3.23 TYPHOID

Bacteriology

Typhoid fever is a clinical syndrome caused by a systemic infection with *Salmonella enterica* subspecies *enterica* serovar Typhi (*S*. Typhi). Paratyphoid fever, caused by infection with *S*. *enterica* serovar Paratyphi A or B, is similar to, and often indistinguishable from, typhoid fever. The two infections are collectively known as enteric fever; there is no vaccine against paratyphoid fever.

NB. *S*. Paratyphi B biovar Java does not cause typhoid-like enteric fever but rather causes a typical gastroenteritis; it can be acquired through handling aquarium fish.[1]

Clinical features

Typhoid fever has a usual incubation period of 7 to 14 days (range 3 to 60 days).[2] Although clinical presentations of typhoid fever can be quite variable, a typical case presents with a low-grade fever, dull frontal headache, malaise, myalgia, anorexia and a dry cough.[2] The fever tends to increase as the disease progresses; constipation (more typically diarrhoea in young children), abdominal tenderness, relative bradycardia and splenomegaly are common. Complications occur in 10 to 15% of patients and tend to occur in patients who have been ill for >2 weeks. The more important complications include gastrointestinal bleeding, intestinal perforation and typhoid encephalopathy.[2]

Relapse occurs in 5 to 10% of patients, usually 2 to 3 weeks after the initial fever resolves. Chronic asymptomatic biliary carriage of *S*. Typhi occurs in up to 5% of patients with typhoid fever, even after treatment. Chronic carriage is defined by the continued shedding of the organism for >1 year, and is a public health risk (eg. if a carrier works in the food industry).[2]

Because travellers are likely to seek medical advice relatively early in the illness, severe typhoid fever with complications is rarely seen in this group of patients. Nevertheless, travellers can still become chronic carriers of *S*. Typhi.

Epidemiology

Humans are the sole reservoir of *S*. Typhi. It is shed in the faeces of those acutely ill and those who are chronic asymptomatic carriers of the organism; transmission usually occurs via the ingestion of faecally-contaminated food or water.

The vast majority of typhoid fever cases occur in less-developed countries where poor sanitation, poor food hygiene and untreated drinking water all contribute to endemic disease with moderate to high incidence and considerable mortality.[3] Geographic regions with high incidence (>100 cases per 100 000 population

per year) include the Indian subcontinent, most southeast Asian countries and several south Pacific nations, including Papua New Guinea.

In developed countries, typhoid fever is predominantly a travel-related disease, with a considerably greater risk following travel to the Indian subcontinent than to other regions.[4,5] Those who travel to endemic regions to visit friends and relatives (ie. immigrants who travel to their former homelands) appear to be at considerably greater risk of acquiring typhoid fever than other travellers.[4,5] There are approximately 50 to 80 cases of typhoid fever reported in Australia each year, with most following travel to regions with endemic disease.

Vaccines

- **Vivotif Oral** – CSL Biotherapies/Berna Biotech Ltd (oral live attenuated typhoid vaccine). Each enteric-coated capsule contains not less than 2 x 10^9 viable organisms of attenuated *S.* Typhi strain Ty21a Berna. 3 capsules in a blister pack.
- **Typherix** – GlaxoSmithKline (purified Vi capsular polysaccharide vaccine). Each 0.5 mL pre-filled syringe contains 25 µg Vi polysaccharide of *S.* Typhi; phenol as preservative; phosphate buffer. 10 dose packs are also available.
- **Typhim Vi** – Sanofi Pasteur Pty Ltd (purified Vi capsular polysaccharide vaccine). Each 0.5 mL pre-filled syringe contains 25 µg Vi polysaccharide of *S.* Typhi; phenol as preservative; phosphate buffer.

Combination vaccine that includes both typhoid and hepatitis A (see Chapter 3.5, *Hepatitis A*)

- **Vivaxim** – Sanofi Pasteur Pty Ltd (inactivated hepatitis A virus and typhoid Vi capsular polysaccharide). Supplied in a unique dual-chamber syringe which enables the 2 vaccines to be mixed just before administration. Each 1.0 mL dose of mixed vaccine contains 160 ELISA units of inactivated hepatitis A virus antigens, 25 µg purified typhoid capsular polysaccharide; 0.3 mg aluminium hydroxide; 2.5 µL phenoxyethanol; formaldehyde; traces of neomycin and bovine serum albumin.

