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TYPHOID FEVER

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Typhoid fever is a systemic infectious disease caused by *Salmonella typhi*, the typhoid bacillus. Most cases in the U.S. today are acquired from travel outside of the United States. *Salmonella typhi* is found only in humans and is spread by food or water being contaminated by the feces of a case/carrier.

Epidemiology

S. typhi and *S. paratyphi* colonize only humans. Therefore, disease can be acquired only through close contact with a person who has had typhoid fever or is a chronic carrier. Most often, acquisition of organisms occurs by ingestion of food or water contaminated with human excreta. Usually, waterborne transmission involves the ingestion of fewer microorganisms and, as a result, has a longer incubation period and lower attack rate than foodborne transmission does. Although direct person-to-person transmission is rare, anal-oral transmission of *S. typhi* has been demonstrated. Laboratory accidents have also resulted in typhoid fever transmission to laboratory workers. Occasionally, health care workers can acquire the disease from infected patients as a result of poor hand-washing.

The disease is endemic in many developing countries, particularly the Indian subcontinent, South and Central America and Africa with annual incidence rates estimated to be as high as 900 per 100,000 population in Asia. Therefore the infection is sometimes seen in travelers returning from endemic areas.

Sewage workers are not at higher risk of acquiring typhoid. This concern is only theoretical.

The long-term carrier state is defined as the persistence of salmonellae in stool or urine for periods longer than 1 year. Long-term carriage develops in 1% to 4% of patients with *S. typhi* infection. The frequency of long-term carriage is higher in women and in persons with biliary abnormalities. Long-term carriage of *S. typhi* and *S. paratyphi* A has been associated with an increased incidence of carcinoma of the gallbladder and other gastrointestinal malignancies.

The incubation period of *S. typhi* ranges from 5 to 21 days depending on the inoculum ingested and the health and immune status of the person.

Clinical Description

Human typhoid and paratyphoid fevers are severe systemic illnesses characterized by fever and abdominal symptoms. The syndrome of enteric fever is most often caused by *S. typhi*. A similar but less severe syndrome is caused by *S. paratyphi* A, *S. paratyphi* B (*Salmonella schottmuelleri*), and *S. typhi* C (*Salmonella hirschfeldii*). When enteric fever is caused by *S. typhi*, it is often referred to as typhoid fever; when caused by *S. paratyphi*, it is referred to as paratyphoid fever.

The symptoms are nonspecific and may be insidious in onset. The diagnosis of enteric fever should be strongly considered in the evaluation of travelers who return from tropical and subtropical areas with fever. The differential diagnosis of gradual onset of fever and abdominal pain with hepatosplenomegaly also includes malaria, amebic liver abscess, visceral leishmaniasis and viral syndromes such as dengue fever.

After ingestion of the organism, enterocolitis may develop along with diarrhea lasting several days; these symptoms usually resolve before the onset of fever. Diarrhea is more common in certain geographic areas, in patients with AIDS and in children younger than 1 year of age. Constipation is present in 10% to 38% of patients.

Although fever is a classic sign of typhoid fever, it does not always develop and the pattern of fever is not clinically useful. In addition, only 20% to 40% of patients will initially have abdominal pain; the frequency of other abdominal symptoms varies widely in different clinical series. Nonspecific symptoms such as chills, diaphoresis, headache, anorexia, cough, weakness, sore throat, dizziness and muscle pains are frequently present before the onset of fever in typhoid.

Neuropsychiatric manifestations, including psychosis and confusion, occur in 5% to 10% of patients with typhoid fever. This so-called typhoid state has been described as "muttering delirium" and "coma vigil." Picking at the bedclothes and at imaginary objects and muscle twitching are characteristic. The pathophysiology of the neuropsychiatric manifestations of typhoid fever is unknown but may be related to cytokine release from *S. typhi*-infected macrophages. Seizures and coma are reported in less than 1% of persons and may represent febrile seizures of childhood. The cerebrospinal fluid is usually normal in patients with typhoid fever. Abnormal cerebrospinal fluid studies or recurrent seizures suggest another diagnosis.

