Non-typhoidal Salmonella in Children: Microbiology, Epidemiology and Treatment

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Abstract

Non-typhoidal *Salmonellae* (NTS) are an important cause of infectious diarrhoea world-wide. In the absence of immune deficiency, gastroenteritis caused by NTS is usually mild, self limiting and rarely requires intervention. NTS are also an important cause of invasive disease, particularly in developing countries, likely secondary to the high prevalence of co-existing malnutrition, malaria and HIV infection. This review provides an overview of the microbiology, epidemiology and pathogenesis of NTS, and compares recommendations for the treatment of NTS gastroenteritis in children.

2.1 Introduction

Non-typhoidal *Salmonellae* (NTS) are an important cause of infectious diarrhoea world-wide. In the absence of immune deficiency, gastroenteritis caused by NTS is usually mild, self limiting and rarely requires intervention. NTS are also an important cause of invasive disease, particularly in developing countries, likely secondary to the high prevalence of co-existing malnutrition, malaria and HIV infection. Antibiotic treatment of NTS gastroenteritis has been the subject of a meta-analysis, but questions regarding exactly which patients should be treated and the optimal regimen remain unanswered. This review provides an overview of the microbiology, epidemiology and pathogenesis of NTS, and compares recommendations for the treatment of NTS gastroenteritis in children.

2.2 Classification and Microbiology

The genus *Salmonella* belongs to the family of Enterobacteraciae. *Salmonella* are separated into two species, *Salmonella enterica* and *Salmonella bongori* (previously classified as subsp. V.), with the former being further classified into six subspecies (I, *S. enterica* subsp. *enterica*; II,

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Table 2.1 Number of serotypes in each subspecies. (Based on data from Grimont et al. [1])

Species	Subspecies	Number of serotypes
Salmonella enterica	*enterica* (I)	1,531
	salamae (II)	505
	arizonae (IIIa)	99
	diarizonae (IIIb)	336
	houtenae (IV)	73
	indica (VI)	13
Salmonella bongori (V)	–	22
Total		2,579

Table 2.2 Examples of clinically significant *Salmonella* serotypes and relevant clinical syndromes according to serogroup. (Based on data from Grimont et al. [1])

Serogroup	Serotype example[a]	Clinical syndrome
A	Paratyphi A	Enteric fever
B	Paratyphi B	Enteric fever
	Typhimurium	NTS
	Heidelberg	NTS
C1	Paratyphi C	Enteric fever
	Choleraesuis	NTS
	Virchow	NTS
C2	Newport	NTS
D1	Typhi	Enteric fever
	Enteritidis	NTS
	Dublin	NTS

[a] All example serotypes are members of subspecies *Salmonella enterica* subspecies *enterica*

S. enterica subsp. *salamae*; IIIa, *S. enterica* subsp. *arizonae*; IIIb, *S. enterica* subsp. *diarizonae*; IV, *S. enterica* subsp. *houtenae*; and VI, *S. enterica* subsp. *indica*) [1]. While an alternative nomenclature describes the genus as a single species, *Salmonella choleraesuis*, the Judicial Commission of the International Committee on the Systematics of the Prokaryotes supports the two-species designation [2].

Salmonellae are motile, Gram negative, facultative anaerobic bacilli which rarely ferment lactose [3]. Within the seven subspecies, more than 2,500 serotypes (or serovars) have been reported (Table 2.1) [1]. Salmonellae are classified according to antigenically diverse surface antigens: polysaccharide O (somatic) antigens, H (flagellar) antigens and Vi (capsular) antigens [3]. Agglutination reactions based on the O-antigen are used by most clinical laboratories to divide Salmonella into serogroups which include, but are not limited to, A, B, C1, C2, D and E (Table 2.2) [1]. Strains in these six serogroups cause most of the NTS infections in humans [4]. Formal serotyping, usually by reference laboratories, is required to differentiate clinically significant serotypes as cross-reactivity occurs. A detailed list of all currently recognised *Salmonella* serotypes is available elsewhere [4].

Salmonella nomenclature and syntax is potentially confusing. An example of a correct *Salmonella* subspecies and serotype designation is *Salmonella enterica* subspecies *enterica* serotype Typhimurium. An accepted abbreviation of this full taxonomic designation is *Salmonella* ser. Typhimurium (capitalised and not italicised) at the first citation and subsequently *Salmonella* Typhimurium [5].

