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Research Article

Effective Prevention Methodology for the Typhoid Fever Disease

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Abstract

Typhoid fever, caused by Salmonella enterica serovar Typhi, remains a major public health challenge in many low- and middle-income countries due to poor sanitation, unsafe water, and limited access to healthcare. Effective prevention strategies are essential to reduce the incidence and transmission of the disease. Vaccination, particularly with typhoid conjugate vaccines (TCVs), offers a safe and long-lasting protective measure and is recommended for routine immunization in endemic regions. In addition to immunization, improvements in water quality, sanitation, and hygiene (WASH) play a critical role in interrupting fecal-oral transmission. Public health education promoting handwashing, safe food practices, and community awareness enhances personal and environmental hygiene. Surveillance systems and outbreak response mechanisms, including rapid diagnosis and targeted vaccination, are vital for controlling the spread. Furthermore, identification and treatment of chronic carriers are important for long-term disease control. A comprehensive, multisectoral approach integrating vaccination, WASH infrastructure, and health education is key to the sustainable prevention of typhoid fever.

Keywords: *Typhoid Fever, Enteric Fever, Vaccination, Paratyphoid, Conjugate Typhoid Vaccines, Treatment of Enteric (Typhoid) Fever, Infection, Antibiotic.*

Introduction:

Prevention

1) Handwashing:

The human-to-human spread by chronic carriers is also important, and attempts should be made to target food handlers and high-risk groups for S. Typhi carriage screening. Once identified, chronic carriers must be counseled as to the risk for disease transmission and the importance of handwashing.

2) Breast Feeding:

In the developing world, breast-feeding is key in prevention because human milk contains secretory IgA and other factors that protect infants from Salmonella spp. Case-control studies conducted in the United States and Australia also found breast-feeding to have a strong protective effect against sporadic Salmonella infections. Pediatric health care providers and community education programs should encourage mothers to breast-feed.

Vaccination:

Types:

- Whole cell inactivated vaccines
- Virulence capsular polysaccharide vaccines
- Live attenuated vaccines; and more recently
- Virulence conjugate vaccines (TCVs). The World Health Organization (WHO) has recommended that countries consider the use of typhoid vaccines for high-risk groups and populations, and for outbreak control.

Figure 1: Typhoid Vaccine

Whole Cell-Inactivated Typhoid/Paratyphoid:

Heat-inactivated phenol-preserved whole-cell typhoid vaccines have been available since the 1890s. The vaccine was moderately efficacious (51–88%) in children and young adults in preventing typhoid fever, and the protection persisted for up to 7 years. Figure 1 and Figure 2 show Typhoid Vaccine. Table 1 shows Antimicrobial Treatment.

Method, Material, Findings and Discussion:

New Generation Typhoid Vaccines: -

Vi Polysaccharide Capsular Conjugate Vaccines:

This vaccine contains highly purified antigenic fraction of Vi-PS antigen of S. typhi, which is a virulence factor of the bacteria. Each dose contains 25 µg of purified polysaccharide in 0.5 mL of phenolic isotonic buffer for intramuscular or subcutaneous use. A single dose of Vi polysaccharide vaccine prevents around two third of typhoid cases in the first year after vaccination (year 1: 69%, 95% CI 63–74%; 3 trials, 99,979 participants; high-certainty evidence.

Administering a booster dose of Vi-PS, one or two months later is not helpful, since unconjugated Vi-PS is a T-independent antigen that does not confer immunological memory.

The Vi polysaccharide vaccine is recommended for use as a single dose in children aged 2 years and above and can safely be given with all other childhood vaccines.

Figure 2: Typhoid Vaccine

Efficacy:

The biological marker is anti-Vi antibodies and 1 µg/mL is proposed as the serologic correlate of protection. The vaccine does not interfere with the interpretation of the Widal test. Efficacy drops over time and the cumulative efficacy at 3 years against culture confirmed typhoid fever is reported as 55%.

Safety:

The adverse effects are mild and include pain and swelling at injection site. The vaccine is contraindicated only in those with previous history of hypersensitivity to the vaccine and can be safely given in the immunocompromised including human immunodeficiency virus (HIV) infected.