On physical examination, patients with typhoid fever usually appear acutely ill; those who have previously been exposed to *S. typhi* or who seek early medical attention can present with a milder illness. Relative bradycardia is neither a sensitive nor a specific sign of typhoid fever and occurs in less than 50% of patients. Approximately 30% of patients will have rose spots--a faint salmon-colored maculopapular rash on the trunk. Organisms can be cultured from punch biopsies of these lesions; the pathology is characterized by a perivascular mononuclear cell infiltrate. The rash can be very subtle, especially in highly pigmented individuals and frequently fades to small macules that appear to be resolving skin hemorrhages. Cervical lymphadenopathy develops in some patients. Examination of the abdomen usually reveals pain on deep palpation with peristalsis frequently increased. Approximately 50% of patients have hepatosplenomegaly. Pain may localize to the right upper quadrant in the approximately 3% of adults with typhoid fever in whom cholecystitis develops.

Most symptoms resolve by the fourth week of infection without antimicrobial therapy in the approximately 90% of patients who survive. However, weakness, weight loss and debilitation may persist for months, and 10% of patients will have a relapse.

Other infectious complications include endocarditis and localized infections such as pericarditis, orchitis and splenic or liver abscesses. Hematologic abnormalities associated with typhoid fever include leukopenia and anemia. Leukocytosis can also be seen, most often in children and in the first ten days of illness. Thrombocytopenia and clotting abnormalities that usually resolve spontaneously, develop in some patients. Moderately elevated liver function parameters (i.e., aspartate and alanine aminotransferase, 300 to 500 units/dl) and muscle enzymes are common.

In the preantibiotic era, approximately 15% of patients with typhoid fever died. Nowadays in the United States, less than 1% of persons with typhoid fever, die.

Laboratory Tests

- Blood cultures (usually done in the hospital setting)
Not usually available at the State Laboratory

- Stool specimens are preferred to rectal swabs. Stool specimens are to be obtained in a specimen bottle containing Cary-Blair culture medium. (These can be obtained from the regional laboratories.) Specimens in Cary-Blair should be refrigerated and transported to the lab under refrigerated conditions as soon as possible. (If necessary to hold 48 hours or longer, freeze sample at -7°C and transport to lab in a frozen-state.)

Febrile agglutination testing for the H antigen or O antigen alone is not specific enough to confirm a case of typhoid.

Serologic tests for the Vi antigen can be useful in distinguishing long-term carriage from acute infection inasmuch as long-term carriers will often have a high antibody titer to this antigen.

Treatment

Appropriate drugs are ampicillin, amoxicillin, cefotaxime, ceftriaxone, chloramphenicol, TMP-SMX, or a fluoroquinolone. For susceptible *S typhi*, administration of a 14-day course of ampicillin, chloramphenicol, or TMP-SMX is adequate. For severely ill patients, parenteral therapy is indicated. For typhoid fever due to multiple antimicrobial-resistant (ampicillin, chloramphenicol, TMP-SMX) strains, such as are acquired routinely in India, Pakistan and Egypt, therapeutic options include a 7 to 10-day course of ceftriaxone or a 5 to 7-day course of ofloxacin or ciprofloxacin. Some patients require more prolonged courses of treatment.

Relapse is common after completion of therapy; re-treatment is indicated. Strain susceptibility should be interpreted with caution; clinical failure has been reported in patients with typhoid fever treated with cephalexin, aminoglycosides, furazolidone and second-generation cephalosporins despite in vitro susceptibility. For Salmonella meningitis, ceftriaxone or cefotaxime is recommended, often for four weeks or longer.

Chronic (1 year or more) *S. typhi* carriage may be eradicated in some children by high-dose parenteral ampicillin or high-dose oral amoxicillin combined with probenecid, or cholecystectomy. Ciprofloxacin is the drug of choice for chronic adult carriers of *S. typhi*.

Since 1989, multidrug-resistant strains of *S. typhi* with H1-type plasmid-encoded resistance to chloramphenicol, ampicillin and trimethoprim have emerged in the Indian subcontinent, Southeast Asia and Africa and have been responsible for numerous outbreaks with increased morbidity and mortality. Although these chloramphenicol-resistant and multidrug-resistant strains belong to different Vi phage types, they typically contain a 120-MDa plasmid of the H1 incompatibility type that often also encodes resistance to streptomycin, sulfonamides and tetracyclines. More recently, chromosomal and plasmid-encoded resistance to ciprofloxacin has appeared in *S. typhi* isolates from the Indian subcontinent, an area where this antimicrobial has been used to control outbreaks of multidrug-resistant *S. typhi* since 1990.

Surveillance

Typhoid fever is a condition reportable within one business day of diagnosis.