Salmonella enterica subspecies *enterica* contains almost all the serotypes pathogenic for humans [3]. Although many *Salmonella* serotypes exist, they can be broadly categorised as typhoidal or non-typhoidal *Salmonella* (NTS) depending on the clinical syndrome with which they are predominantly associated (Table 2.2). The typhoidal Salmonella include the *S. enterica* subspecies *enterica* serotypes Typhi and Paratyphi A-C and typically cause systemic illness with little or no diarrhoea. The much larger group of NTS primarily induce acute, self-limiting gastroenteritis and is the focus of this review.

2.3 Epidemiology

In contrast to *Salmonella* Typhi and *Salmonella* Paratyphi, which are rarely encountered outside endemic countries or in returned travellers, NTS have a worldwide distribution. While the true incidence is unknown, there are an estimated 93.8 million episodes and 155,000 deaths each year attributable to NTS [6]. Data from the World Health Organization (WHO) Global Foodborne Infections Network (GFN) indicate that

Salmonella Typhimurium and *Salmonella* ser. Enteritidis account for nearly 80 % of all human isolates reported globally [7].

Unlike *Salmonella* Typhi and *Salmonella* Paratyphi, which have host specificity for humans, NTS can be acquired from both animal and humans. While poultry and eggs remain the most common source of NTS, other animal reservoirs include reptiles, rodents, cats and dogs [8, 9]. A case control study in the United States found that up to 6 % of all sporadic NTS infections are attributable to reptile or amphibian contact [10].

Transmission is predominantly foodborne, although other modes include consumption of contaminated water, contact with infected animals and nosocomial exposure [4, 11]. The incubation for NTS gastroenteritis depends on the host and the inoculum. It is usually 12–36 h, although incubation periods of up to nearly 2 weeks have been reported with certain strains [12–14].

2.4   Pathogenesis

Salmonellae are facultative intracellular pathogens that can survive within host macrophages [15]. Unlike typhoidal salmonella, which have the ability to evade the immune system, NTS tend to induce a localised inflammatory response in immunocompetent individuals, provoking a large influx of polymorphonuclear leukoytes to the intestinal lumen [16]. They can also colonise small and large intestinal mucosa thus facilitating prolonged periods of shedding [16].

Host factors predisposing to severe NTS infection include reduced gastric acidity, impaired cell mediated and humoral immunity, and impaired phagocytic function [16–18]. Salmonellae are unable to survive at a gastric pH less than 2.5 [19] and patients with anatomical or functional achlorhydria are at increased risk of developing infection [20]. This is especially relevant to neonates where the combination of relative achlorhydria and frequent milk feeds may contribute to their increased risk of NTS bacteraemia [21].

T-cell immunity is important in controlling *Salmonella* as evidenced by increased suscep-

tibility to invasive NTS in HIV-infection [22, 23] and with corticosteroid use [24]. Children with congenital defects in humoral immunity including X-linked agammaglobulinaemia and common variable immunodeficiency, are also reported to have increased risk of persistent diarrhoea and invasive disease [16]. Impaired phagocytic function seen in chronic granulomatous disease, haemoglobinopathies and malaria similarly increase the risk of invasive NTS infection [16]. In addition, co-infection with *Schistosoma* has been reported to cause prolonged and severe illness due to altered macrophage function and replication and survival of *Salmonella* within the parasite [25].

2.5   Clinical Syndromes

Clinical manifestations of NTS can be broadly divided into four groups:
1. Acute gastroenteritis
2. Extra-intestinal infection
3. Non-infectious sequelae
4. Salmonella carriage

2.5.1   Acute Gastroenteritis

Non-typhoidal salmonellae usually cause an acute self-limiting gastroenteritis. In contrast to typhoidal salmonella, infection with NTS results in diarrhoea. This is profuse and usually non-bloody. Associated symptoms of fever, abdominal cramping, nausea and vomiting may also occur [4]. Diagnosis is confirmed on stool culture. Fluid and electrolyte disturbances are the most frequent complication of NTS gastroenteritis. Asymptomatic gastrointestinal infection can also occur; however, given the rate of convalescent NTS excretion following acute infection, the true incidence is unknown [26].

2.5.2   Extra-intestinal Infection

Overall, NTS bacteraemia is reported in up to 9 % of patients with acute gastroenteritis [27].

