml/kg/hora) que podem ser repetidas tantas vezes quanto necessárias para reverter a depleção volumétrica. É importante ressaltar que ao redor de 25% desta solução permanece dentro do espaço intravascular, sendo que os restantes 75% se distribuem no espaço intersticial. Repete-se estas expansões até que ocorra resposta hemodinâmica (melhora do pulso, diminuição da taquicardia, retorno da diurese, etc.).

A fase de recuperação da reidratação por via endovenosa deve ser o mais breve possível, para que utilize preferentemente a via oral. Entretanto, em um grande contingente de pacientes de UTI e de salas de emergência, em razão de situações associadas (sepse, pós-operatório, alterações do sensório, etc), esta fase de recuperação é mantida por via endovenosa e pode perdurar por cerca de 20 horas. Após a restauração da volemia, o objetivo é administrar a manutenção hidroeletrolítica adicionada das possíveis perdas e das deficiências eletrolíticas ainda existentes. A estimativa do volume a ser administrado depende da causa da desidratação, da resposta à infusão inicial e do próprio grau de desidratação. Utilizamos infundir a manutenção hídrica diária (~100 ml/kg/dia emlactentes) sob a forma de solução fisiológica (150 mEq/L de sódio) com 5% de glicose ou uma proporção de 50% de cada uma destas soluções. Nesta etapa deve ser adicionado potássio na proporção de 20 a 40 mEq/ para cada litro de solução. No caso de haver perdas volumosas durante este período (vômitos, drenagem volumes pela sonda gástrica, gastroenterites, etc), optamos por fazer novas expansões com Solução fisiológica (20 ml/kg em 20 minutos).

Após as primeiras 24 horas de tratamento, a grande maioria dos pacientes apresenta reversão do quadro com melhora clínica e compensação fisiológica dos distúrbios hidroeletrolíticos e ácido-básicos. Nesta fase de equilíbrio, a hidratação venosa pode ser reduzida, incentivando-se a administração por via oral.