Case Definition

Clinical description: An illness caused by *Salmonella typhi* that is often characterized by insidious onset of sustained fever, headache, malaise, anorexia, relative bradycardia, constipation or diarrhea and non-productive cough. However, many mild and atypical infections occur. Carriage of *S. typhi* may be prolonged.

Laboratory criteria for diagnosis: Isolation of *S. typhi* from blood, stool, or other clinical specimen. Isolation of the organism is required for confirmation. Serologic evidence alone is not sufficient for diagnosis. Asymptomatic carriage should not be reported as typhoid fever.

Case classification

Probable: a clinically compatible case that is epidemiologically linked to a confirmed case in an outbreak

Confirmed: a clinically compatible case that is laboratory confirmed

Investigation

The purpose of investigation is to identify cases and sources of infection, to exclude infected individuals from handling food and to institute disease control measures.

- Upon receipt of a report of a typhoid case, contact the physician and/or hospital to confirm the diagnosis. Request physician and/or hospital forward the culture (blood, stool, etc.) to the state laboratory for confirmation.
- If a culture (blood, stool, etc.) has not been done and the diagnosis is based on symptoms and a fourfold rise in an O or an H titer, encourage the physician to obtain stool cultures and, if the patient is not yet on antibiotics, blood cultures as well.
- Determine the source of the infection. Ask if the person with typhoid fever traveled internationally three days to three months prior to the onset of his/her illness.
- If the person with typhoid fever reports no international travel, attempt to connect the case with a known carrier. If a reasonable connection is made, no additional culturing of contacts, other than immediate household, is necessary.
- If there is no connection with a known carrier, obtain three stool cultures, each at least 24 hours apart from all adult family members and close contacts, especially close elderly contacts; one stool culture will probably be sufficient for young family members and contacts. If all contacts are negative, it may be necessary to obtain stool cultures in an ever widening circle of contacts. Remember that if positive cultures are only obtained from young contacts, chances are these are also part of the spread from the carrier who was responsible for the original case and further investigation is warranted.
- If a positive culture is obtained from a person likely to be a carrier, it will be necessary to obtain stool cultures for a year to document whether the person is truly a carrier. This should be done by obtaining three stool cultures, each at least 24 hours apart every three months for a year (3, 6, 9, 12 months).

Carrier detection

One month after completion of specific drug therapy, obtain three stool specimens each at least 24 hours apart from the typhoid case. If results are negative, the case is closed and no further action is necessary. If test results are positive, it will be necessary to obtain specimens every three months for a year or until two consecutive series of specimens are negative. Once negative the case is closed and no further action is necessary. If a case is still positive at one year, the case should be considered as a typhoid carrier and added to the carrier list maintained by the Infectious Disease Epidemiology Section.

Household contacts of case/carrier are to be offered the typhoid vaccine, although this may be of questionable value.

Household contacts of cases should not be employed as foodhandlers until at least two (2) negative stool cultures, taken at least 24 hours apart, are obtained.

Immunization

Three typhoid vaccines are currently available for use in the United States:

- an oral live-attenuated vaccine (Vivotif Berna vaccine, manufactured from the Ty21a strain of *Salmonella typhi* (2) by the Swiss Serum and Vaccine Institute);
- a parenteral heat-phenol-inactivated vaccine that has been widely used for many years (Typhoid Vaccine, manufactured by Wyeth-Ayerst);
- a newly licensed capsular polysaccharide vaccine for parenteral use (Typhim Vi, manufactured by Pasteur Mérieux).
- a fourth vaccine, an acetone-inactivated parenteral vaccine, is currently available only to the armed forces.

The Ty21a vaccine does elicit both serum and intestinal antibodies and cell-mediated immune responses. Vaccine organisms can be shed transiently in the stool of vaccine recipients. However, secondary transmission of vaccine organisms has not been documented.

