90 *Salmonella* Infections

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Salmonella is a gram-negative bacillus that results in a myriad of human diseases ranging from mild gastroenteritis to severe typhoid fever. Non-typhoidal *Salmonella* infections are a major cause of diarrheal disease in children accounting for 20% of the two million death that occur annually due to diarrheal illnesses especially in developing world. Typhoid or enteric fever is still endemic in many of the developing countries, particularly south central and southeastern Asia. Worldwide, almost 21 million cases of typhoid fever occur every year, resulting in 217,000 deaths. *Salmonella paratyphi* is increasing in incidence in many of Asian countries as a cause of enteric fever.

Microbiology

Salmonella is a gram-negative, motile, flagellated, and encapsulated bacillus that belongs to Enterobacteriaceae family. It is non-lactose fermenter. It grows in most artificial culture media; however, selective media are used to inhibit the other bacteria and allow *Salmonella* to grow in pure culture so it can be identified.

Salmonella nomenclature is confusing; however, the last agreement was to divide *Salmonella* into three species: *Salmonella enterica*, *Salmonella bongari*, and *Salmonella subterraned*. Each species has a number of subspecies, and each subspecies has a number of serotypes or serovars Table 90.1. Most cases of gastroenteritis are caused by *S. enteritides* group, whereas enteric fever is caused by *S. typhi, S. paratyphi A, B, and* C.

Pathogenesis

Salmonella reaches the gastrointestinal tract after ingesting contaminated foods or drinks, especially poultry or dairy products. The infecting dose is usually 10^5–10^6 organisms; however, lower doses produce illness in more vulnerable hosts like young infants, immunocompromised patients, patients with hemoglobinopathies, elderly patients, and patients with achlorohydria or who have gastrectomy.

Once in the intestine, it adheres to the mucosa and then passes to the lamina propria where they proliferate and stimulate an inflammatory response which is mainly of polymorphonuclear cells in cases of gastroenteritis and mononuclear cells in cases of enteric fever. Polymorphonuclear cells stimulate production of prostaglandins which in turn stimulate fluid secretion and diarrhea. In cases of enteric fever, mononuclear cells travel from lamina propria via lymphatics into local lymphoid tissue in the Peyer's patches and then via thoracic duct into systemic circulation (primary bacteremia) where they then disseminate into the reticuloendothelial tissues in the liver, spleen, and bone marrow. From there, they then invade blood, causing secondary bacteremia with resultant dissemination to different organs.

Clinical Features

Non-typhoidal Salmonellosis

Almost all species of *Salmonella* can cause human diseases mostly in the form of enteritis. However the most common serovars belong to *Salmonella enterica*. The acquisition of infection occurs through eating contaminated foods or water. Most of culprit foods are those of poultry origin, specifically eggs. Many outbreaks have been attributed to eating contaminated eggs. Other sources include contact with infected animals, especially birds and reptiles.

Gastroenteritis

Gastroenteritis is the most common presentation of *Salmonella* infections. After an incubation period of 6–48 h, the patient starts to have diarrhea which is usually watery and associated with blood in some occasions. In contrast to shigellosis, there is not much mucoid secretion with diarrhea. Other symptoms of fever, abdominal pain, and dehydration are usually present. The symptoms persist for 2–7 days and then resolve spontaneously.

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Table 90.1
Current *Salmonella* nomenclature

Taxonomic position (writing format) and nomenclature				No. of serotypes in each species or subspecies [22]
Genus (capitalized, italic)	Species (italic)	Subspecies (italic)	Serotypes (or serovars) (capitalized, not italic)	
Salmonella	*enterica*	*enterica* (or subspecies I)	Choleraesuis, Enteritidis, Paratyphi, Typhi, Typhimurium	1,504
		salamae (or subspecies II)	9,46:z:z39	502
		arizonae (or subspecies IIIa)	43:z29:-	95
		diarizonae (or subspecies IIIb)	6,7:1,v:1,5,7	333
		houtenae (or subspecies IV)	21:m,t:-	72
		indica (or subspecies VI)	59:z36:-	13
	bongori	subspecies V	13,22:z39:-	22
	subteranea			

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Bacteremia

Five percent to 10% of patients with *Salmonella* infections may develop bacteremia. This might have been preceded by diarrhea, or it may arise without any preceding gastrointestinal symptoms. In immunocompetent children, it is rare and usually transient and benign. However, invasive disease in association with bacteremia is more common in certain groups of hosts, including those who are 3 months old or younger and immunocompromised hosts. Affected patients usually present with fever, lethargy, loss of weight, and headache. Most of the patients have isolated bacteremia; however, 10% may have their bacteremia complicated by local suppuration which most commonly involves meninges, bones, or lungs. Other organs may be involved like joints, liver, kidneys, prostate, testicles, pericardium, or endocardium. A rare complication that is more common in adults is aortitis. This complication is associated with high mortality. Recurrent bacteremia is an indication of an underlying immunodeficiency status, especially interleukin-12 deficiency.

