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Review Article

Shigellosis: A Comprehensive Review: History, Symptoms, Pathophysiology, Cause for the Disease, Diagnosis, Transmission, Epidemiology, Treatment, and Prevention Measures

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A B S T R A C T

Shigellosis, caused by the bacterium of the genus *Shigella*, is a significant global public health concern due to its high morbidity and mortality rates, particularly in low-resource settings. This review provides a comprehensive overview of shigellosis, encompassing its historical context, clinical manifestations, underlying pathophysiology, and factors contributing to its emergence and spread. The disease primarily manifests with symptoms ranging from mild diarrhoea to severe dysentery, often accompanied by fever and abdominal cramps. *Shigella* bacteria invade the lining of the intestines, causing inflammation and disrupting normal gastrointestinal function. The disease is predominantly transmitted through faecal-oral routes, emphasising the critical importance of sanitation and hygiene measures in prevention. Epidemiologically, shigellosis exhibits a wide global distribution, with higher incidences observed in regions with limited access to clean water and sanitation facilities. Prompt diagnosis via stool culture or molecular techniques is essential for effective treatment and public health surveillance. Although various antibiotics are available for treatment, rising antibiotic resistance poses a growing challenge. Vaccination presents a promising avenue for shigellosis prevention; however, the development of an effective and widely accessible vaccine remains a priority. The review also addresses practical considerations such as vaccine pricing and safety, particularly in pregnancy. Understanding the nuances of shigellosis, including its historical context, clinical presentation, and prevention strategies, is pivotal in guiding healthcare interventions and policy decisions to mitigate its impact on global health.

Keywords: Shigellosis, Pathophysiology, Epidemiology, Treatment

Introduction

Shigellosis, a prevalent form of bacterial diarrhoea, is caused by the gram-negative bacteria known as *Shigella* species. This ailment is particularly widespread in developing nations and is often a consequence of contaminated food, unsanitary living conditions, or direct person-to-person contact.[1] *Shigella* has the potential to infect individuals of all age groups, with particular concern for the very young, elderly, and those with compromised immune systems. Notably, *Shigella* species exhibit a notable resilience to stomach acid, requiring only a small number of organisms to initiate infection.[2] Following ingestion, the bacteria undergo multiplication in the small intestine before establishing residence in the colon.[3] It is in the colon that *Shigella* produces critical enterotoxins, including serotype toxin, ultimately leading to the onset of watery or bloody diarrhoea. Clinical symptoms typically manifest within 12 to 72 hours post-exposure, with an average incubation period of 3 days. These indications encompass high fever, vomiting, and diffuse colicky abdominal pain, followed by the distinctive presentation of bloody mucoid diarrhoea and tenesmus.[4] Fortunately, for most individuals, the condition tends to resolve on its own within a span of 5 to 7 days from symptom onset. However, it is essential to note that high-risk individuals may face potential complications stemming from shigellosis.

Literature Review

Aetiology

Shigellosis, a gastrointestinal illness, is caused by the bacterium *Shigella*. *Shigella* is a type of gram-negative, nonmotile, facultatively anaerobic, and non-spore-forming rod-shaped bacterium. It is categorised into four main serotypes:

- **Serotype A:** *Shigella dysenteriae* (comprising 12 distinct serotypes)
- **Serotype B:** *Shigella flexneri* (with 6 different serotypes)
- **Serotype C:** *Shigella boydii* (including 23 serotypes)
- **Serotype D:** *Shigella sonnei* (1 serotype)[5]

