Pediatrics and Neonatology (2013) 54, 147–152

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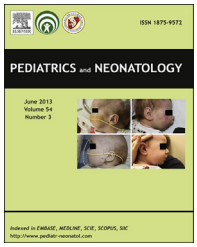

REVIEW ARTICLE

# Nontyphoid *Salmonella* Infection: Microbiology, Clinical Features, and Antimicrobial Therapy

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Received Jul 31, 2012; received in revised form Oct 13, 2012; accepted Jan 22, 2013

**Key Words**
antimicrobial resistance;
antimicrobial therapy;
*Salmonella* infection

Nontyphoid *Salmonella* is the most common bacterial pathogen causing gastrointestinal infection worldwide. Most nontyphoid *Salmonella* infection is limited to uncomplicated gastroenteritis that seldom requires antimicrobial treatment. Nevertheless, invasive infections, such as bacteremia, osteomyelitis, and meningitis, may occur and require antimicrobial therapy. Continuous genetic and genomic evolution in *Salmonella* leading to increased virulence and resistance to multiple drugs are of significant public health concern. Two major changes in the epidemiology of nontyphoid salmonellosis in Europe and in the USA occurred in the second half of the 20th century: the emergence of foodborne human infections caused by *Salmonella enterica* serotype Enteriditis and by multidrug-resistant strains of *Salmonella enterica* serotype Typhimurium. In the 21st century, a worsening situation is the increasing resistance to fluoroquinolones and third-generation cephalosporins in nontyphoid *Salmonella*. Clinical isolates showing carbapenem resistance also have been identified. Although antimicrobial therapy is usually not indicated for uncomplicated *Salmonella* gastroenteritis, recent studies indicated that a short-course ceftriaxone therapy (3–5 days) for patients with severe gastroenteritis would lead to a faster clinical recovery. Continuous surveillance of *Salmonella* in both humans and animals is mandatory. A better understanding of the mechanisms that lead to the emergence of antimicrobial resistance in *Salmonella* may help in the devising of better

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http://dx.doi.org/10.1016/j.pedneo.2013.01.010

interventional strategies to reduce the spread of resistant *Salmonella* between humans and reservoirs along the food chain.


## 1. Introduction

*Salmonella* are important pathogens in humans and animals. There are approximately 1.4 million salmonellosis cases each year in North America, with at least 22% of cases requiring hospitalization for medical treatment.[1] Over the last decade, there has been a 25% reduction in the incidence of foodborne illness caused by pathogens such as *Escherichia coli* O157 and *Campylobacter* but only negligible reductions in salmonellosis.[2] A recent report also indicated that the global burden of nontyphoid *Salmonella* gastroenteritis remains high at 93.8 million cases, with 155,000 deaths and an average incidence of 1.14 episodes/100 person-years each year.[3] The figures are extraordinarily highest in Asia, with 83.4 million cases, 137.7 thousand deaths, and an average incidence of 4.72/100 person-years each year.[3]

*Salmonella* has been recognized as a cause of intestinal diseases for many years. Control of *Salmonella* infection is difficult due to the bacterium's high tolerance to environmental stress, widespread distribution, multiple drug resistance, and adaptability. The present report aims to provide an overview of the organism, including microbiological and clinical features, current situations of antimicrobial resistance and therapy.

## 2. Taxonomy

The genus *Salmonella* comprises three species, *Salmonella enterica*, *Salmonella bongori*, and *Salmonella subterranean*.[4] The type species, *S. enterica*, is further classified into six subspecies: *enterica* (subsp. I), *arizonae* (subsp. IIIa), *diarizonae* (subsp. IIIb), *houtenae* (subsp. IV), *indica* (subsp. VI), and *salamae* (subsp. II).[4] *Salmonella* strains belong to over 50 serogroups based on the O antigen, and to over 2500 serotypes (each having a unique combination of somatic O, and flagellar H1 and H2 antigens). Most of these serotypes belong to one single *Salmonella* subspecies, *enterica*, and are associated with >99% of *Salmonella*-caused diseases in humans, including gastroenteritis and enteric fever.[5]

Genome sequencing and comparative genomic analysis revealed a close similarity of core regions from various *Salmonella* genomes, together with evidence of recombination and rearrangement, genomic degradation, pseudogenes, and clonal diversity both within and among the serotypes.[6,7] Genomic comparisons of host-restricted (*S.* Typhi, *S.* Paratyphi, and *S.* Gallinarum) and host-adapted (*S.* Typhimurium and *S.* Enteridis) *S. enterica* serotypes indicated that genomic degradation is a common evolutionary mechanism for host adaptation and increased pathogenicity of *Salmonella*.[6,7] As described in the following sections, continuous genetic re-assortment in *Salmonella*, leading to increased virulence and the emergence of resistance to multiple drugs, is of significant public health concern.