Choleraesuis, Heidelberg and Dublin are among some of the serotypes more frequently associated with bacteraemia [28]. The incidence of invasive disease is also modified by factors such as age, region and underlying immune status. Surveillance data from the United States showed the incidence of invasive NTS was 7.8 cases per 100,000 in infants (aged less 1 year) compared to less than 0.8 cases per 100,000 in older children [29]. Significant discordance in the burden of invasive NTS between continents exists with an estimated annual incidence of up to 388 per 100,000 children (aged less 5 years) in Africa [30]. In this continent, the common invasive serotypes are Typhimurium and Enteritidis. The high prevalence of malaria in Africa, and its association with invasive NTS, has been postulated as one reason for this difference [31]. Interestingly, recent studies in the Gambia, Kenya and Tanzania have shown that the marked decline in malaria prevalence has been paralleled by a similar reduction in invasive NTS [32].

Bacteraemia may result in focal NTS infection at any site, including the central nervous system [33, 34]. Risk factors for focal disease are similar to those for bacteraemia [35], although focal infections in non-immunocompromised children are well described [36]. In one study, 7 of 12 (58 %) immunocompromised children developed focal infection compared with 5 of 132 (4 %) non-immunocompromised children [37].

Salmonella bacteraemia usually presents with fever and/or sepsis. Persistent bacteraemia has been documented in afebrile, well-appearing infants with NTS gastroenteritis emphasising the importance of blood cultures in this population [38]. Conversely, bacteraemia has been described in immunosuppressed patients without a history of gastroenteritis [24]. Notably, in the African setting, the majority of invasive NTS cases do not have gastroenteritis.

Salmonella can be cultured from standard blood culture media [3]. Positive urine culture with *Salmonella spp*. may indicate bacteraemia rather than faecal contamination [39]. Similar to *Salmonella* Typhi, culture of bone marrow sam-ples may increase the diagnostic yield of NTS [30, 40].

2.5.3 Non-infectious Sequelae

Non infectious sequelae following infectious gastroenteritis are well described [41]. Reactive arthritis after NTS infection has been reported in up to 29 % of patients [42]. There are conflicting data on the association between antibiotic treatment for acute NTS gastroenteritis and subsequent development of musculoskeletal symptoms, some suggesting a decreased risk and others an increased risk [42].

2.5.4 Salmonella Carriage

Salmonella carriage is defined as asymptomatic excretion following acute infection and can be divided into convalescent carriage and chronic carriage.

2.5.4.1 Convalescent Carriage
Convalescent carriage occurs frequently after symptomatic or asymptomatic NTS infection. Fig. 2.1 shows the duration of excretion of NTS in 13 studies according to age [43]. The median duration of NTS excretion in children less than 5 years of age is 7 weeks, with 18 % remaining culture positive at 6 months. Carriage is shorter in older children with a median duration of 3–4 weeks with only 0.3 % remaining culture positive at 6 months. In addition to younger age, factors associated with prolonged duration of excretion include symptomatic infection, treatment with antibiotics and infection with strains other than *Salmonella* Typhimurium (Fig. 2.2) [43]. Episodic excretion is not uncommon.
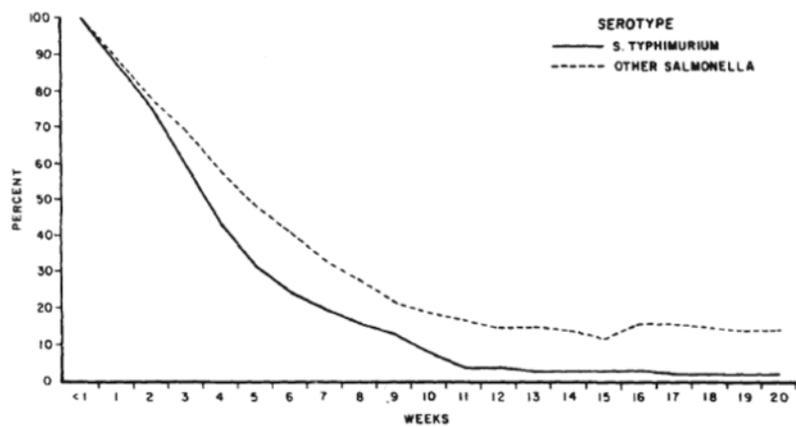
2.5.4.2 Chronic Carriage
Documented excretion of NTS for more than 1 year is defined as chronic carriage [44]. This occurs in up to 2.6 % of children under 5 years of age and 0.3 % of older children [43].