Table 1.Literature Review for Shigellosis

Khan et al., 2013[5]	Both severe intestinal disease and extra-intestinal manifestations of shigellosis occur with infection by any of the four species of *Shigella* but are most common with *S. dysenteriae* type 1. Among the inpatient children, the risk of death was high with infection of any of the four *Shigella* species.
Kotloff et al., 2018[6]	Shigellosis is a clinical syndrome caused by the invasion of the epithelium lining the terminal ileum, colon, and rectum by *Shigella* species. Although infections occur globally, and in people of all ages, endemic infections among children aged 1–4 years living in low-income and middle-income settings constitute most of the disease burden. The versatile manifestations of these highly contagious organisms range from acute watery diarrhoea to fulminant dysentery characterised by frequent scant bloody stools with fever, prostration, and abdominal cramps. A broad array of uncommon, but often severe, intestinal and extra-intestinal complications can occur.
Jonas et al., 2016[7]	*Shigella sonnei* infections with a specific pulsed-field gel electrophoresis (PFGE) pattern linked to a multistate outbreak were recognised among men who have sex with men (MSM) in the Portland metropolitan area, and an outbreak investigation was initiated. In November 2015, isolates with PFGE patterns indistinguishable from the outbreak strain were identified in cases reported in four women, none of whom had epidemiologic links to other affected persons; however, three reported homelessness. In the ensuing months, additional S. sonnei infections were reported among homeless persons in the Portland area.
Crickard et al., 2016[8]	We analysed Foodborne Diseases Active Surveillance Network data for infections caused by *Shigella* among adults ≥ 18 years old during 2002–2014. Criteria to define severe shigellosis included hospitalisation, bacteraemia, or death. We estimated an annual incidence of shigellosis per 100,000 among adult populations and conducted multivariable mixed-effects logistic regression to assess associations between severe shigellosis, demographic factors and *Shigella* species among adults with shigellosis.

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Watson et al., 2004[8]	The article reports a study "*Shigella flexneri* serotype 3 infections among men who have sex with men--Chicago, Illinois, 2003-2004." Cases of shigellosis, a reportable disease in Illinois, were investigated by the Chicago Department of Public Health. The questionnaire asked about sexual orientation and sexual activities prior to the onset of the illness. Isolates were tested for antimicrobial susceptibility. The CDC editorial note mentions the low inoculum required for shigellosis and the risk factors for sexual transmission of *Shigella*.
Painter et al., 2013[9]	Developed a method of attributing illnesses to food commodities that uses data from outbreaks associated with both simple and complex foods. Using data from outbreak-associated illnesses for 1998–2008, we estimated annual US foodborne illnesses, hospitalisations, and deaths attributable to each of the 17 food commodities. We attributed 46% of illnesses to produce and found that more deaths were attributed to poultry than to any other commodity. To the extent that these estimates reflect the commodities causing all foodborne illnesses, they indicate that efforts are particularly needed to prevent contamination of produce and poultry. Methods to incorporate data from other sources are needed to improve attribution estimates for some commodities and agents.
Eikmeier et al., 2015[10]	Increasing rates of shigellosis among adult males, particularly men who have sex with men (MSM), have been documented in the United States, Canada, and Europe,[1–4] and MSM appear to be at greater risk for infection with *Shigella* that are not susceptible to ciprofloxacin or azithromycin[5–8]. Azithromycin is the first-line empiric antimicrobial treatment for shigellosis among children and is a second-line treatment among adults. Isolates collected in 2014 in two US cities from outbreaks of shigellosis displayed highly similar pulsed-field gel electrophoresis (PFGE) patterns and decreased susceptibility to azithromycin (DSA). This report summarises and compares the findings from investigations of the two outbreaks, which occurred among MSM in metropolitan Minneapolis-St Paul, Minnesota, and Chicago, Illinois.
Teferra et al., 2007[11]	Although shigellosis is a potentially fatal disease that may cause a number of extra-intestinal manifestations, intractable septic shock is an unusual complication. Here we describe a 6-month-old infant who developed severe septic shock and convulsions during an episode of dysentery caused by multidrug-resistant *Shigella dysenteriae*. The case presentation demonstrates how shigellosis can lead to rare and potentially misleading complications such as septic shock when not treated adequately and promptly.

Table 2.Characteristics of Shigellosis Species and Their Clinical Significance

Species	Characteristics
Shigella flexneri	- Serogroups: Divided into multiple serotypes (e.g., 1a, 1b, 2a, 2b, 3a, - Common in developing countries - Causes bacillary dysentery - Primarily affects children under 5 years of age - Can cause severe complications, including seizures and haemolytic uraemic syndrome (HUS)
Shigella sonnei	-Serogroup D - Prevalent in industrialised countries - Most common species in the United States and Europe - Often causes milder symptoms compared to other species - Associated with person-to-person transmission and foodborne outbreaks

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Shigella boydii	- Serogroups: Divided into multiple serotypes (e.g., 1–18) - Common in India, Bangladesh, and Pakistan - Causes bacillary dysentery - Symptoms similar to those caused by *Shigella flexneri*
Shigella dysenteriae	- Serogroups: Divided into multiple serotypes (e.g., 1–15) - Contains the deadly Shiga toxin - Most severe species, associated with epidemics and high mortality rates - Can lead to severe complications, including HUS and neurological symptoms[13]