## 3. Host Specificity

The degree of host adaptations varies among *Salmonella* serotypes and affects the pathogenicity for man and animals (Table 1).[8] Serotypes adapted to man, such as *S.* Typhi and *S.* Paratyphi, usually cause severe septic typhoid syndrome (enteric fever) in humans. These serotypes are not usually pathogenic to animals.

Serotypes that are highly adapted to animal hosts, such as *S.* Gallinarum (poultry) or *S.* Abortusovis (sheep), may only produce very mild symptoms in humans. However, *S.* Choleraesuis, which swine is the primary host, also

**Table 1** Host specificity and disease spectrum of representative *Salmonella* serotypes.[8]

| *Salmonella* serogroup/serotype | Host | Disease |
|---|---|---|
| D/Typhi | Humans | Septicemia, fever |
| A,B,C/Paratyphi | Humans | Septicemia, fever |
| B/Typhimurium | Humans, cattle, swine, horses, sheep, poultry, wild rodents | Gastroenteritis, septicemia, fever |
| D/Enteritidis | Humans, poultry, wild rodents | Gastroenteritis, septicemia, fever |
| D/Dublin | Cattle, swine, sheep | Gastroenteritis, septicemia, abortion, fever |
| B/Derby | Birds, swine | Gastroenteritis, septicemia |
| D/Gallinarum | Poultry | Gastroenteritis, septicemia |
| B/Abortusovis | Sheep | Septicemia, abortion |
| B/Abortusequi | Horses | Septicemia, abortion |
| C/Choleraesuis | Swine | Septicemia, fever |

causes severe systemic illness in man. In the same way, S. Dublin, which has a preference for cattle as the host, is primarily responsible for the systemic form of salmonellosis in humans. This disease causes high mortality in young calves and results in fever, reduced milk yield, diarrhea, abortion, and occasionally death in mature cattle. Ubiquitous serotypes, such as S. Enteritidis or S. Typhimurium, which affect both man and animals, generally cause gastrointestinal infections with less severity than enteric fever. However, they also have the capacity to produce typhoid-like infections in mice and humans or asymptomatic intestinal colonization in chickens.[4]

## 4. *Salmonella* Infection

The most common mode of *Salmonella* infection is acute gastroenteritis. The incubation period may vary from 4 hours to 72 hours after the ingestion of contaminated food or water. Symptoms are acute onset of fever and chills, nausea and vomiting, abdominal cramping, and diarrhea. If a fever is present, it generally subsides in 72 hours. Diarrhea is usually self-limiting, lasting 3—7 days, and may be grossly bloody. *Salmonella* is excreted in feces after infection, a process that may last for a median of 5 weeks. In young children, the excretion may be prolonged. In older children and adults, *Salmonella* excretion lasting >8 weeks after infection is uncommon. Bacteremia occurs in 5—10% of infected persons, and some of them may progress to have focal infection, such as meningitis, and bone and joint infection. Immunocompromised patients, especially those who have impaired cellular immunity, may have prolonged or recurrent *Salmonella* infection.[9]

Although nontyphoid *Salmonella*-associated bloodstream or focal infection is relatively infrequent in most developed and developing countries,[10] the organisms are among the most common bacteria causing bloodstream infection, particularly in susceptible children and HIV-infected adults, in some less developed countries.[11] A recent systematic review and meta-analysis indicated a high prevalence (19%) of invasive nontyphoid *Salmonella* infection among the community-acquired bloodstream infections in Africa.[12] Even with proper microbiological examination as well as appropriate antimicrobial therapy, invasive nontyphoid *Salmonella* infection was reported to be associated with a high mortality of 22—47% in African adults and children.[13,14]