Fig. 2.1 Duration of excretion of NTS by age (by permission of Oxford University Press). [43]
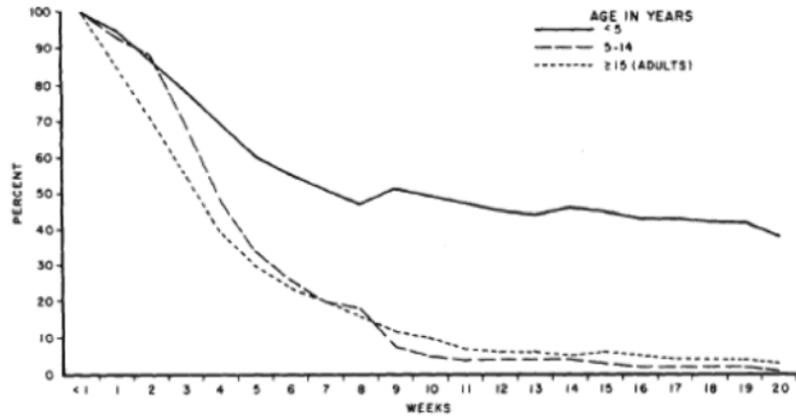
Fig. 2.2 Duration of excretion of NTS by serotype (by permission of Oxford University Press). [43]

2.6   Treatment

Recommendations for the treatment of acute gastroenteritis due to NTS vary (Table 2.3). The rationale for treatment of both acute NTS gastroenteritis and carriage will be the focus of the remainder of this review. Recommendations for the treatment of extra-intestinal complications of NTS are available elsewhere [4].

Antibiotic agents with *in vitro* and *in vivo* activity against NTS include ampicillin/amoxicillin, trimethoprim-sulfamethoxazole, tetracyclines, third generation cephalosporins, macrolides and fluoroquinolones. Aminoglycosides show good *in vitro* activity but poor clinical efficacy and are not recommended [9, 45]. Ciprofloxacin and other fluoroquinolones have previously been restricted in children due an association with arthropathy, first described in young beagles

[46]. However, a systematic review of the safety of ciprofloxacin in children has found that musculoskeletal adverse effects are infrequent (risk 1.6 %, 95 % CI 0.9–2.6 %), generally mild and usually reversible [47].

2.6.1   NTS Gastroenteritis

A Cochrane review of trials investigating antibiotic treatment of NTS concluded that there was no evidence to support antibiotic therapy in otherwise healthy children and adults with non-severe diarrhoea [58]. It included 12 randomised controlled trials (RCT) published before 1998, of which only five reported on clinical outcomes that were extractable for meta-analysis. Importantly, almost all trials excluded infants less than 6 weeks and patients with underlying disease and

Table 2.3 Recommendations for the treatment of acute NTS gastroenteritis. (With duration of treatment and/or specified antibiotic choice when stated in source)

Source	Age <3 months	Severe infection	Immuno-compro-mised	Haemo-globinopa-thies	Chronic GI disease	Other
Infectious diseases and paediatric reference books						
Textbook of Pediatric Infectious Diseases (Feigin and Cherry) [48]	Yes, 5d	–	Yes, 5d	Yes, 5d	–	–
Forfar and Arneil's Text-book of Pediatrics [49]	Yes	–	Yes	–	–	–
Evidence-based Pediatric Infectious Diseases (Isaacs) [50]	Yes, 5–7d, cipro-floxacin or azithro-mycin (empiric) and amoxicillin if susceptible	Yes, 5–7d	Yes, 5–7d	Yes, 5–7d	Yes, 5–7d	Malnourished, 5–7d
Principles and Practice of Pediatric Infectious Diseases (Long) [51]	Yes	–	Yes	–	Yes	–
Mandell, Douglas and Bennett's Principles and Practice of Infectious Diseases [4]	Yes, 2–3d	–	Yes, 7–14d, fluoroqui-nolone	–	–	Valvular heart disease; joint disease, 2–3d
Nelson Textbook of Pediat-rics [52]	Yes, 7–14d	–	Yes, 7–14d	Yes, 7–14d	–	–
Oski's Principles and Prac-tice of Pediatrics [53]	Yes	–	Yes	Yes	–	Malnourished
Red Book: 2009 Report of the Committee on Infec-tious Diseases [12]	Yes, as per susceptibilities	–	Yes, as per suscepti-bilities	Yes, as per suscepti-bilities	Yes, as per suscepti-bilities	–
Infectious Diseases of the Fetus and Newborn (Remington & Klein) [21]	Yes, 3–5d	–	Yes, 3–5d	–	–	–
Rudolph's Pediatrics [54]	Yes	–	Yes	–	–	–
The Sanford Guide to Anti-microbial Therapy [45]	Yes (<1y), 7–10d, fluoroquinolone	Yes[b], 7–10d, fluoroqui-nolone	Yes, 14d, fluoroqui-nolone	Yes, 7–10d, fluoroqui-nolone	–	Haemodialysis; vascular aneu-rysm; prosthetic joints, 7–10d, fluoroquinolone
Other sources						
IDSA Guidelines 2001 [55]	Yes (<6m), 3–7d	Yes, 3–7d	Yes, mini-mum 14d	–	–	Valvular heart disease, 3–7d
NICE guidelines: Diar-rhoea and Vomiting Caused by Gastroenteritis [56]	Yes (<6m)	–	Yes	–	–	Malnourished
UpToDate [57]	Yes, 3–10d	Yes[a], 3–7d	Yes, mini-mum 1d	Yes, mini-mum 14d	–	–

