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Shigellosis The discovery of Shigella as the etiologic agent of dysentery—a clinical syndrome of fever, intestinal cramps, and frequent passage of small, bloody, mucopurulent stools—is attributed to the Japanese microbi ologist Kiyoshi Shiga, who isolated the Shiga bacillus (now known as Shigella dysenteriae type 1) from patients' stools in 1897 during a large and devastating dysentery epidemic. Shigella cannot be distinguished from Escherichia coli by genome comparison and remains a separate species only on historical and clinical grounds. ■ ■ETIOLOGIC AGENT Shigella is a non-spore-forming, gram-negative bacterium that, unlike E. coli, is nonmotile and does not produce gas from sugars, decarbox ylate lysine, or hydrolyze arginine. Some serovars produce indole, and occasional strains utilize sodium acetate. Shigella dysenteriae, Shigella flexneri, Shigella boydii, and Shigella sonnei (serogroups A, B, C, and D, respectively) can be differentiated on the basis of biochemical and serologic characteristics. Genome sequencing of E. coli K12, S. flexneri 2a, S. sonnei,

S. dysenteriae type 1, and S. boydii has revealed that these species have ~93% of genes in common. The three major genomic "signa tures" of Shigella are (1) a 215-kb virulence plasmid that carries most of the genes required for pathogenicity (particularly invasive capacity); (2) the lack or alteration of genetic sequences encoding products (e.g., lysine decarboxylase) that, if expressed, would attenuate pathogenicity; and (3) in S. dysenteriae type 1, the presence of genes encoding Shiga toxin, a potent cytotoxin. PART 5 Infectious Diseases ■ ■EPIDEMIOLOGY The human intestinal tract is the major reservoir of Shigella, which is also found (albeit rarely) in the higher primates. Because excretion of shigel lae is greatest in the acute phase of disease, the bacteria are transmitted most efficiently by the fecal–oral route via hand carriage; however, some outbreaks reflect foodborne or waterborne transmission. In impover ished areas, Shigella can be transmitted by flies. The high-level infectivity of Shigella is reflected by the very small inoculum required for experi mental infection of volunteers (100 colony-forming units [CFU]), by the very high attack rates during outbreaks in day-care centers (33–73%), and by the high rates of secondary cases among family members of sick children (26–33%). Shigellosis can also be transmitted sexually. Throughout history, bacillary dysentery epidemics have often occurred in settings of human crowding under conditions of poor hygiene—e.g., among soldiers in campaigning armies, inhabitants of besieged cities, groups on pilgrimages, and refugees in camps. Epidemics followed a cyclical pattern in areas such as the Indian subcontinent and sub-Saharan Africa. These patterns of devastating epidemics, which were most often caused by S. dysenteriae type 1, were characterized by high attack and mortality rates. In Bangladesh, for instance, an epidemic caused by

S. dysenteriae type 1 was associated with a 42% increase in mortality rate among children 1–4 years of age. This pattern of severe cyclic disease has steeply declined over the last few decades. Along with the increasingly rare isolation of S. dysenteriae 1, the current epidemiology of shigellosis is generally attributed to a significant global reduction of extreme poverty; this coincides with the tremendous decrease in child mortality. Nevertheless, apart from these severe epidemics of the past, shig ellosis remains an endemic disease, with 99% of cases occurring in developing countries, with the highest prevalence in the most impov erished areas, where personal and general hygiene is below standard. S. flexneri isolates predominate in the least developed areas, whereas S. sonnei is more prevalent in economically emerging countries and in the industrialized world. Prevalence in the Developing World In a review published under the auspices of the World Health Organization (WHO), the total