The number of bacteria that must be ingested to cause symptomatic disease in healthy adults is $10^6$—$10^8$ nontyphoid *Salmonella* organisms. In infants and persons with certain underlying conditions, a smaller inoculum can produce diseases, so that direct person-to-person transmission, although uncommon, sometimes occurs. This is why nontyphoid *Salmonella* infection tends to occur in children, especially in children aged <2 years.[15]

Figure 1 demonstrates the distribution of *Salmonella* cases among various age groups of patients treated in Chang Gung Children's Hospital and Chang Gung Memorial Hospital during 2001—2011. Among the total of 8163 cases, 62% were children younger than 5 years. The incidence increased rapidly right after birth. At the second year of life, the case numbers of serogroups C and D infection continued to grow, but that of serogroup B infection became flattened. Infection caused by all *Salmonella* serogroups decreased very rapidly among children after age 3 years and remained at a low level throughout the adult ages.

Similar to a previous report,[15] the changing trend of *Salmonella* cases among different age groups of patients was generally the same for various serogroups, but children younger than 5 years were more likely to have serogroup B infection than older children ($p < 0.0001$, Chi-square test). Furthermore, although serogroup B has caused the largest proportion of nontyphoid *Salmonella* infections, the

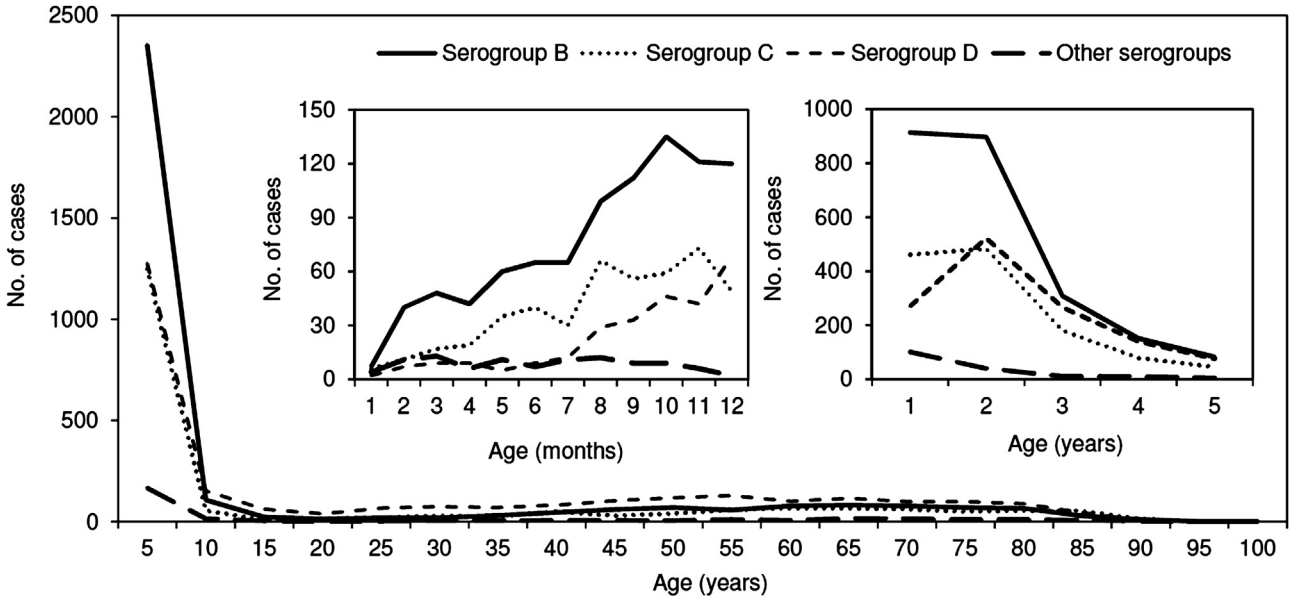


**Figure 1** Distribution of *Salmonella* cases among various age groups of patients treated in Chang Gung Children's Hospital and Chang Gung Memorial Hospital during 2001—2011.

infection caused by serogroup D *Salmonella* obviously exceeded that of serogroup B for patients older than 5 years (Figure 1).