The attenuated non-pathogenic *S.* Typhi strain Ty21a was derived by chemical treatment attenuation of a wild-type strain. Attenuated features of Ty21a include the absence of the enzyme, UDP-galactose-4-epimerase, and the Vi capsular polysaccharide antigen (an important virulence determinant of *S.* Typhi). These features partially contribute to the non-pathogenicity and, therefore, the safety of the oral live vaccine.[6]

The oral vaccine Ty21a strain cannot be detected in faeces more than 3 days after administration of the vaccine. It stimulates vigorous secretory intestinal IgA and cell-mediated immune responses.[6] Clinical trials, with different formulations of

the vaccine and with a variety of schedules, have been undertaken in several countries (Egypt, Chile, Indonesia) with endemic typhoid fever. These have documented varying degrees of protection against the disease.[2,6]

The parenteral Vi polysaccharide vaccine is produced by fermentation of the Ty2 strain followed by inactivation with formaldehyde, and then extraction of the polysaccharide from the supernatant using a detergent.[6] The vaccine elicits prompt serum IgG anti-Vi responses in 85 to 95% of adults and children >2 years of age. The vaccine has also been used in clinical trials in endemic regions (Nepal, South Africa, China), indicating moderate protection against typhoid fever.[2,6]

Neither the oral nor the parenteral vaccines have been studied in prospective clinical trials in travellers to endemic regions. Because many travellers do not have any naturally-acquired immunity, the protection conferred through typhoid vaccination may be less than that documented in the clinical trials mentioned above. However, there is circumstantial evidence that the vaccines do provide protection to travellers to endemic regions,[4,5] and that 3-yearly revaccination is necessary to prolong the protection.[7]

Transport, storage and handling

Transport according to *National Vaccine Storage Guidelines: Strive for 5*.[8] Store all typhoid vaccines at +2°C to +8°C. Protect from light. Do not freeze.

Because the vaccinee will be responsible for looking after the course of the oral live attenuated vaccine, details of how it should be transported (from the pharmacy to the home) and stored in the refrigerator (at home) must be carefully explained.

Dosage and administration

Oral live attenuated vaccine

The vaccine is registered for use in individuals ≥6 years of age; it is presented in a pack of 3 capsules. The dose (a whole capsule) is the same for both adults and children.

It may be administered at the same time as either OPV (no longer used in Australia), or yellow fever vaccine.[6] It may also be given concurrently with mefloquine or with atovaquone/proguanil combination (Malarone).

The vaccination schedule consists of 1 capsule of vaccine on days 1, 3, and 5, taken 1 hour before food. The capsule must be swallowed whole with water and must not be chewed since the organisms can be killed by gastric acid. Do not give the vaccine concurrently with antibiotics, or other drugs that are active against *Salmonellae*. If possible, antibiotics and other relevant drugs should be delayed for 3 days after the last dose of the vaccine.

A fourth capsule taken on day 7 has been shown (in a single study[9]) to result in a lower incidence of typhoid fever than 3 doses. However, the use of a fourth dose requires partial use of a second pack and, therefore, may involve considerable extra expense.

Oral live attenuated typhoid vaccine should be separated from the administration of inactivated oral cholera vaccine by an interval of at least 8 hours (see 'Precautions' below).

Parenteral Vi polysaccharide vaccines

Both vaccines (Typherix and Typhim Vi) are registered for use in individuals ≥2 years of age; the dose (0.5 mL) is the same for both adults and children. (The dose of the combined Vi polysaccharide and hepatitis A vaccine is 1 mL.) The vaccines are given by IM injection.

Booster doses

The optimal timing of revaccination against typhoid fever is uncertain and, therefore, international recommendations can vary considerably.[2,5,6]

However, if continued exposure to *S.* Typhi exists (such as occurs with either prolonged travel or residence in an endemic region) it is reasonable to recommend a dose of the parenteral vaccine 3 years after the initial primary parenteral vaccination. If a 3-dose schedule of the oral live attenuated vaccine was used initially, a repeat 3-dose course can be given after 3 years; if a 4-dose schedule of the oral vaccine was used initially, a repeat 4-dose course can be given after 5 years.[6]

Recommendations

Typhoid vaccination is recommended for all travellers ≥2 years of age going to endemic regions, where food hygiene may be suboptimal and drinking water may not be adequately treated. Travellers include the military. Vaccination should be completed at least 2 weeks before travel.