annual number of cases in 1966–1997 was estimated at 165 million, and 69% of these cases occurred in children <5 years of age. In this review, the annual number of deaths was calculated to range between 500,000 and 1.1 million. Data (2000–2004) from six Asian countries indicate that, even though the incidence of shigellosis remains stable, mortality rates associated with this disease may have decreased sig nificantly, possibly as a result of improved nutritional status. However, extensive and essentially uncontrolled use of antibiotics, which may also account for declining mortality rates, has increased the emergence of multidrug-resistant Shigella strains. A 2013 prospective, matched, case-control study of children <5 years of age emphasized the importance of Shigella in the burden and etiology of diarrheal diseases in developing countries. Shigella was one of the top four pathogens associated with moderate to severe diarrhea and ranked first among children 12–59 months of age. These moderate to severe cases accounted for an 8.5-fold increase in mortality incidence over the average diarrheal disease-related mortality. The study con cluded that Shigella remained a major pathogen to be targeted by health care programs. Global reevaluation of the Shigella disease burden is warranted because an often-overlooked complication of shigellosis is the short- and long-term impairment of the nutritional status of infected children in endemic areas. Combined with anorexia, the exudative enteropathy resulting from mucosal abrasions contributes to rapid deterioration of the patient’s nutritional status. Shigellosis thus now appears as a major contributor to stunted growth among children in endemic regions. Peaking in incidence in the pediatric population, endemic shigel losis is rare among young and middle-aged adults, probably because of naturally acquired immunity. Incidence then increases again in the elderly population. Prevalence in the Industrialized World In pediatric popula tions, local outbreaks occur when proper and adapted hygiene policies are not implemented in group facilities such as day-care centers and institutions for the developmentally disabled. In adults, as in children, sporadic cases occur among travelers returning from endemic areas, and rare outbreaks of varying size can follow waterborne or foodborne infections. ■ ■PATHOGENESIS AND PATHOLOGY Shigella infection occurs essentially through oral contamination via direct fecal–oral transmission, the organism being poorly adapted to survive in the environment. Resistance to low-pH conditions allows Shigella to survive passage through the gastric barrier. The watery diarrhea that usually precedes dysenteric symptoms is attributable to active secretion and abnormal water reabsorption in the jejunum, as described in experimentally infected rhesus monkeys. This initial purge is possibly due to the combined action of an entero toxin (ShET-1) and mucosal inflammation. The dysenteric syndrome, manifested by bloody and mucopurulent stools, reflects invasion of the colonic mucosa. The pathogenesis of Shigella is essentially determined by a large virulence plasmid of 214 kb comprising ~100 genes, of which 25 encode a type III secretion

system that inserts into the membrane of the host cell to allow effectors to transit from the bacterial cytoplasm to the host cell cytoplasm (Fig. 172-1). Bacteria are thereby able to invade intestinal epithelial cells by inducing their own uptake either directly at the opening of colonic crypts or following the initial crossing of the epithelial barrier through M cells (the specialized translocating epithelial cells in the follicle-associated epithelium that covers mucosal lymphoid nodules). Shigella induces apoptosis of subepithelial resident macrophages. Once inside the cytoplasm of intestinal epithelial cells, Shigella effectors trigger the cytoskeletal rearrangements necessary to direct uptake of the organism into the epithelial cell. The Shigellacontaining vacuole is then quickly lysed, releasing bacteria into the cytosol. Intracellular shigellae next use cytoskeletal components to propel themselves inside the infected cell; when the moving organism and the host cell membrane come into contact, cellular protrusions form and

Shigella M cell Activation of NF-κB caused by IL-1β and intracellular NLR activation IcsA + IpaA Macrophages IL-8 IL-1β Disruption of epithelial permeability barrier by PMNs Massive invasion of epithelium IL-18 FIGURE 172-1 Invasive strategy of Shigella flexneri. IL, interleukin; NF-κB, nuclear factor κB; NLR,

