Epidemiology of Typhoid Fever

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Typhoid fever

- Is the result of systemic infection mainly by S. typhi found only in man.
- The disease is clinically characterized by:
- A typical continuous fever for 3 to 4 weeks.
- Relative bradycardia.
- Involvement of lymphoid tissue.
- And considerable constitutional symptoms.

- The term "enteric fever" includes both typhoid and paratyphoid fevers.
- The disease may occur sporadically, epidemically or endemically.

Problem statement

- WORLD
- Typhoid fever occurs in all parts of the world where water supplies and sanitation are sub-standard.
- The disease is now uncommon in the developed countries where most of the cases that occur are either acquired abroad or imported by immigrants .
- Improved living conditions and the introduction of antibiotics in the late 1940s resulted in drastic reduction of typhoid fever morbidity and mortality in industrialized countries.
- In developing areas of Asia ,Africa, Latin America, however, the disease continues to be public health problem, albeit with incidence rate that vary considerably between and within countries.
- Majority of this burden occurs in Asia

- Approximately 5700 cases per year in the United States, with approximately 75% of these cases occurring among travelers to other countries.
- An estimated 27 million cases of typhoid fever and 210,000 deaths occur worldwide

- Since 1950, the organism's resistance to antibiotics has also been a growing problem; by 1989 resistance was reported in a number of countries, particularly in Asia and Middle East.
- Typhoid fever caused by multidrug-resistant (MDR) strains of salmonella typhi that is resistant to all 3 of the first line of antibiotics (chloramphenicol, ampicillin and cotrimoxazole).
- It is associated with more severe illness and higher rates of complications and death, especially in children aged less than 2 years.
- Pakistan has one of the highest rates of drug-resistant typhoid- more than 15,000 cases officially recorded – with contaminated water and poor sanitation contributing to the spread of the disease.

- Also, compared with typhoid fever caused by sensitive strains, a ten-fold higher rate of post-treatment symptomatic bacterial carriers has been reported with MDR S. typhi infection.
- Without effective treatment, typhoid fever kills almost 10 per cent of those infected.
- The socio-economic impact of the disease is huge, because typhoid survivors may take several months to recover and resume work.

Epidemiological determinants

- Agent factors
- (a) AGENT : S. typhi is the major cause of enteric fever. S. para A and S. para B are relatively infrequent.
- S. typhi has three main antigens 0, H and Vi and a number of phage types (at least 80).
- Phage typing has proved a useful epidemiological tool in tracing the source of epidemics.
- S. typhi survives intracellularly in the tissues of various organs.
- It is readily killed by drying, pasteurization, and common disinfectants.
- The factors which influence the onset of typhoid fever in man are the infecting dose and virulence of the organism.

- (b) RESERVOIR OF INFECTION : Man is the only known reservoir of infection, viz cases and carriers.
- (i) CASES : The case may be mild, missed or severe.
- A case (or carrier) is infectious as long as bacilli appear in stools or urine.

- (ii) CARRIERS: The carriers may be temporary (incubatory, convalescent) or chronic.
- Convalescent carriers excrete the bacilli for 6 to 8 weeks, after which their numbers diminish rapidly.
- By the end of three months, not more than 4 per cent of cases are still excreting the organisms; and by the end of one year, the average carrier rate is around 3 per cent.

- Persons who excrete the bacilli for more than a year after a clinical attack are called chronic carriers.
- In most chronic carriers, the organisms persist in the gall bladder and in the biliary tract.
- A chronic carrier state may be expected to develop in 2 to 5 per cent of cases.
- A chronic carrier may excrete the bacilli for several years (may be as long as 50 years) either continuously or intermittently.
- The famous case of "Typhoid Mary" is a good example of a chronic carrier.

- Mary Mallon was a cook in Oyster Bay, New York early 1900s.
- Gave rise to more than 1300 cases in her life time.
- She died of pneumonia after 26 years in quarantine.

SOURCE OF INFECTION :

- The primary sources of infection are faeces and urine of cases or carriers; the secondary sources contaminated water, food, fingers and flies.
- There is no evidence that typhoid bacilli are excreted in sputum or milk.
- Faecal carriers are more frequent than urinary carriers.
- Chronic urinary carrier state is often associated with some abnormality of the urinary tract.

Host factors

- (a) Age : Typhoid fever may occur at any age.
- Highest incidence of this disease occurs in the 5-19 years of age group.
- Prospective population-based surveillance in some Asian urban slum areas has shown that in the age group 5-15 years.
- In some of these areas, pre-school-age children less than 5 years, show incidence rates similar to those of school-age children.
- After the age of 20 years, the incidence falls probably due to acquisition of immunity from clinical or subclinical infection.

Sex:

- More cases are reported among males than females, probably as a result of increased exposure to infection.
- But carrier rate is more in females.

(c) Immunity:

- All ages are susceptible to infection.
- Antibody may be stimulated by the infection or by immunization; however, the antibody to the somatic antigen (0) is usually higher in the patient with the disease, and the antibody to the flagellar antigen {H) is usually higher in immunized individuals.
- Serum antibodies are not the primary defenses against infection; S. typhi being an intracellular organism, cell-mediated immunity plays a major role in combating the infection.
- Natural typhoid fever does not always confer solid immunity; second attacks may occur when challenged with a large oral dose.