## 5. Antimicrobial Resistance

An inevitable side effect of antibiotic use, which is associated with the adaptability of bacteria and microbial genome evolution, is the emergence and dissemination of resistant bacteria, not only in pathogenic bacteria but also in the endogenous flora of man and animals. Resistant commensal bacteria of food animals, such as zoonotic bacteria, might contaminate meat products, thus reaching the intestinal tract of humans.[9] Resistance genes against antibiotics that are or have only been used in animals were soon after their introduction found not only in animal bacteria, but also in the commensal flora of humans, in zoonotic pathogens such as *Salmonella*, and in strictly human pathogens, such as *Shigella*. There is evidence that resistance determinants can transfer between unrelated bacteria, such as *Bacteroides*, on the one hand, and *Salmonella* and *Escherichia* on the other.[16] Therefore, not only may the clonal spread of resistant strains occur, but there is also a transfer of resistance genes between human and animal bacteria.[16]

Antimicrobial resistance in nontyphoid *Salmonella* serotypes is a global problem. Surveillance data demonstrate an obvious increase in overall antimicrobial resistance among salmonellae from 20—30% in the early 1990s to as high as 70% in some countries at the turn of the century.[5] The resistance rate, however, varies with different serotypes and different antibiotics.[17—19] *S.* Enteritidis, one of the most prevalent *Salmonella* serotypes, is relatively more susceptible to antimicrobial agents than are other serotypes.[5] A much higher rate of resistance was found in *S.* Typhimurium, another globally prevalent serotype. Multidrug-resistant *S.* Typhimurium definitive phage type (DT) 104 emerged during the last 2 decades as a global health problem because of its involvement in diseases among both animals and humans.[20] Multidrug-resistant strains of this phage type were first detected in the UK in cattle and humans in the late 1980s but have since become common in other animal species such as poultry, pigs, and sheep.[21] Human infections with multidrug-resistant DT104 isolates have been associated with the consumption of chicken, beef, pork, sausages, and meat paste. The *S.* Typhimurium DT104 epidemic is now worldwide, with a considerable number of outbreaks since 1996 in the USA and Canada. These multidrug-resistant strains are generally resistant to ampicillin, chloramphenicol/florfenicol, streptomycin/spectinomycin, sulfonamides, and tetracyclines.[20] Genes associated with these resistance properties have been found to be chromosomally encoded. Multidrug resistance in *S.* Typhimurium DT104 is mainly due to *Salmonella* genomic island 1 (SGI1), an integrative mobile element, carrying various antibiotic resistance gene clusters, and to conjugative R plasmids that confer resistance to many antibiotics including extended-spectrum cephalosporins.[22,23] Additional resistance to trimethoprim, occasionally seen among *S.* Typhimurium DT104 strains, may be encoded by a nonconjugative but mobilizable plasmid (approximately 40 kb in length) which also encodes resistance to sulfonamides.[24]

The increasing rates of resistance to traditional agents (i.e., ampicillin, chloramphenicol, and trimethoprim—sulfamethoxazole) have turned the treatment of invasive salmonellosis into a clinical dilemma. The emergence of resistance to fluoroquinolones among nontyphoid *Salmonella* is of particular concern, since this class of antimicrobial agents constitutes the drug of choice for treating potentially life-threatening *Salmonella* infections caused by multiple-antibiotic resistant strains in adults.[25] All fluoroquinolones have the same mechanisms of action regardless of whether they are in clinical or veterinary medicine. These antibiotics inhibit the topoisomerase genes, leading to inhibition of DNA replication. This common mechanism of action means that resistance to one fluoroquinolone will confer resistance to all other fluoroquinolones.[26] In *Salmonella*, quinolone resistance was initially attributed to point mutations in the *gyrA* gene encoding the A subunit of gyrase, whose complex with DNA is the primary target of quinolones. Resistance mutations of *gyrA* occur in a region of the gene product between amino acids 67 and 106, termed the quinolone resistance-determining region (QRDR). Amino acid changes at Ser-83 (to Phe, Tyr, or Ala) or at Asp-87 (to Gly, Asn, or Tyr) are the most frequently observed in nalidixic acid (Nal)-resistant strains.[27] Fluoroquinolone-resistant isolates can also have an altered *gyrB* gene encoding the B subunit of gyrase.[28] This consists of a single mutation in the QRDR of *gyrB* leading to amino acid change Ser464Phe.[29] Fluoroquinolone-resistant isolates can also carry a fourth mutation in the QRDR of *parC* encoding the ParC subunit of topoisomerase IV, which is the secondary target for quinolones.[26,27] The mutation identified led to amino acid change Ser80Ile.[30]