Shigella sonnei stands out from the other serotypes due to its expression of ornithine decarboxylase, while serotypes A, B, and C cannot be distinguished by any specific biochemical marker. *Shigella sonnei* typically leads to milder symptoms, potentially limited to watery diarrhoea. On the other hand, *Shigella flexneri* and *Shigella dysenteriae* are associated with more severe cases, often involving dysentery characterised by bloody diarrhoea. This distinction is crucial in understanding the varied clinical presentations of shigellosis caused by different *Shigella* serotypes.[12]

Epidemiology and Incidence

Shigellosis, a bacterial infection caused by *Shigella*, presents a significant global health concern. Annually, there are an estimated 188 million cases worldwide, resulting in approximately 1 million deaths. In more developed regions, the incidence is around 1.5 million cases per year, with the United States accounting for about 450,000 cases annually. Notably, the primary culprit in the US is *S. sonnei* (77%).[13] In developing nations, *S. flexneri* is the predominant serotype. Young children, especially those under 4 years of age, are most susceptible, with reported rates of 28 cases per 100,000. Additionally, *Shigella* is the leading cause of diarrhoeal illness in children under 5 years in regions like Saharan Africa and South Asia. It is worth noting that shigellosis shows no specific gender or racial preference.[14]

Pathophysiology and Route of Transmission

Shigellosis primarily spreads through the faecal-oral route, both in developed countries and through water or food in developing areas. It can also be transmitted sexually, particularly among men who have sex with men. Flies can serve as a vector as well. Humans are the sole natural reservoir for *Shigella*. The disease exhibits low sensitivity to stomach acid, requiring an inoculum of 10 to 200 organisms for infection due to host antibacterial protein downregulation.[15]

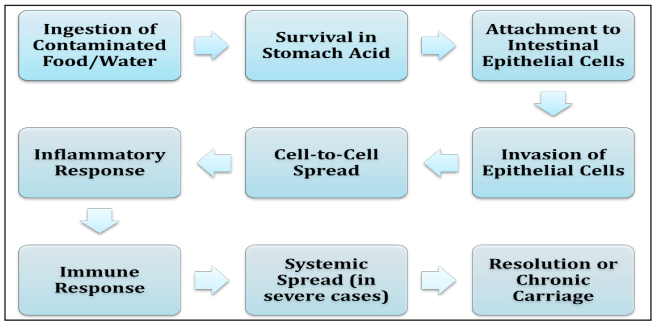

Figure 1.Pathogenesis of Shigellosis

Pathogenesis

Upon ingestion, *Shigella* first proliferates in the small intestine before advancing to the large intestine. It inflicts cell damage and causes complications through direct invasion of the colonic mucosa and the release of enterotoxins. In the large intestine, *Shigella* uses transcytosis to invade, employing M cells for immune activation. This prompts macrophages and cellular apoptosis, leading to the release of inflammatory cytokines. *Shigella* then re-invades adjacent epithelium and the immune system through actin polymerisation. This triggers nuclear factor (kappa B) activation, producing IL-8, which recruits neutrophils, exacerbating inflammation and epithelial damage. Toxin production further contributes to cell injury, impairing fluid and nutrient absorption, leading to *Shigella*-associated diarrhoea. The cytotoxin of *S. dysenteriae* serotype 1 induces cytotoxicity and vascular lesions, potentially resulting in complications like haemolytic uraemic syndrome (HUS).[16]

Histopathology

In cases of shigellosis, examining infected tissue under a microscope, particularly in the colon, rectum, or distal ileum, reveals distinct features. These include the infiltration of polymorphonuclear cells into the epithelial cells and the formation of inflammatory patches called pseudomembranes. *Shigella* bacteria multiply in the colonic

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epithelium, causing cell death. This multiplication then spreads laterally, infecting and killing adjacent epithelial cells, ultimately leading to ulceration of the mucosa, resulting in inflammation and bleeding.[17]

History and Physical

Shigellosis presents with a range of symptoms. These can vary from mild abdominal discomfort to severe, crampy abdominal pain (occurring in 70% to 90% of cases). Patients often experience small volume, mucoid diarrhoea (70% to 80%) followed by bloody diarrhoea (30% to 50%). Additional symptoms may include fever, nausea, vomiting, loss of appetite, fatigue, and a sensation of incomplete bowel emptying (tenesmus), while rare, severe symptoms may include delirium, encephalopathy, reduced urine output (anuria), seizures, signs of meningitis (meningismus), and even coma.