Dosage:

The Vi polysaccharide vaccine is recommended for use as a single dose in children aged 2 years and above and can safely be given with all other childhood vaccines. Revaccination is recommended every 3 years

Vi Capsular Polysaccharide Conjugate Vaccines

Vi-PS Conjugate Vaccine Conjugated with Pseudomonas aeruginosa Exotoxin an Unconjugated, polysaccharide typhoid vaccines have the disadvantage of no effectiveness below the age of 2 years, limited efficacy (of around 60%), T-cell independent response which lacks immune memory and is not boostable, and finally no protection against paratyphoid fever. Oral typhoid vaccines have the limitations of administration, age stability, and availability issues. Conjugation of the Vi antigen with a protein carrier is hence desirable as it would induce a T-cell dependent immune response. The scientists at the US National Institute of Child Health and Disease (NICHD) have developed an improved Vi-PS conjugate typhoid vaccine by using exotoxin A of Pseudomonas aeruginosa as a carrier protein. This vaccine candidate underwent many human clinical trials in Vietnam. The safety and immunogenicity were evaluated in adults, 5–14 years old children, and 2–4 years old children.

Vi-PS Conjugate Typhoid Vaccines in India:

Different Vi-PS conjugate vaccines have been licensed in India in last 8 years. Conjugate vaccines have solved the issue of able to administer below 2 years, incorporate in programmatic schedules of nations with high endemicity and high incidence of typhoid fever below 4 years of age. India fits in to this situation along with Southeast Asia and parts of Africa.

Treatment of Enteric (Typhoid) Fever

Antimicrobial Treatment:

Indication	Agent	Dosage (Route)	Duration, Days
Preemptive Treatment[a]			
	Ciprofloxacin[b]	500 mg bid (PO)	2–3
Severe Gastroenteritis[c]			
	Ciprofloxacin	500 mg bid (PO) or 400 mg q12h (IV)	3–7
	Trimethoprim-sulfamethoxazole	160/800 mg bid (PO)	
	Amoxicillin	1 g tid (PO)	
	Ceftriaxone	1–2 g/d (IV)	
Bacteremia			
	Ceftriaxone[d]	2 g/d (IV)	7–14
	Ciprofloxacin	400 mg q12h (IV), then 500 mg bid (PO)	
Endocarditis or Arteritis			
	Ceftriaxone	2 g/d (IV)	42
	Ciprofloxacin	400 mg q8h (IV), then 750 mg bid (PO)	
	Ampicillin	2 g q4h (IV)	
Meningitis			
	Ceftriaxone	2 g q12 h (IV)	14–21
	Ampicillin	2 g q4h (IV)	
Other Localized Infection			
	Ceftriaxone	2 g/d (IV)	14–28
	Ciprofloxacin	500 mg bid (PO) or 400 mg q12h (IV)	
	Ampicillin	2 g q6h (IV)	

Table: 1 Antimicrobial Treatment

Supportive Treatment:

- Best rest, soft diet, fluid and electrolyte therapy.
- Symptomatic treatment for fever, vomiting.
- Steroids iv for 5 to 7 days may be used with severe toxemia, shock or mental obtundation, though prolonged steroid therapy increases the risk of intestinal perforation.

Gastroenteritis

As with all forms of gastroenteritis, fluid and electrolyte replacement and maintenance are the first objective of management. For most patients, oral rehydration is all that is necessary to treat Salmonella gastroenteritis.

Generally, Salmonella gastroenteritis should not be treated with antibiotics because these agents do not shorten the course of illness but prolong excretion of Salmonella. Salmonella serotypes typically have been grouped together for these treatment studies, however, as though they were all the same organism.

Extra-Intestinal Infection:

Any child who appears to be sufficiently toxic that bacteremia is suspected also should be started on antibiotic treatment until blood cultures exclude the diagnosis. For children with bacteremia NTS and focal extraintestinal complications, a third-generation cephalosporin ceftriaxone, cefotaxime or fluoroquinolone is an appropriate choice.

If the patient seems to have a life-threatening infection, ampicillin and chloramphenicol should be used only if evidence exists that the pathogen is not resistant to ampicillin or chloramphenicol and that no meningitis or related involvement is suspected.