Individuals travelling to endemic regions to visit friends and relatives are probably at considerable risk of acquiring typhoid fever, and vaccination is strongly recommended for them.

NB. Travellers must also be advised about personal hygiene, food safety and about drinking boiled or bottled water only. They should be advised that raw (or undercooked) shellfish, salads, cold meats, untreated water and ice (in drinks) are all potentially 'high-risk', as are short (day) trips away from higher quality accommodation venues.

Laboratory personnel routinely working with *S.* Typhi should also be considered for vaccination.

Contraindications

The only absolute contraindications to typhoid vaccines are:

- anaphylaxis following a previous dose of a typhoid vaccine, or
- anaphylaxis following any component of a particular typhoid vaccine.

Oral live attenuated vaccine

The oral live attenuated vaccine should *not* be administered

- to pregnant women; parenteral Vi polysaccharide vaccine should be used instead;
- to individuals with impaired immunity, including those known to be infected with HIV; parenteral Vi polysaccharide vaccine should be used instead; or
- to individuals taking antibiotics; parenteral Vi polysaccharide vaccine should be used instead.

Parenteral Vi polysaccharide vaccines

There are no other contraindications to these vaccines.

Precautions

There should be an interval of at least 8 hours between the administration of the inactivated oral cholera and oral typhoid vaccines, as the buffer in the cholera vaccine may affect the transit of the capsules of oral typhoid vaccine through the gastrointestinal tract.

The Vi polysaccharide vaccines should not be administered to children <2 years of age.

The oral live attenuated vaccine should not be administered to children <6 years of age; parenteral Vi polysaccharide vaccine should be used instead in children 2–5 years of age.

Adverse events

Typhoid vaccines, both oral and parenteral, are associated with very few adverse events and, when adverse events do occur, they tend to be mild and transient.[10]

Oral live attenuated vaccine

Abdominal discomfort, diarrhoea, nausea, vomiting and rashes have occasionally been reported.

Parenteral Vi polysaccharide vaccines

Local adverse events such as erythema, swelling and pain at the injection site are very common (10 to 20%). Systemic adverse events are common and include fever (3%), malaise and nausea.

Public health management of typhoid fever

Typhoid fever is a notifiable disease in all States and Territories in Australia.

Upon notification, the relevant public health authority should ascertain the likely source of infection, and determine if the case has an occupation (eg. as a food handler or carer of children, the elderly or of those with impaired immunity) where there might be the potential for the spread of *S.* Typhi.[11] Cases in such occupations should be excluded from work until 2 consecutive faecal samples, collected a week apart after the completion of antibiotic treatment, are negative for *S.* Typhi.[11] Cases not in such occupations should also be proved to have cleared the organism from 2 consecutive faecal samples, but they can return to work once they have recovered and any diarrhoea has ceased.

All those who have been in close contact with a case of typhoid fever in the 30 days before the clearance of *S.* Typhi from the case's faeces should have their occupation assessed (as above). Contacts in 'risk' occupations should be excluded from work until 2 faecal samples, collected at least 24 hours apart, have proved negative for *S.* Typhi.[11] Contacts not in such occupations can remain at work, but should have at least 1 faecal sample collected. Further instructions about the management of cases of typhoid fever, and their contacts, should be obtained from State/Territory public health authorities (see Appendix 1, *Contact details for Australian, State and Territory Government health authorities and communicable disease control*).

Use in pregnancy

The oral live attenuated vaccine should not be given in pregnancy. However, pregnancy is not a contraindication to vaccination with a parenteral Vi polysaccharide vaccine. Refer to Chapter 2.3, *Groups with special vaccination requirements,* Table 2.3.1 *Vaccinations in pregnancy*.

Variations from product information

The product information for the oral live attenuated vaccine does not mention the use of a 4-dose course of the vaccine for either primary or booster vaccination.

Although NHMRC considers pregnancy a contraindication to the oral live attenuated typhoid vaccine, the product information does not include pregnancy among the listed contraindications.

The Typhim Vi product information recommends a booster dose every 2 to 3 years. However, revaccination with a dose of Vi polysaccharide vaccine 3 years after an initial dose is recommended by NHMRC.

References

Full reference list available on the electronic *Handbook* or website http://immunise.health.gov.au.