NOD-like receptor; PMN, polymorphonuclear leukocyte. are engulfed by neighboring cells. This series of events permits bacte rial cell-to-cell spread. Cytokines released by a growing number of infected intestinal epithelial cells massively attract immune cells—particularly poly morphonuclear leukocytes [PMNs]—to the infected site, thus further destabilizing the epithelial barrier, exacerbating inflammation, and leading to the acute colitis that characterizes shigellosis. Evidence indi cates that some type III secretion system–injected effectors can control the extent of inflammation, thus facilitating bacterial survival. Shiga toxin produced by S. dysenteriae type 1 increases disease severity. This toxin belongs to a group of A1-B5 protein toxins whose B subunit binds to the receptor globotriaosylceramide on the target cell surface and whose catalytic A subunit is internalized by receptormediated endocytosis and interacts with the subcellular machinery to inhibit protein synthesis by expressing RNA N-glycosidase activity on 28S ribosomal RNA. This process leads to inhibition of binding of the amino-acyl-tRNA to the 60S ribosomal subunit and thus to a general shutoff of cell protein biosynthesis. Shiga toxins are translocated from the bowel into the circulation. After binding of the toxins to target cells in the kidney, pathophysiologic alterations may result in hemolyticuremic syndrome (HUS; see below). ■ ■CLINICAL MANIFESTATIONS The presentation and severity of shigellosis depend to some extent on the infecting serotype but even more on the age and the immuno logic and nutritional status of the host. Poverty and poor standards of hygiene are strongly related to the number and severity of diarrheal episodes, especially in children <5 years following weaning. Shigellosis typically evolves through four phases: incubation, watery diarrhea, dysentery, and the postinfectious phase. The incubation period usually lasts 1–4 days but may be as long as 8 days. Typical initial manifestations are transient fever, limited watery diarrhea, malaise, and anorexia. Signs and symptoms may range from mild abdominal discomfort to severe cramps, diarrhea, fever, vomiting, and tenesmus. The manifestations are usually exacerbated in children, with temperatures up to 40°–41°C (104.0°–105.8°F) and more severe anorexia and watery diarrhea. This initial phase may represent the only clinical manifestation of shigellosis, especially in developed countries. Otherwise, dysentery follows within hours or days and is characterized by uninterrupted excretion of small volumes of bloody mucopurulent stools with increased tenesmus and abdominal cramps. At this stage, Shigella produces acute colitis involving mainly the distal colon and the rectum. Unlike most

diarrheal syndromes, dysenteric syndromes rarely present with dehydration as a major feature. Endoscopy, if performed, shows an edematous and hemorrhagic mucosa, with ulcerations and possibly overlying exudates resembling pseudomembranes. The extent of the lesions correlates with the number and frequency of stools and

with the degree of protein loss by exudative mecha nisms. Most episodes are self-limited and resolve without treatment in 1 week. With appropriate treatment, recovery takes place within a few days to a week, with no sequelae.

Epithelial cells Acute life-threatening complications are seen most often in children <5 years (particularly those who are malnourished) and in elderly patients. Risk factors for death in a clinically severe case include nonbloody diarrhea, moderate to severe dehydration, bacteremia, absence of fever, abdomi nal tenderness, and rectal prolapse. Major com plications are predominantly intestinal (e.g., toxic megacolon, intestinal perforations, rectal prolapse) or metabolic (e.g., hypoglycemia, hyponatremia, dehydration). Bacteremia is rare and is reported most frequently in severely malnourished and HIV-infected patients. Alterations of conscious ness, including seizures, delirium, and coma, may occur, especially in children <5 years, and are associated with a poor prognosis; fever and severe metabolic alterations are more often the major causes of altered consciousness than is meningitis or the Ekiri syn drome (toxic encephalopathy associated with bizarre posturing, cere bral edema, and fatty visceral degeneration), which has been reported mostly in Japanese children. Pneumonia, vaginitis, and keratocon junctivitis due to Shigella are rarely reported. In the absence of serious malnutrition, severe and very unusual clinical manifestations, such as meningitis, may be linked to genetic defects in innate immune func tions (i.e., deficiency in interleukin 1 receptor–associated kinase 4 [IRAK-4]) and may require genetic investigation. Cell-to-cell spread IpaB IpaC type III secretion Macrophage apoptosis Caspase-I activation by IpaB Bacterial survival Initiation of inflammation CHAPTER 172 Two complications of particular importance are toxic megacolon and HUS. Toxic megacolon is a consequence of severe inflammation extending to the colonic smooth-muscle layer and causing paralysis and dilation. The patient presents with abdominal distention and ten derness, with or without signs of localized or generalized peritonitis. The abdominal x-ray characteristically shows marked dilation of the transverse colon (with the greatest distention in the ascending and descending segments); thumbprinting caused by mucosal inflamma tory edema; and loss of the normal haustral pattern associated with pseudopolyps, often extending into the lumen. Pneumatosis coli is an occasional finding. If perforation occurs, radiographic signs of pneu moperitoneum may be apparent. Predisposing factors (e.g., hypokale mia and use of opioids, anticholinergics, loperamide, psyllium seeds, and antidepressants) should be investigated. Shigellosis Shiga toxin produced by S. dysenteriae type 1 has been linked to HUS in developing countries but rarely in industrialized countries, where enterohemorrhagic E. coli (EHEC) predominates as the etiologic agent of this syndrome. HUS is an early complication that most often develops after several days of diarrhea. Clinical examination shows pallor, asthenia, and irritability and, in some cases, bleeding of the nose and gums, oliguria, and increasing edema. HUS is a nonimmune (Coombs-negative) hemolytic anemia defined by a diagnostic triad: microangiopathic hemolytic anemia (hemoglobin level typically <80 g/L [<8 g/dL]), thrombocytopenia (mild to moderate in severity; typically <60,000 platelets/μL), and acute renal failure due to thrombosis of the glomerular capillaries (with markedly elevated creatinine levels). Anemia is severe, with fragmented red blood cells (schizocytes) in the peripheral smear, high serum concentrations of