Physical Examination

During a physical examination, individuals with shigellosis may appear lethargic or in a state of toxicity. Vital signs may show an elevated body temperature (fever), increased heart rate (tachycardia), rapid breathing (tachypnoea), and low blood pressure (hypotension). The abdominal examination may reveal a swollen abdomen with heightened bowel sounds. Tenderness, especially in the lower abdomen, may be present due to the involvement of the sigmoid colon and rectum.[18]

Evaluation - Laboratory Evaluation

- **Complete Blood Count (CBC):** This test assesses various components of the blood. In cases of shigellosis, it may show elevated white blood cell count (leucocytosis) with a shift towards immature cells (left shift). Alternatively, a low white blood cell count (leucopenia) can also occur. Anaemia (low red blood cell count) and low platelet count (thrombocytopenia) may also be observed.
- **Stool Examination:** Analysis of stool samples can reveal important information. Faecal leucocytes and blood may be present, indicating an inflammatory response in the intestines. Microscopic examination might show evidence of white blood cells in the stool smear. Stool culture is a more effective method than rectal swab culture for identifying the specific bacteria causing the infection.
- **Liver Function Test:** In severe cases of shigellosis, there may be a slight increase in bilirubin levels, a marker of liver function.
- **Renal Function:** Dehydrated individuals or very young and elderly patients may show elevated levels of blood urea nitrogen (BUN) and creatinine, indicating potential kidney stress.
- **Hyponatraemia:** This refers to low levels of sodium in the blood. In shigellosis, it is often caused by the syndrome of inappropriate antidiuretic hormone secretion.
- **Inflammatory Markers:** Tests for markers of inflammation like Erythrocyte Sedimentation Rate (ESR) and C-Reactive Protein (CRP) may be elevated, indicating an ongoing inflammatory process.
- **Blood Culture:** In complicated cases, a blood culture may be performed. This test looks for the presence of bacteria in the bloodstream. It is more commonly positive in children compared to adults, and the presence of bacteria in the blood (bacteraemia) is associated with an increased risk of mortality.
- **Stool Alpha-1 Antitrypsin:** This marker is elevated during the acute phase of shigellosis and may remain high in cases where initial medical therapy has not been successful.
- **ELISA and Polymerase Chain Reaction (PCR):** These specialised tests may be required in a minority of cases. ELISA can detect a specific toxin produced by *Shigella dysenteriae* type-1 in stool samples. PCR is used to identify specific genes associated with virulence in the *Shigella* bacteria.[19]

Management of Shigellosis

Managing *shigellosis* primarily involves medical intervention with a focus on hydration and electrolyte balance. Oral rehydration is often sufficient in many cases. It is important to note that the use of antimotility drugs like loperamide, paregoric, or diphenoxylate is discouraged, as they can potentially prolong the infection and increase the shedding of the organism.

The choice of antibiotics for treatment depends on the patient's age and regional susceptibility patterns. Antibiotic susceptibility testing is crucial due to common resistance issues. In adults, empirical antibiotics are chosen based on demographics and regional resistance, for instance, fluoroquinolones are recommended for patients with no risk factors for resistance, while high-risk patients, including those in Africa and Asia, international travellers, HIV-infected individuals, and men who have sex with men, are advised to use third-generation cephalosporins. The antibiotic regimen should be adjusted once susceptibility results are available. Second-generation cephalosporins, ampicillin, and trimethoprim-sulfamethoxazole can also be considered based on susceptibility.

For paediatric patients, azithromycin is the first-line drug when antibiotic susceptibility is unknown. Studies have shown azithromycin to be successful in a majority of cases. In South Asia, cefixime and ceftibuten are preferred due to widespread antibiotic resistance. Pivmecillinam, an extended-spectrum penicillin, is another effective

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alternative for reducing diarrhoea duration and eradicating *Shigella* organisms in the stool.