Children at high risk for having recurrence of bacteremia (children with congenital or acquired immunodeficiencies, such as AIDS) may require a third-generation cephalosporin or a fluoroquinolone to achieve cure. Combinations of fluoroquinolones, cephalosporins, and azithromycin are used in patients with severe disease who fail to respond promptly, or in the face of potential drug-resistant strains, or potentially to reduce the emergence of resistant strains during the course of treatment

Meningitis should be treated with a third-generation cephalosporin because these agents have good penetration into the CSF; ampicillin and chloramphenicol use are associated with higher relapse rates and lower cure rates. Meningitis must be treated for at least 4 to 6 weeks for children with apparent good response; for complicated patients (ventriculitis, hydrocephalus, extensive damage) prolonged therapy of more than 12 weeks could be necessary; approximately three-fourths of patients who have relapses have been treated for 3 weeks or less.86 Salmonella may persist for more than 3 weeks inside CSF mononuclear leukocytes despite negative CSF cultures.

Treatment of Relapse:

Relapse are common with chloramphenicol therapy or partial treatment with other antibiotics.

Some authors suggest combined antimicrobial therapy with cefotaxime or ceftriaxone plus ciprofloxacin for meningitis. Dexamethasone before or at the time of initiation of antimicrobials, aimed at reducing the severity of sequelae of bacterial meningitis in children, is recommended by extension to Salmonella meningitis by some authors but available data are very limited and lead to no definitive conclusions. Table 2 and Table 3 show Antibiotics in Typhoid Fever.

TABLE 111.6 **Recommended Antibiotic Treatment of Typhoid Fever**

Susceptibility	Antibiotic	Days
Fully susceptible	Chloramphenicol *or*	14–21
	Amoxicillin *or*	14
	Trimethoprim-sulfamethoxazole *or*	14
	Third-generation cephalosporin (e.g., cefixime or ceftriaxone) *or*	7–10[a]
	Fluoroquinolone (e.g., ofloxacin or ciprofloxacin)	7–10[a]
Multidrug-resistant	Azithromycin	5–7
	Third-generation cephalosporin (e.g., cefixime or ceftriaxone) *or*	7–10[a]
	Fluoroquinolone (e.g., ofloxacin or ciprofloxacin)	7–10[a]
Quinolone-resistant	Azithromycin *or*	5–7[a]
	Third-generation cephalosporin (e.g., cefixime) *or*	7–10[a]
	Parenteral third-generation cephalosporin (e.g., ceftriaxone) *or*	7–10[a]

Table 2: Antibiotics in Typhoid Fever

Moderate to severe sequelae could affect more than half of infants after complete antimicrobial therapy for Salmonella meningitis. Carbapenems such as imipenem and meropenem have been used with good results in a few cases of Salmonella meningitis.

For other extraintestinal infections in children, the duration of antibiotic treatment usually is 10 to 14 days for bacteremia and 4 to 6 weeks for acute osteomyelitis. Collections of pus should

be drained, and, for intracranial collections, the total duration of antimicrobial therapy should be extended to 4 to 6 weeks after drainage if this is feasible.[2]

If combined resistance to all first- and second line drugs develops, the Carbapenems (e.g., Imipenem, Meropenem, and Ertapenem), and Tigecycline could be potential alternatives.

Treatment of Non Typhoidal Salmonellosis

Antibiotics should not be used routinely to treat uncomplicated NTS gastroenteritis. The symptoms are usually self-limited, and the duration of fever and diarrhoea is not significantly decreased by antibiotic therapy. In addition, antibiotic treatment has been associated with increased rates of relapse, prolonged gastrointestinal carriage, and adverse drug reactions. Dehydration secondary to diarrhea should be treated with fluid and electrolyte replacement.

Preemptive antibiotic treatment should be considered for patients at increased risk for invasive NTS infection, including neonates (probably up to 3 months of age. Treatment should consist of an oral or IV antibiotic administered for 48–72 h or until the patient becomes afebrile. Immunocompromised persons may require up to 7–14 days of therapy. The <1% of persons who develop chronic carriage of NTS should receive a prolonged antibiotic course, as described above for chronic carriage of S. Typhi.

Because of the increasing prevalence of antibiotic resistance, empirical therapy for life-threatening NTS bacteremia or focal NTS infection should include a third-generation cephalosporin or a fluoroquinolone.