The newly licensed parenteral vaccine (Vi capsular polysaccharide [ViCPS]) is composed of purified Vi (“virulence”) antigen, the capsular polysaccharide elaborated by

Vaccine Usage

Routine typhoid vaccination is not recommended in the United States. However, vaccination is indicated for the following groups:

- Travelers to areas in which there is a recognized risk of exposure to *S. typhi*. Risk is greatest for travelers to developing countries (e.g., countries in Latin America, Asia and Africa) who have prolonged exposure to potentially contaminated food and drink. Multidrug-resistant strains of *S. typhi* have become common in some areas of the world (e.g., the Indian subcontinent and the Arabian peninsula), and cases of typhoid fever that are treated with ineffective drugs can be fatal. Travelers should be cautioned that typhoid vaccination is not a substitute for careful selection of food and drink. Typhoid vaccines are not 100% effective, and the vaccine’s protection can be overwhelmed by large inocula of *S. typhi*.
- Persons with intimate exposure (e.g., household contact) to a documented *S. typhi* carrier.
- Microbiology laboratorians who work frequently with *S. typhi*.
- Routine vaccination of sewage sanitation workers is not warranted in the United States and is indicated only for persons living in typhoid-endemic areas. Also, typhoid vaccine is not indicated for persons attending rural summer camps or living in areas in which natural disasters (e.g., floods) have occurred. No evidence has indicated that typhoid vaccine is useful in controlling common-source outbreaks.

Choice of Vaccine

The parenteral inactivated vaccine causes substantially more adverse reactions but is no more effective than Ty21a or ViCPS. Thus, when not contraindicated, either oral Ty21a or parenteral ViCPS is preferable. Each of the three vaccines approved by the Food and Drug Administration has a different lower age limit for use among children (Table 1). In addition, the time required for primary vaccination differs for each vaccine. Primary vaccination with ViCPS can be accomplished with a single injection, whereas one week is required for Ty21a and four weeks are required to complete a primary series for parenteral inactivated vaccine. Finally, the live-attenuated Ty21a vaccine should not be used for immunocompromised persons or persons taking antibiotics at the time of vaccination

Table 1: Typhoid vaccine dosage

Vaccination	Age	Dosage			
		Dose/mode of administration	Number of doses	Interval between doses	Boosting interval
Oral live-attenuated Ty21a vaccine					
Primary series	≥6 yrs	1 capsule*	4	2 days	—
Booster	≥6 yrs	1 capsule*	4	2 days	every 5 yrs
Vi capsular polysaccharide vaccine					
Primary series	≥2 yrs	0.50 mL†	1	—	—
Booster	≥2 yrs	0.50 mL†	1	—	every 2 yrs
Heat-phenol-inactivated parenteral vaccine					
Primary series	6 mos–10 yrs	0.25 mL§	2	≥4 wks	—
	≥10 yrs	0.50 mL§	2	≥4 wks	—
Booster	6 mos–10 yrs	0.25 mL§	1	—	every 3 yrs
	≥10 yrs	0.50 mL§	1	—	every 3 yrs
	≥6 mos	0.10 mL¶	1	—	every 3 yrs

* Each orally administered capsule contains contains 2–6 x 10⁹ viable *S. typhi* Ty21a and 5–50 x 10⁹ nonviable *S. typhi* Ty21a.

† Intramuscularly.

§ Subcutaneously.

¶ Intradermally.

— Not applicable.

Vaccine Administration

Ty21a: Primary vaccination with live-attenuated Ty21a vaccine consists of one entericcoated capsule taken on alternate days for a total of four capsules. The capsules must be kept refrigerated (not frozen), and all four doses must be taken to achieve maximum efficacy. Each capsule should be taken with cool liquid no warmer than 37° C (98.6°F), approximately one hour before a meal. Although adverse reactions to Ty21a are uncommon among children 1–5 years of age; data are unavailable regarding efficacy for this age group. This vaccine has not been studied among children less than one year of age. The vaccine manufacturer recommends that Ty21a not be administered to children less than six years of age.

ViCPS: Primary vaccination with ViCPS consists of one 0.5-mL (25-mg) dose administered intramuscularly. This vaccine has not been studied among children less than one year of age. The vaccine manufacturer does not recommend the vaccine for children less than two years of age.

Parenteral Inactivated Vaccine: Primary vaccination with parenteral inactivated vaccine consists of two 0.5-mL subcutaneous injections, each containing approximately 5 x 10⁸ killed bacteria, separated by greater than four weeks. The vaccine manufacturer does not recommend the vaccine for use among children less than six months of age. If the two doses of parenteral inactivated vaccine cannot be separated by four weeks because of time constraints, common practice has been to administer three doses of the vaccine at weekly intervals in the volumes listed above. However, vaccines administered according to this schedule may be less effective.