In severe cases of shigellosis, especially in children with signs of bacteraemia or underlying immune deficiencies, parenteral antibiotics like ceftriaxone are indicated. Frequent handwashing, particularly after using the bathroom and before food preparation, is strongly recommended. Food handlers should refrain from preparation duties if stool cultures remain positive, as negative cultures usually occur around two days after starting antibiotic therapy. This comprehensive approach to management aims to effectively treat shigellosis and prevent further spread of the infection.[20]

Current Treatment Options for Shigellosis

Tetracycline and Sulfonamides

- No longer recommended due to widespread bacterial resistance

Ampicillin and Trimethoprim-Sulfamethoxazole (TMP-SMZ)

- Effective and have been the drugs of choice for the past 15 years
- Inexpensive, available in oral forms, and safe for children
- Increasing incidence of multiresistant strains poses challenges

Nalidixic Acid

- Commonly used for strains resistant to ampicillin and TMP-SMZ
- Clinical cure rates equivalent to ampicillin, but *Shigella* eradication from stool takes longer
- Can lead to arthropathy in high doses but not a major concern in humans
- Rapid development of resistance observed after its introduction

Newer Quinolones (e.g., Ciprofloxacin, Norfloxacin, Enoxacin)

- A successful treatment option for strains that are resistant
- High serum concentrations achieved, and longer half-life compared to nalidixic acid
- Ciprofloxacin demonstrated superiority over ampicillin in clinical trials

Amdinocillin Pivoxil

- Selectively binds to penicillin-binding protein 2, less susceptible to resistance
- Effective treatment option with equivalent response to ampicillin in clinical trials
- Routine susceptibility testing may be more practical using disk diffusion.

Limitations

- Newer quinolones can cause arthropathy in immature animals, limiting use in children.
- Cost is a significant barrier to access, particularly in resource-limited settings.

It is important to note that the choice of treatment should consider factors like local resistance patterns, patient age, and cost-effectiveness. A multidisciplinary approach and ongoing research are essential in addressing the challenges posed by evolving resistance patterns in the treatment of shigellosis.[21]

Possible Future Therapeutic Agents for Shigellosis

Next-Generation Cephalosporins

Second- and third-generation cephalosporins, known for their good absorption and efficacy against multiresistant *Shigella* strains, hold promise as potential treatment options. However, previous studies have yielded mixed results, warranting further evaluation.[21]

Gentamicin

Shigella remains largely susceptible to gentamicin, but its oral administration is unlikely to be effective. Parenteral administration may be considered for seriously ill patients with access to healthcare facilities.[22]

Combination Therapy with Ampicillin and {beta}-Lactamase Inhibitors

Combining ampicillin with {beta}-lactamase inhibitors like clavulanic acid or sulbactam shows promise in overcoming ampicillin resistance. However, in vitro studies have shown fewer promising results.[23]

Nalidixic Acid and Amdinocillin Pivoxil

These are alternative options for treating shigellosis, but their effectiveness should be weighed against potential limitations.[24]

Newer Quinolones

While newer quinolones hold potential, their current practicality is limited by cost and insufficient safety data, particularly in paediatric populations.

The management of shigellosis, particularly in developing countries, is challenged by the widespread resistance to commonly used antibiotics like ampicillin and TMP-SMZ. This resistance is particularly concerning for severe strains of S. dysenteriae type 1. Alternatives like nalidixic acid, amdinocillin pivoxil, and newer quinolones are being explored, but their accessibility and safety profiles need further assessment. Early initiation of effective antimicrobial therapy remains a critical strategy for reducing *Shigella*-related mortality. Cooperation between healthcare

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agencies and pharmaceutical companies will be vital in identifying, evaluating, and potentially providing cost-effective antimicrobial agents for shigellosis treatment.[25,26]

Conclusion

This comprehensive review provides a thorough understanding of shigellosis, a bacterial infection caused by various species of the *Shigella* genus. Delving into its history, symptoms, and pathophysiology, the review highlights the significant impact of this disease on public health. The causative factors, including contaminated food and water sources, are discussed, shedding light on the importance of sanitation and hygiene measures in its prevention. The diagnostic methods outlined equip healthcare professionals with effective tools to identify and treat shigellosis promptly. Moreover, insights into its epidemiology underscore the global burden and emphasise the need for continued vigilance. Treatment options, ranging from antibiotics to rehydration therapies, are explored, emphasising the critical role of early intervention. Prevention measures, including safe food handling and personal hygiene practices, are pivotal in reducing the incidence of shigellosis. By consolidating historical context, clinical insights, and preventative strategies, this review serves as a valuable resource for both healthcare practitioners and the general public, ultimately contributing to the broader understanding and effective management of shigellosis.

Conflict of Interest: None

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