

ENTERIC DISEASES

Severe paediatric shigellosis

A 6-year-old boy living on a farm in Clanwilliam, Western Cape Province, was admitted to Vredendal Hospital on 23 February 2021. There was a four-day history of fever and diarrhoea, and a one-day history of confusion. He was transferred to Tygerberg Hospital, where he was admitted to the intensive care unit with a diagnosis of septic shock. On examination, a few petechiae were present behind the ears, but no eschar was noted. There was no history of a tick bite or any exposure to livestock or wild animals.

Empiric antibiotic therapy included ceftriaxone and ciprofloxacin.

During the preceding three weeks, three other family members (the patient's sister, mother and father) had also experienced symptoms suggestive of gastroenteritis, including fever, abdominal cramps and diarrhoea. In all cases, illness was fairly mild and resolved within a few days; none sought healthcare. The family reported that the patient drank untreated water from a nearby dam and that he had recent exposure to sewage following blockage of the septic tank.

Shigella flexneri was isolated from a stool sample collected within a day of admission, and the isolate was susceptible to third generation cephalosporins and ciprofloxacin. A blood culture collected on admission (as well as subsequent blood cultures) yielded no growth. Although their illnesses had resolved, stool samples were collected from the patient's mother and sister on 1 March 2021 and tested using a multiplex RT-PCR. *Shigella* spp. was detected from the sister's stool sample, whilst no enteric pathogens were detected from the mother's stool sample. The *S. flexneri* isolate was referred to the Centre for Enteric Diseases, NICD, for further characterisation. It was confirmed as *S. flexneri* type 2a. The patient developed sepsis-related complications, but ultimately recovered and was discharged home on 23 March 2021.

Discussion

This is a case of severe shigellosis in the context of a household cluster. It highlights two important aspects of this disease. Firstly, that although uncommon, severe intestinal and extraintestinal complications can occur, and secondly, that owing to a very low infectious inoculum, shigella has a propensity for person-to-person transmission within the home and other congregate settings, greatly facilitated by suboptimal sanitation and personal hygiene.

The genus *Shigella* includes four species, *S. sonnei*, *S. flexneri*, *S. boydii* and *S. dysenteriae*, which are further divided into serotypes and subserotypes. The less virulent *S. sonnei* predominates globally and in higher-income settings, while *S. flexneri* is more prominent in low-income settings in Africa and Asia. In South Africa, the predominant serotypes are *S. sonnei* and *S. flexneri* type 2a, which is typical of a transitional economy setting.

Shigellosis occurs predominantly in children aged 1-4 years residing in low- and middle-income countries. Other risk groups for shigellosis include travellers to endemic areas, children in daycare with subsequent household transmission, and men having sex with men. Humans are the only natural host for shigellae. Person-to-person spread is the commonest mode of transmission. Infection and outbreaks can also be caused by contaminated food or water, and flies may transmit disease in settings of inadequate disposal of human faeces.

Following an incubation period of one to four days, infection with *Shigella* can result in a spectrum of disease from asymptomatic infection to severe bloody diarrhoea (the classical 'bacillary dysentery'). Fever, headache, malaise and vomiting are often the initial symptoms, followed by the onset of watery diarrhoea (indicating invasive infection of the small bowel). Most illness is mild, and symptoms resolve in a few days. In some cases, the infection progresses to involve the colon, resulting in frank dysentery which is characterised by the passage of smaller volume, bloody mucoid stools along with abdominal cramps and tenesmus (a repeated, painful urge to defaecate without excreting stool).

Shigellosis is usually self-limiting, but severe disease may be associated with complications including dehydration, severe hyponatraemia, seizures in infants and young children, encephalopathy, and occasional focal infections such as meningitis, osteomyelitis or vaginitis. Bacteraemia is rare in otherwise healthy patients and occurs most commonly in young or malnourished infants and children or people infected with HIV. A post-shigella reactive arthritis may develop, particularly in HLA-B27 -positive patients. Intestinal complications are uncommon but usually severe, including rectal prolapse, intestinal obstruction, toxic megacolon and perforation; these are seen more frequently in *S. dysenteriae* type 1 infections. In high income settings, shigella infections have been linked to irritable bowel syndrome in adults. In young children repeated infections can result in malnutrition and stunting, causing long term adverse effects on physical and

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cognitive development. Historically, leukaemoid reactions and haemolytic uraemic syndrome was associated with Shiga toxin-producing *S. dysenteriae* type 1. However, multiple strains of *S. flexneri* and *S. dysenteriae* type 4 that also produce Shiga toxin have recently emerged. The clinical implications of these new strains remains to be determined.

Conventional bacterial culture remains the gold standard for the diagnosis of shigellosis, and allows for antimicrobial susceptibility testing. However, shigella are notoriously fastidious organisms and viability decreases rapidly with delay from stool sample collection to plating out. The use of appropriate transport media may improve viability when delay cannot be avoided, albeit to a limited extent. Testing with PCR based-methods increases the diagnostic yield substantially, but commercial assays are not able to differentiate between *Shigella* spp. and enteroinvasive *E. coli* (because they are so closely genetically related), and do not provide information on serotype or subserotype.

The cornerstone of treatment remains maintenance of hydration and electrolyte balance. Antibiotic therapy is indicated for shigella dysentery, because it reduces the duration of fever and diarrhoea by 1-2 days, reduces the risk of serious complications and death, and decreases the duration of shedding of shigella from stool, resulting in reduced transmission and public health benefit.

Ciprofloxacin, ceftriaxone and azithromycin are recommended as first-line therapy for children and adults with dysentery. Currently, there is no evidence to support any benefit of

antibiotic therapy for non-dysenteric shigella diarrhoea. Of concern is that antimicrobial resistance is increasingly common in shigella and international travel facilitates the introduction of resistant strains into new populations.

Following the introduction of rotavirus vaccines, the global reduction in rotavirus infection has increased the proportional burden of other aetiological pathogens including shigella. The Global Enteric Multicenter Study (GEMS), investigated the aetiology of acute, medically attended moderate to severe diarrhoeal disease in children less than 5 years of age living in south Asia and sub-Saharan Africa. Results showed shigella (identified on culture) to be the commonest cause of diarrhoea in children aged 24-59 months and the second commonest aetiological agent in children aged 12-23 months. Reanalysis of the GEMS samples using quantitative PCR resulted in an almost twofold increase in the attributable incidence of shigella.

Handwashing with soap and water is an important preventive strategy; it reduces transmission from index cases to household members by 70%. The primary public health measures to prevent transmission in the context of a community, include handwashing, optimal personal hygiene, access to safe water, sanitation, and in the context of institutional outbreaks, cohorting of ill persons.

Vaccine development has been driven by the recognition of the high burden and severity of shigellosis, which is compounded by rapidly increasing antimicrobial resistance. Several candidate shigella vaccines are currently being evaluated.