[a] Defined as high fever, severe diarrhoea (>9 stools per day), need for hospitalisation
[b] Defined as hospitalised with fever and severe diarrhoea

severe illness. Five studies were in infants and children ($n=258$), with only one study including infants less than 4 weeks [59–63]. The review did not identify significant differences in length of illness, diarrhoea or fever between any antibiotic regimen and placebo. Furthermore, although antibiotics were associated with more negative stool cultures during the first week of treatment, clinical relapse was more common and there were more cases of positive cultures at three weeks in the antibiotic-treated group. Adverse drug reactions, including rash, gastrointestinal upset and headache, were also more common in the antibiotic group [58]. Given the exclusion criteria, these results can not be extrapolated to patients at higher risk of severe and invasive infection.

Although the treatment of patients with risk factors for invasive disease seems reasonable, a benefit has not been documented in a RCT. This paucity of data likely explains the discrepancies in treatment recommendations between guidelines and reference books detailed in Table 2.3. Despite this variability, recommendations for the treatment of infants under 3–6 months of age and immunocompromised patients are consistent between all identified references. A 1988 consensus statement for the management of *Salmonella* infections in the first year of life similarly recommends treatment in infants less than 3 months following a blood culture irrespective of the severity of illness [64]. Other conditions where treatment has been recommended, albeit less consistently, include haemaglobinopathies, chronic gastrointestinal disease (for example inflammatory bowel disease), severe infection, malnourished state and vascular or joint disease.

Agents for treatment of NTS can be divided into non-absorbable (colistin and neomycin), absorbable (ampicillin, amoxicillin, tetracycline, macrolide and trimethoprim-sulfamethoxazole) and those with potent intra-cellular activity (fluoroquinolones) [58]. As *Salmonellae* are intracellular pathogens, it is postulated that the latter may be more effective in treatment of this infection and is specifically recommended for treatment of immunocompromised patients in two sources [4, 45]. The Cochrane review included eight trials involving fluroquinolones [58]. Subgroup analysis showed no benefit of treatment with fluoroquinolones, although negative stool cultures in the first week of treatment were more likely with fluroquinolone treatment compared to other absorbable antibiotics. Consequently, as there are insufficient data to recommend a particular agent, empiric treatment should be based on local susceptibility data and modified according to susceptibility results.

The optimal duration of treatment of NTS gastroenteritis has not been studied. Recommendations vary amongst sources between 3 and 14 days depending on the underlying condition (Table 2.3). Of the trials included in the Cochrane review, duration varied between 1 and 14 days, with 5 days being the most common treatment regimen. The authors commented that the two studies with longer antibiotic treatment duration (10 and 14 days) showed an apparent benefit of antibiotics at 8–21 days [58]. Subsequent to this review, a study reported that 10 days of ofloxacin compared with 5 days resulted in earlier eradication of NTS without an increase in carriage [65]. However, this study was relatively small and did not include a placebo arm.

Other trials have also been published since the last Cochrane review update in 1999 with conflicting results [66, 67]. An updated meta-analysis is awaited [68].

2.6.2 Convalescent NTS Carriage

Treatment of convalescent NTS carriage in children has not been subject to RCT but is generally not recommended (Table 2.4).