Booster Doses: If continued or repeated exposure to *S. typhi* is expected, booster doses of vaccine are required to maintain immunity after vaccination with parenteral typhoid vaccines. The ViCPS manufacturer recommends a booster dose every two years after the primary dose if continued or renewed exposure is expected. In a study in which efficacy was not examined, revaccination of U.S. adults at either 27 or 34

months after the primary vaccination increased mean antibody titers to the approximate levels achieved with the primary dose. The optimal booster schedule for persons administered Ty21a for primary vaccination has not been determined; however, the longest reported follow-up study of vaccine trial subjects indicated that efficacy continued for five years after vaccination. The manufacturer of Ty21a recommends revaccination with the entire four-dose series every five years if continued or renewed exposure to *S. typhi* is expected. This recommendation may change as more data become available about the period of protection produced by the Ty21a vaccine. If the parenteral inactivated vaccine is used initially, booster doses should be administered every three years if continued or renewed exposure is expected. A single booster dose of parenteral inactivated vaccine is sufficient, even if more than three years have elapsed since the prior vaccination. When the heat-phenol-inactivated vaccine is used for booster vaccination, the intradermal route causes less reaction than the subcutaneous route. The acetone-inactivated vaccine should not be administered intradermally or by jet-injector gun because of the potential for severe local reactions.

No information has been reported concerning the use of one vaccine as a booster after primary vaccination with a different vaccine. However, using either the series of four doses of Ty21a, or one dose of ViCPS for persons previously vaccinated with parenteral vaccine, is a reasonable alternative to administration of a booster dose of parenteral inactivated vaccine.

Adverse Reactions

Ty21a produces fewer adverse reactions than either ViCPS or the parenteral inactivated vaccine. During volunteer studies and field trials with oral live-attenuated Ty21a vaccine, side effects were rare and consisted of abdominal discomfort, nausea, vomiting, fever, headache and rash or urticaria. In placebo-controlled trials, monitored adverse reactions occurred with equal frequency among groups receiving vaccine and placebo. In several trials, ViCPS produced fever (occurring in 0%–1% of vaccinees), headache (1.5%–3% of vaccinees), and erythema or induration greater than 1 cm (7% of vaccinees). In a study conducted in Nepal, the ViCPS vaccine produced fewer local and systemic reactions than did the control (the 23-valent pneumococcal vaccine). In a direct comparison, ViCPS produced reactions less than half as frequently as parenteral inactivated vaccine, probably because ViCPS contains negligible amounts of bacterial lipopolysaccharide.

Parenteral inactivated vaccines produce several systemic and local adverse reactions, including fever (occurring in 6.7%–24% of vaccinees), headache (9%–10% of vaccinees), and severe local pain and/or swelling (3%–35% of vaccinees); 21%–23% of vaccinees missed work or school because of adverse reactions. More severe reactions, including hypotension, chest pain, and shock, have been reported sporadically.

Precautions and Contraindications

The theoretical possibility for decreased immunogenicity when Ty21a, a live bacterial vaccine, is administered concurrently with immunoglobulin, antimalarials, or viral vaccines, has caused concern.

--However, because Ty21a is immunogenic even in persons with preexisting antibody titers, its immunogenicity should not be affected by simultaneous administration of immunoglobulin.

--Mefloquine can inhibit the growth of the live Ty21a strain in vitro; if this antimalarial is administered, vaccination with Ty21a should be delayed for 24 hours. The minimum inhibitory concentration of chloroquine for Ty21a is >256 mg/mL; this antimalarial should not affect the immunogenicity of Ty21a.

--The vaccine manufacturer advises that Ty21a should not be administered to persons receiving sulfonamides or other antimicrobial agents; Ty21a should be administered \geq 24 hours after an antimicrobial dose.

--No data exist on the immunogenicity of Ty21a when administered concurrently or within 30 days of viral vaccines (e.g., oral polio, measles/mumps/rubella, or yellow fever vaccines). In the absence of such data, if typhoid vaccination is warranted, it should not be delayed because of the administration of viral vaccines.

No data have been reported on the use of any of the three typhoid vaccines among pregnant women. Live-attenuated Ty21a should not be used among immunocompromised persons, including those persons known to be infected with human immunodeficiency virus. The two available parenteral vaccines present theoretically safer alternatives for this group. The only contraindication to vaccination with either ViCPS or with parenteral inactivated vaccine is a history of severe local or systemic reactions following a previous dose.

Hospital precaution and isolation: Contact precautions