lactate dehydrogenase and free circulating hemoglobin, and elevated reticulocyte counts. Acute renal failure occurs in 55–70% of cases; however, renal function recovers in most of these cases (up to 70% in various series). Leuke moid reactions, with leukocyte counts of 50,000/μL, are sometimes present in association with HUS. The postinfectious immunologic complication known as reactive arthritis can develop weeks or months after shigellosis, especially in patients expressing the histocompatibility antigen HLA-B27. About 3% of patients infected with S. flexneri later develop this syndrome, with arthritis, ocular inflammation, and urethritis—a condition that can

last for months or years and can progress to difficult-to-treat chronic arthritis. Postinfectious arthritis occurs only after infection with S. flexneri and not after infection with the other Shigella serotypes.

■ ■LABORATORY DIAGNOSIS The differential diagnosis in patients with a dysenteric syndrome depends on the clinical and environmental context. In developing areas, infec tious diarrhea caused by other invasive pathogenic bacteria (Salmonella,

Campylobacter jejuni, Clostridium difficile, Yersinia enterocolitica) or par asites (Entamoeba histolytica) should be considered. Only bacteriologic and parasitologic examinations of stool can truly differentiate among these pathogens. A first flare of inflammatory bowel disease, such as Crohn’s disease or ulcerative colitis (Chap. 337), should be considered in patients in industrialized countries. Despite the similarity in symptoms, anamnesis discriminates between shigellosis, which usually follows recent travel in an endemic zone, and these other conditions. Microscopic examination of stool smears shows erythrophagocytic trophozoites with very few PMNs in E. histolytica infection, whereas bacterial enteroinvasive infections (particularly shigellosis) are char acterized by high PMN counts in each microscopic field. However, because shigellosis often manifests only as watery diarrhea, systematic attempts to isolate Shigella are necessary. The “gold standard” diagnosis of Shigella infection remains the isola tion and identification of the pathogen from fecal material. One major difficulty, particularly in endemic areas where laboratory facilities are not immediately available, is the fragility of Shigella and its com mon disappearance during transport, especially with rapid changes in temperature and pH. In the absence of a reliable enrichment medium, buffered glycerol saline or Cary-Blair medium can be used as a holding medium, but prompt inoculation onto isolation medium is essential. The probability of isolation is higher if the portion of stools that con tains bloody and/or mucopurulent material is directly sampled. Rectal swabs can be used, as they offer the highest rate of successful isolation during the acute phase of disease. Blood cultures are positive in fewer than 5% of cases but should be done when a patient presents with a clinical picture of severe sepsis. PART 5 Infectious Diseases In addition to quick processing, the use of several media increases the likelihood of successful isolation: a nonselective medium such as bromocresol-purple agar lactose; a low-selectivity medium such as Mac Conkey or eosin-methylene blue; and a high-selectivity medium such as Hektoen, Salmonella-Shigella, or xylose-lysine-deoxycholate agar. After incubation on these media for 12–18 h at 37°C (98.6°F), shigellae appear as non-lactose-fermenting colonies that measure 0.5–1 mm in diameter and have a convex, translucent, smooth surface. Suspected colonies on nonselective or low-selectivity medium can be subcultured on a highselectivity medium before being specifically identified or can be identi fied directly by standard commercial systems on the basis of four major characteristics: glucose positivity (usually without production of gas), lactose negativity, H2S negativity, and lack of motility. The four Shigella serogroups (A–D) can then be