2.6.3 Chronic NTS carriage

There are no RCT investigating the treatment of chronic NTS carriage in healthy children. In adults with chronic carriage, norfloxacin and azithromycin were no better than placebo in eradicating carriage and were associated with higher rates of re-infection and selection of drug-resistant isolates in endemic areas [69]. However, although antibiotics have been shown to prolong NTS excretion, this paradoxical finding may only

Table 2.4 Recommendations for treatment of convalescent and chronic NTS. (With duration of treatment and/or specified antibiotic choice when stated in source)

Source	Convalescent excretion	Chronic carriage (> 1 year)
Infectious diseases and paediatric reference books		
Textbook of Pediatric Infectious Diseases (Feigin and Cherry) [48]	–	Not recommended
Forfar and Arneil's Textbook of Pediatrics [49]	Not recommended	–
Evidence-based Pediatric Infectious Diseases (Isaacs) [50]	Not recommended	
Principles and Practice of Pediatric Infectious Diseases (Long) [51]	–	–
Mandell, Douglas and Bennett's Principles and Practice of Infectious Diseases [4]	'Not recommended for uncomplicated convalescent excretion'	'Treatment of persons with asymptomatic carriage of NTS is controversial'
Nelson Textbook of Pediatrics [52]	–	–
Oski's Principles and Practice of Pediatrics [53]	Not recommended	Not recommended
Red Book: 2009 Report of the Committee on Infectious Diseases [12]	–	Not recommended
Infectious Diseases of the Fetus and Newborn (Remington & Klein) [21]	Not recommended for infants	–
Rudolph's Pediatrics [54]	–	–
The Sanford Guide to Antimicrobial Therapy [45]	–	–
Other sources		
IDSA Guidelines 2001 [55]	–	–
NICE Guideline: Diarrhoea and Vomiting Caused by Gastroenteritis [56]	–	–
UpToDate [57]	–	Recommended for all patients. Duration: 4–6 weeks; fluoroquinolone
		HIV infection: 'consider suppressive prophylactic therapy if failure to eradicate'

be relevant following treatment of acute NTS infection. In the Cochrane review, only three trials included asymptomatic patients (7.2 % of all participants) and separate data were not available for subgroup analysis [58].

Treatment of chronic NTS carriage is recommended in one source, based on data for the eradication of chronic *Salmonella* Typi and Paratyphi [57, 70] (Table 2.4). In patients with HIV infection, prolonged ciprofloxacin (minimum 3 months) may also reduce NTS relapse [71] and up to 6 months suppressive treatment is recommended for HIV-infected adolescents and adults with recurrent NTS bacteraemia [72].

2.7 NTS and Pregnancy

Pregnancy does not appear to increase the risk of maternal NTS infection. Screening of a large cohort of pregnant women (30,471) at the time of delivery detected NTS in only 60 (0.2 %), of which 17 (28 %) were symptomatic [73]. Of the 60 babies born, only seven (11.7 %) excreted NTS and five (8.3 %) had gastroenteritis. Transplacental infection can occur in the setting of maternal NTS bacteraemia and is often lethal to the foetus [74]. Transmission of NTS through breast milk has also been described, including three nursery outbreaks due to infected pooled milk [75]. More