SUSCEPTIBILITY	OPTIMAL THERAPY			ALTERNATIVE EFFECTIVE DRUGS		
	Antibiotic	Daily Dose (mg/kg/day)	Days	Antibiotic	Daily Dose (mg/kg/day)	Days
UNCOMPLICATED TYPHOID FEVER						
Fully sensitive	Chloramphenicol	50-75	14-21	Fluoroquinolone, e.g., ofloxacin or ciprofloxacin	15	5-7*
	Amoxicillin	75-100	14			
Multidrug resistant	Fluoroquinolone	15	5-7	Azithromycin	8-10	7
	or					
	Cefixime	15-20	7-14	Cefixime	15-20	7-14
Quinolone resistant †	Azithromycin	8-10	7	Cefixime	20	7-14
	or					
	Ceftriaxone	75	10-14			
SEVERE TYPHOID FEVER						
Fully sensitive	Fluoroquinolone (e.g., ofloxacin)	15	10-14	Chloramphenicol	100	14-21
				Amoxicillin	100	
Multidrug resistant	Fluoroquinolone	15	10-14	Ceftriaxone	60	10-14
				or		
				Cefotaxime ‡	80	10-14
Quinolone resistant	Ceftriaxone	60	10-14	Azithromycin	10-20	7
	Cefotaxime ‡	80	10-14	Fluoroquinolone	20	7-14

Table 3: Antibiotic in Typhoid Fever

If the bacteremia is low-grade (<50% of blood cultures positive), the patient should be treated for 7–14 days. Patients with HIV/AIDS and NTS bacteremia should receive 1–2 weeks of IV antibiotic therapy followed by 4 weeks of oral therapy with a fluoroquinolone. Patients whose infections relapse to this regimen should receive long-term suppressive therapy with a fluoroquinolone or TMP-SMX, as indicated by bacterial sensitivities.

If the patient has endocarditis or arteritis, treatment for 6 weeks with an IV β-lactam antibiotic (such as ceftriaxone or ampicillin) is indicated. IV ciprofloxacin followed by prolonged oral therapy is an option. Early surgical resection of infected aneurysms or other infected endovascular sites is recommended.

Patients with infected prosthetic valves that cannot be resected have been maintained successfully on chronic suppressive oral therapy.

For extraintestinal nonvascular infections, a 2- to 4-week course of antibiotic therapy (depending on the infection site) is usually recommended. In chronic osteomyelitis, abscess, or urinary or hepatobiliary infection associated with anatomic abnormalities, surgical resection or drainage may be required in addition to prolonged antibiotic therapy for eradication of infection.

Consclusion

Antibiotic Resistant Pressure

Since the mid-1960s, Salmonella spp. has become increasingly resistant to ampicillin, chloramphenicol, and trimethoprim sulfamethoxazole (TMP-SMX). Multi-resistant strains have included S. ser. Typhimurium, which is the most common serotype in Europe and the United States. Table 4 shows Antibiotic Resistance.

Multidrug-resistant S. Typhimurium phage type DT104 (DT104) rapidly emerged globally in the 1990s and became the most prevalent phage type isolated from humans and animals in many countries. DT104 is typically resistant to ampicillin, chloramphenicol, streptomycin, TMPSMX, and tetracycline, along with its capacity to acquire additional resistance to other clinically important antimicrobials, including fluoroquinolones.

The development of NTS isolates resistant to extended-spectrum cephalosporins, such as ceftriaxone, represents a substantial global public health concern. Antibiotic resistance usually is transferable between organisms through plasmids that carry genes encoding resistance factors.

Some serotype-specific virulence plasmids form hybrid plasmids through recombination with resistance plasmids or acquire gene cassettes consisting of multiple resistance genes.

Plasmid analysis and antibiotic susceptibility patterns have linked Salmonella outbreaks to specific farms and slaughterhouses

Increasing antibiotic resistance in NTS species is a global problem and has been linked to the widespread use of antimicrobial agents in food animals and especially in animal feed. In the early 1990s, S. Typhimurium definitive phage type 104 (DT104), characterized by resistance to at least five antibiotics (ampicillin, chloramphenicol, streptomycin, sulfonamides, and tetracyclines; R-type ACSSuT), emerged worldwide.