differentiated by additional characteris tics. This approach adds time and difficulty to the identification process; however, after presumptive diagnosis, the use of serologic methods (e.g., slide agglutination, with group- and then type-specific antisera) should be considered. Group-specific antisera are widely available; in contrast, because of the large number of serotypes and subserotypes, type-specific antisera are rare and more expensive and thus are often restricted to reference laboratories. Molecular methods of diagnostics, including polymerase chain reac tion based on Shigella-specific virulence gene sequences or mass spec trometry, are not yet standardized for global use. However, serotyping may soon be replaced by genome-based techniques. TREATMENT Shigellosis ANTIBIOTIC SUSCEPTIBILITY OF SHIGELLA As an enteroinvasive disease, shigellosis requires antibiotic treat ment. Since the mid-1960s, however, increasing resistance to

multiple drugs has been a dominant factor in treatment deci sions. Resistance rates are highly dependent on the geographic area. Clonal spread of particular strains and horizontal transfer of resistance determinants, particularly via plasmids and transposons, contribute to multidrug resistance. The current global status—i.e., high rates of resistance to classic first-line antibiotics such as amoxicillin—has led to a rapid switch to quinolones such as nali dixic acid. However, resistance to such early-generation quinolones has also emerged and spread quickly as a result of chromosomal mutations affecting DNA gyrase and topoisomerase IV; this resis tance has necessitated the use of later-generation quinolones as first-line antibiotics in many areas. For instance, a review of the antibiotic resistance history of Shigella in India found that, after their introduction in the late 1980s, the second-generation quino lones norfloxacin, ciprofloxacin, and ofloxacin were highly effective in the treatment of shigellosis, including cases caused by multidrugresistant strains of S. dysenteriae type 1. However, investigations of subsequent outbreaks in India and Bangladesh detected resistance to norfloxacin, ciprofloxacin, and ofloxacin in 5% of isolates. In the United States, the resistance rate of Shigella to fluoroquinolones reached 87% during 2014−2015. The incidence of multidrug resis tance parallels the widespread, uncontrolled use of antibiotics and calls for the rational use of effective drugs. Despite the alarming proportion of resistant Shigella, there is a lack of studies assessing the resistance of community-acquired strains. ANTIBIOTIC TREATMENT OF SHIGELLOSIS (TABLE 172-1) With effective antibiotic therapy, clinical improvement occurs within 48 h, resulting in a decreased risk of complications and death, shorter duration of symptoms, and elimination of Shigella from the stools. Because of the transmissibility of Shigella, current public health recommendations in the United States are that every case be treated with antibiotics. The use of fluoroquinolones (firstline, preferably ciprofloxacin) and cephalosporins and β-lactams (second-line) for 7−10 days is recommended for the treatment of shigellosis. Whereas infections caused by non-dysenteriae Shigella in immunocompetent individuals are routinely treated with a 3-day course of antibiotics, it is recommended that S. dysenteriae type 1 infections be treated for 5 days and that Shigella infections in immunocompromised patients be treated for 7–10 days. TABLE 172-1 Recommended Antimicrobial Therapy for Shigellosis TREATMENT SCHEDULE ANTIMICROBIAL AGENT LIMITATIONS CHILDREN ADULTS First-Line Ciprofloxacin 15 mg/kg 500 mg 2 times per day for 3 days, PO Second-Line Pivmecillinam 20 mg/kg 100 mg Cost 4 times per day for 5 days PO No pediatric formulation Frequent administration Emerging resistance Ceftriaxone 50–100 mg/kg — Efficacy not validated Must be injected Once a day IM for 2–5 days Azithromycin 6–20 mg/kg 1–1.5 g Cost Once a day for 1–5 days PO Efficacy not validated Minimum inhibitory concentration near serum concentration Rapid emergence of resistance and spread to other bacteria Source: Reproduced with permission from World Health Organization: Guidelines for the control of shigellosis, including

epidemics due to Shigella dysenteriae type 1. https://www.who.int/publications/i/item/9241592330.

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