Table 2.5 Infection control recommendations

Source	Recommendation
Infectious diseases and paediatric reference books	
Textbook of Pediatric Infectious Diseases, (Feigin and Cherry) [53]	Hospitalised patient: standard and contact precautions until stool cultures are negative. Surveillance cultures on all neonates in nursery
Forfar and Arneil's Textbook of Pediatrics [49]	'No restriction of activities if stool is normal'
Evidence-based Pediatric Infectious Diseases (Isaacs) [50]	–
Principles and Practice of Pediatric Infectious Diseases (Long) [51]	Hospitalised patient: standard and contact precautions
Mandell, Douglas and Bennett's Principles and Practice of Infectious Diseases [4]	Hospitalised patient: standard and contact precautions
	Health care worker: exclusion until asymptomatic and passing formed stool
Nelson Textbook of Pediatrics [52]	–
Oski's Principles and Practice of Pediatrics [53]	–
Red Book: 2009 Report of the Committee on Infectious Diseases [12]	Hospitalised patient: Standard and contact precautions for diapered and incontinent children for duration of illness
	Child care: exclusion until diarrhoea resolves. Contacts do not require stool culture. Exclude symptomatic contacts until diarrhoea resolves
Infectious Diseases of the Fetus and New-born (Remington & Klein) [21]	Hospitalised neonate: standard and contact precautions. 'When two or more cases are recognized, environmental cultures, cultures of all infants, cohorting, early discharge of infected infants, and thorough cleaning of all possible fomites in the nursery and delivery rooms are recommended. If cases continue to occur, the nursery should be closed to further admissions'
Rudolph's Pediatrics [54]	–
The Sanford Guide to Antimicrobial Therapy [45]	–
Infection control sources	
CDC: 2007 Guideline for Isolation Precautions [95]	Hospitalised patient: standard and contact precautions for diapered or incontinent persons for duration of illness
NHMRC: Australian Guidelines for Prevention and Control of Infection in Healthcare [96]	Hospitalised patient: contact precautions for faecally incontinent patients for duration of illness
	Health care worker: exclusion until 24 h after symptoms have resolved
Other sources	
IDSA Guideline 2001 [55]	–
NICE guideline: Diarrhoea and Vomiting caused by Gastroenteritis [56]	Childcare/school: exclusion until 48 h after symptoms have resolved
UpToDate [57]	Healthcare workers: exclusion until diarrhoea resolves
	Food handlers: as above

recently, outbreaks associated with formula feed have been reported [76].

Treatment of asymptomatic maternal NTS carriage is unlikely to be of benefit, but should be considered for severe infection. There are no guidelines for empiric treatment of neonates with known maternal excretion. Due to the increased risk of severe infection in this group, consideration should be given to screening and treatment, as outlined previously, if NTS is detected in the stool [77].

2.8 Antibiotic Resistance

Antibiotic-resistant NTS are associated with increased treatment failure and risk of invasive disease [78]. Worldwide surveillance data has demonstrated an overall increase in antibiotic resistance among NTS, although significant geographical and serotype variability exist [79, 80]. The widespread use of antibiotics in food animals has been implicated in the increasing prevalence of antibiotic resistant NTS [81].

The European Centre for Disease Control (formally Enter-net) and the National Antimicrobial Resistance Monitoring System (NARMS) provide comprehensive surveillance data on rates of NTS drug resistance in Europe and the United States [82, 83]. Data from these studies, as well as reports from middle to low income countries, indicate high rates of ampicillin, amoxicillin and trimethoprim-sulfamethoxazole resistance, particularly among the globally prevalent serotypes *Salmonella* Enterididis and *Salmonella* Typhimurium [82–84]. Of particular concern is the emergence of extended spectrum beta-lactamase (ESBL) genes in NTS [80], as well as reports of carbapenemase-containing NTS isolates [85, 86], both of which confer high level antimicrobial resistance.

Fluoroquinolones and third generation cephalosporins are frequently used for the treatment of NTS that are resistant to conventional antibiotics, although reports of increasing resistance to these second line agents are emerging [80]. Isolates resistant to nalidixic acid are frequently resistant to fluoroquinolones, and this is a recommended screening test for ciprofloxacin resistance [3]. However, although a study found the nalidixic acid disk diffusion method was 100 % sensitive for the detection of reduced ciprofloxacin susceptibility (defined as MIC > 0.125 μg/ml) [87], there have been subsequent reports of isolates that are susceptible to nalidixic acid but exhibit reduced susceptibility to ciprofloxacin [88].

2.9 Infection Control

Outbreaks of NTS have been reported in neonatal units, paediatric wards and child care facilities [11, 89]. However, despite the frequency of asymptomatic NTS excretion following acute infection, the risk of transmission from asymptomatic health care workers to patients appears to be small when strict adherence to hand hygiene is observed [90]. Similarly, transmission from asymptomatic food handlers is rare, with one survey identifying only 2 % of food handlers as the source of 566 NTS outbreaks [91].

Methods to control the spread of *Salmonella* include appropriate food preparation, water sanitation and strict hand hygiene. Most resources recommend exclusion of children, health care workers and food handlers from childcare/school or work until 24–48 h after resolution of symptoms (Table 2.5). For symptomatic hospitalised patients, standard and contact precautions are recommended. There are also some non-randomised data that suggest the prophylactic use of antibiotics (trimethoprim-sulfamethoxazole or ciprofloxacin) in addition to strict barrier nursing, may control nosocomial *Salmonella* epidemics [92–94]. Confirmation of clearance of NTS is generally not recommended.

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