Because of increased resistance to conventional antibiotics such as ampicillin and TMP-SMX, extended spectrum cephalosporins and fluoroquinolones have emerged as the agents of choice for the treatment of MDR NTS infections. Most of ceftriaxone resistant isolates were from children <18 years of age, in whom ceftriaxone is the antibiotic of choice for treatment of invasive NTS infection.

These strains contained plasmid-encoded AmpC β-lactamases that were probably acquired by horizontal genetic transfer from Escherichia coli strains in food-producing animals an event linked to the widespread use of the veterinary cephalosporin. Most recently, carbapenem resistant NTS strains have been reported in Europe, North Africa, and southern Asia.

Antibiotic	Patients (No.)	Responded (N%)	Resistant (N%)	Effervescences period*
Ampicillin	32	7 (21.8%)	25 (78.12%)	7.5
Amoxycillin	40	9 (22.5%)	31 (77.5%)	8.0
Cotrimoxazole	19	3 (15.78%)	16 (84.2%)	7.2
Ciprofloxacin	42	34 (80.5%)	8 (19.5%)	5.5
Ofloxacin	14	12 (85.71%)	2 (14.28%)	5.0
Amikacin	9	8 (88.8%)	1 (11.9%)	5.0
Cefixime	6	6 (100%)	-	6.5
Cefotaxime	5	4 (80%)	1 (20.0%)	6.5
Ceftriaxone	38	38 (100%)	-	5.0
Chloramphenicol	2	-	2 (100%)	-

*Mean in days

Table 4: Antibiotic Resistance

The worldwide frequency of antibiotic-resistant S. ser. Typhi has been increasing since the 1960s. Drug resistance in Salmonella Typhi (resistance or partial resistance to ciprofloxacin) has increased significantly from about 20% in 1999 to more than 70% in 2011.

Travel associated infections are more likely to be antibiotic resistant. The CDC has reported some level of resistance (resistance or partial resistance) to ciprofloxacin in 67% of Salmonella Typhi tested (3-year average, 2009–11).

Extensive protracted outbreaks have been reported throughout Asia, the Middle East, and Central and South America. These outbreaks may have been related to widespread and inappropriate use of antimicrobial agents in these areas.

After sporadic outbreaks of chloramphenicol-resistant typhoid between 1970 and 1985, many strains of S. ser. Typhi developed plasmid mediated, multidrug resistance to the three primary antimicrobials used (i.e., ampicillin, chloramphenicol, and TMP-SMX).

This pattern of simultaneous resistance of S. ser. Typhi to formerly recommended first-line antimicrobials (i.e., ampicillin, chloramphenicol, and TMP-SMX) is defined as multidrug-resistant typhoid fever.

With the advent of quinolone resistance, third generation cephalosporins were used for treatment, followed initially by occasional reports of resistance.

Today Salmonella serovar Typhi isolates displaying resistance to extended-spectrum cephalosporins are described worldwide. For example, extended-spectrum β-lactamase (ESBL) enzymes of the SHV-12 and CTX-M types and an AmpC β-lactamase of the ACC-1 type have been reported among isolates from Germany, the Philippines, Bangladesh, and India.

Differential Diagnosis

As shown in Table 5, In endemic areas, typhoid fever may mimic many common febrile illnesses without localizing signs. In children with multisystem features and no localizing signs, the early stages of enteric fever may be confused with alternative conditions, such as acute gastroenteritis, bronchitis, and bronchopneumonia.

BOX 111.3 Differential Diagnosis of Enteric Fever

Epstein-Barr infection	Tularemia
Dengue	Ehrlichiosis
Tuberculosis	Plague
Brucellosis	Typhus
Bartonella henselae	Malaria
Leptospirosis	Disseminated histoplasmosis

Table 5: Differential Diagnosis of Enteric Fever

Subsequently, the differential diagnosis includes malaria; sepsis with other bacterial pathogens; infections caused by intracellular microorganisms, such as tuberculosis, brucellosis, tularemia, leptospirosis, and rickettsial diseases; and viral infections suchas Dengue fever, acute hepatitis, and infectious mononucleosis.

Infection by Salmonella in general, and typhoid or paratyphoid fever in particular, should be thoroughly considered in the differential diagnosis and workup for fever in a returned traveler.

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