Illustrative case:

A 2-year-old girl presented with history of fever and diarrhea. Blood culture grew *Salmonella enteritidis*. There was no evidence of any focal infection. Her symptoms recovered after receiving appropriate antibiotic. Two weeks after discharge, she presented with fever. Blood culture grew again *Salmonella enteritidis*. She was treated with antibiotic and responded well. She was investigated for possible focal lesion, including CT scan of brain, which came to be normal. CSF analysis was normal, and CSF culture was negative. Bone scan was negative. She was discharged home after treatment completion. Again she came back 2 weeks later with fever and blood culture grew *Salmonella enteritidis*. At this point, immunological work up was done and came to be normal. Interleukin 12 assay was done and came to be deficient. She was placed on cotrimoxazole prophylaxis after completion of therapy and continued to do well.

Enteric Fever

S. typhi and *S. paratyphi* A, B, or C may result in a severe form of infection, called enteric fever. Enteric fever is a syndrome characterized by insidious onset of lethargy, myalgia, headache, loss of appetite and loss of weight, and fever. It is still a major cause of morbidity and mortality in developing countries, especially Asian ones. In year 2000, almost 21 million cases of *Salmonella typhi* and five million of *Salmonella paratyphi* occurred worldwide. Endemic persistence in these countries is attributed to poor sanitarian conditions. Although there has been success with use of typhoid vaccine, paratyphi is becoming more in frequency. The other concern about enteric fever endemicity is increasing incidence of resistance to fluoroquinolones and third-generation cephalosporins. The main clinical feature of enteric fever is the presence of fever which follows a stepladder pattern starting to increase gradually until it reaches a maximum of 40–41°C in 5–7 days. Some patients present with fulminant illness with high fever, drowsiness, anemia, and shock, but this is rare. During the first week of illness, most patients are constipated; however, by the second week, diarrhea

develops. Rose spot rashes usually appear by end of the first week as faint blanching macular erythematous or rose-colored lesions over the chest and upper abdomen. They last for 2–3 days and then disappear.

Complications of enteric fever occur in up to 3–5% of patients and include intestinal hemorrhage and perforation (the most common) occurring by the second to third week of illness. Other complications include arthritis, osteomyelitis, pneumonia, meningitis, pyelonephritis, hepatitis, cholecystitis, orchitis, parotitis, tonsillitis, and lymphadenitis.

Diagnosis

The gold standard method of diagnosis is isolating the organism from infected specimens. In cases of gastroenteritis, stool can be cultured on Xylose-Lysine-Deoxycholate (XLD) medium or Hekton enteric medium. These media are used to prevent the growth of other normal flora of the intestine.

Specimens from sterile body sites can be cultured on blood or chocolate agar, and the organism can be identified by microscan or ABI-20 identification system. In addition, biochemical characters of *Salmonella* can help in identification.

These include ability to ferment glucose but not lactose. On TSI or KIA tube, they form alkaline slant and acid butt with gas and H_2S production. *S. typhi* produces only a scant amount of H_2S.

In cases of enteric fever, *Salmonella* can be isolated from blood during the first week and from stool or urine by the second week of illness. However, bone marrow remains the most sensitive specimen for isolating the organism even if the patient has been pretreated with antibiotics.

Other diagnostic aids include WBC, which is usually low in count and is associated with neutropenia and bandemia. Liver transaminases, alkaline phosphatase, and LDH are usually elevated. Serology remains shorthanded in diagnosing *Salmonella*. The standard test is Widal test; however, it lacks sensitivity and specificity and cannot be relied upon in diagnosing *Salmonella* infections.

New serology test for detecting antibodies and antigens are in progress. Currently, there is latex agglutination slide test which is used to identify organism isolated in the culture media therefore shortening the period of identifying the organism.

Treatment

Antibiotic therapy of *Salmonella* infections is indicated in the following situations:

1. Gastroenteritis in infants <3 months of age, in immunocompromised hosts, in patients with hemoglobinopathies, in patients who are toxic and moribund, and in those with associated bacteremia
2. Any patients with bacteremia
3. Enteric fever
4. Patient with focal suppuration like meningitis, osteomyelitis, etc.

Over the last two decades, there has been increasing emergence of multiresistant *Salmonella,* especially *S. typhi,* which renders therapy difficult. Therefore, therapy should be directed by local sensitivity pattern of the organism. Based on available data, a significant portion of *S. typhi* is resistant to chloramphenicol, amoxicillin, and trimethoprim/sulfamethoxazole in most of the developing countries. The available alternative includes third-generation cephalosporins (cefotaxime or ceftriaxone) and fluoroquinolones which are not recommended in children. Recently, there is an increasing report of some *Salmonella* strains that have reduced susceptibility to fluoroquinolones. These strains have an MIC between 0.25–1 mg/L. In addition these strains are usually resistant to nalidexic acid. Therefore strains that are resistant to nalidexic acid should be checked for reduced susceptibility to flouroquinolones. The empiric therapy of strains suspected to have reduced susceptibility to flouroquinolones is usually cefotaxime or ceftriaxone. Azithromycin may be an alternative therapy for multi-drug resistance strains.

Aminoglycosides, tetracyclines, and first- and second-generation cephalosporins should not be used in treating enteric fever, even if in vitro sensitivity showed them to be effective as they are ineffective in vivo. Chronic carriers are better treated by cholecystectomy preceded and followed by antibiotics therapy with either ampicillin or fluoroquinolones. Chloramphenicol should be avoided in treatment of chronic carrier status.

Prevention

Hygiene, improved sanitation, improved food (poultry) processing are the most important methods in decreasing the infection rate. Surveillance of food handlers and removing those who are infected from contact with foods is also important.

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