Another worrisome situation is the emergence of ceftriaxone resistance in nontyphoid *Salmonella*, which is a big problem in Asian countries, including Taiwan.[17,31] Ceftriaxone resistance of nontyphoid *Salmonella* is usually attributed to the presence of a plasmid-mediated β-lactamase gene, $bla_{CMY-2}$, which is usually located on a transposon-like DNA element bearing a specific IS*Ecp1*-$bla_{CMY-2}$-*blc*-*sugE* structure.[7,31] This conserved DNA fragment, subsequently named Tn*6092*,[32] has been reported from different geographic areas and is being widely distributed among various *Salmonella* serotypes and other members of the family *Enterobacteriaceae*.[33] It was recently found that the Tn*6092* is carried by a conjugative IncI1 plasmid and may have already spread widely among other serotypes of nontyphoid *Salmonella*, particularly among *S.* Typhimurium.[31]

For patients with invasive *Salmonella* infections that are resistant to both ciprofloxacin and ceftriaxone, carbapenems may be the last drug of choice.[34] However, in 2010, a carbapenem-resistant *S.* Typhimurium was identified from a patient with urinary tract infections.[35] The ceftriaxone-resistant strain found in this patient initially carried a $bla_{CMY-2}$-containing Tn*6092* on a conjugative IncI1 plasmid. In addition to its original OmpD deficiency, the strain further developed OmpC deficiency during ertapenem therapy, and hence became resistant to carbapenems.[35] The emergence and dissemination of multidrug resistance

in nontyphoid *Salmonella* poses a serious threat to the public health and warrants continuous surveillance.

## 6. Antimicrobial Therapy

Antimicrobial therapy is usually not indicated for nontoxic immunocompetent patients. Acute gastroenteritis caused by nontyphoid *Salmonella* is a self-limiting disease, and treatment should consist mainly of fluid replacement. A meta-analysis demonstrated that there is no evidence of any clinical benefit of antibiotic therapy in otherwise healthy children and adults with nonsevere *Salmonella* gastroenteritis.[36] However, while the risk of developing bacteremia is low (<5% of all patients), certain patients, such as young infants <3 months old, patients with toxic appearance and suspected extraintestinal infection, immunocompromised patients, and patients with severe colitis, would benefit from empirical antibiotic treatment.[37]

If bacteremia or an extraintestinal focal infection is confirmed, the choice of the antibiotics would depend on the susceptibility pattern of the strain and the clinical condition. Options may include ampicillin, trimethoprim–sulfamethoxazole, fluoroquinolones or third-generation cephalosporins, such as ceftriaxone, depending on the results of *in vitro* susceptibility testing. A recent study by Tsai et al showed that complications occurred in 7.9% of pediatric patients with *Salmonella* gastroenteritis, with bacteremia being the most common.[38] Patients with high C-reactive protein (≥100 mg/L) were more frequently put on empirical antimicrobial therapy and had more complications than those without.[38] Interestingly, these patients usually became afebrile within 2–3 days after initiation of adequate antimicrobial treatment.[38] It is concluded that a short course of ceftriaxone therapy (3–5 days) for such patients would lead to a faster clinical recovery.[38] However, antibiotics should be discontinued as soon as possible when the patient's clinical condition improves. Although fluoroquinolones are not recommended in children, they may be used in serious infections if there is no other alternative treatment available.

## 7. Conclusions

*Salmonella* is an important source of foodborne infection. The majority of patients are children younger than 5 years. Laboratory findings and clinical observation both suggest that the organism is very adaptive to antimicrobial selection pressure.[39] Continuous surveillance of *Salmonella* in both humans and animals is mandatory for a better control of the infections caused by the organism.

## Acknowledgments

The collection of data in Chang Gung Memorial Hospital and Chang Gung Children's Hospital on the prevalence of nontyphoid *Salmonella* was in part supported by grant CMRPG381593 from Chang Gung Memorial Hospital, Taiwan. The authors thank Dr Chyi-Liang Chen for his critical review of the article.

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