- Among the host factors that contribute to resistance to S. typhi are gastric acidity and local intestinal immunity.

Environmental and social factors

- Enteric fevers are observed all through the year..
- an increase in fly population.
- Outside the human body, the bacilli are found in water, ice, food, milk and soil for varying periods of time.
- Typhoid bacilli do not multiply in water; many of them perish within 48 hours, but some may survive for about 7 days.
- They may survive for over a month in ice and ice cream.

Environmental and social factors

- They may survive for up to 70 days in soil irrigated with sewage.
- Food being a bad conductor of heat, provides shelter to the bacilli which may multiply and survive for sometime in food.
- Typhoid bacilli grow rapidly in milk without altering its taste or appearance in anyway.

Environmental and social factors

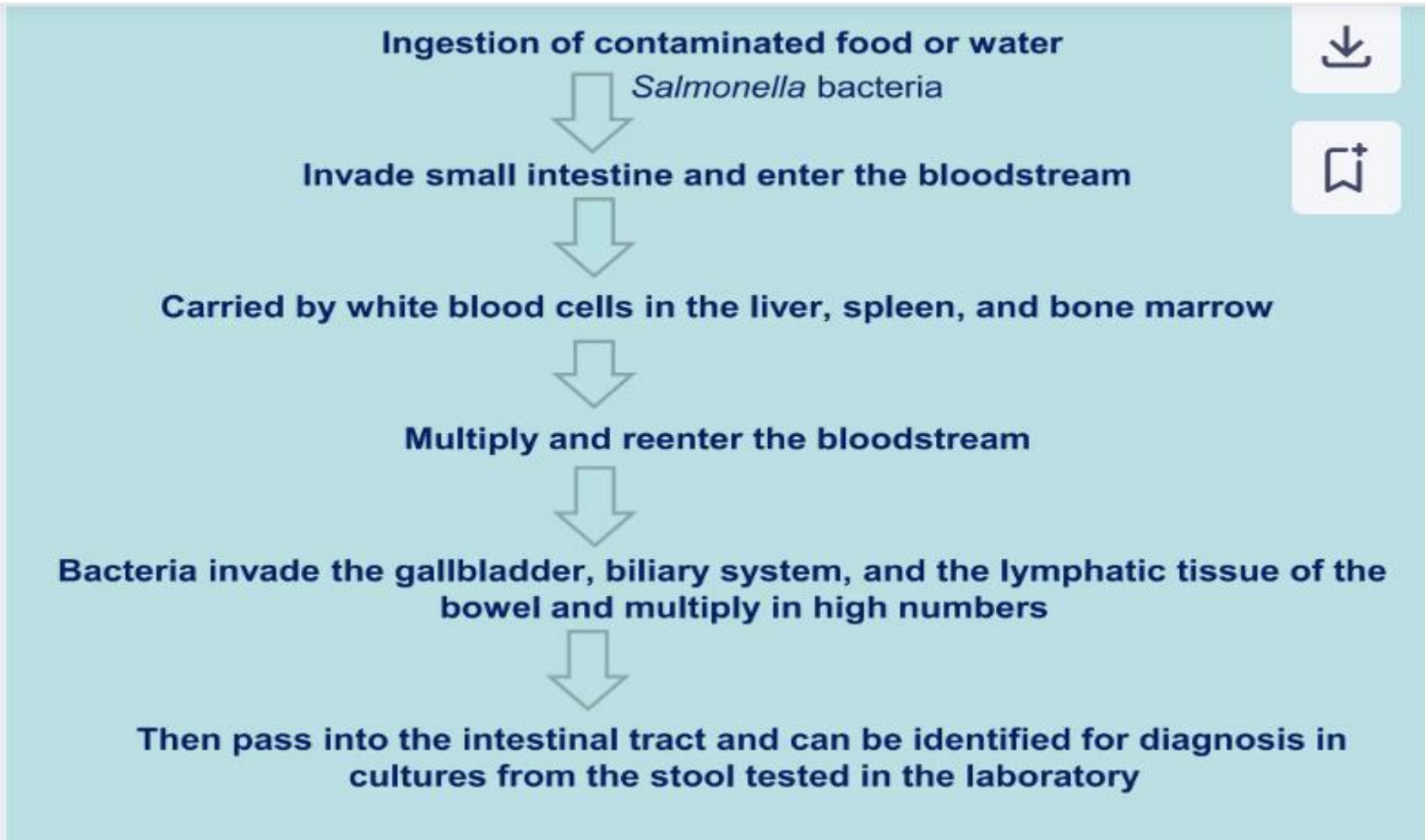
- Vegetables grown in sewage farms or washed in contaminated water are a positive health hazard.
- These factors are compounded by such social factors as pollution of drinking water supplies, open air defecation and urination, low standards of food and personal hygiene and health ignorance.
- Typhoid fever may therefore be regarded as an index of general sanitation in any country.

Incubation period

- Usually 10-14 days.
- But it may be as short as 3 days or as long as three weeks depending upon the dose of the bacilli ingested.

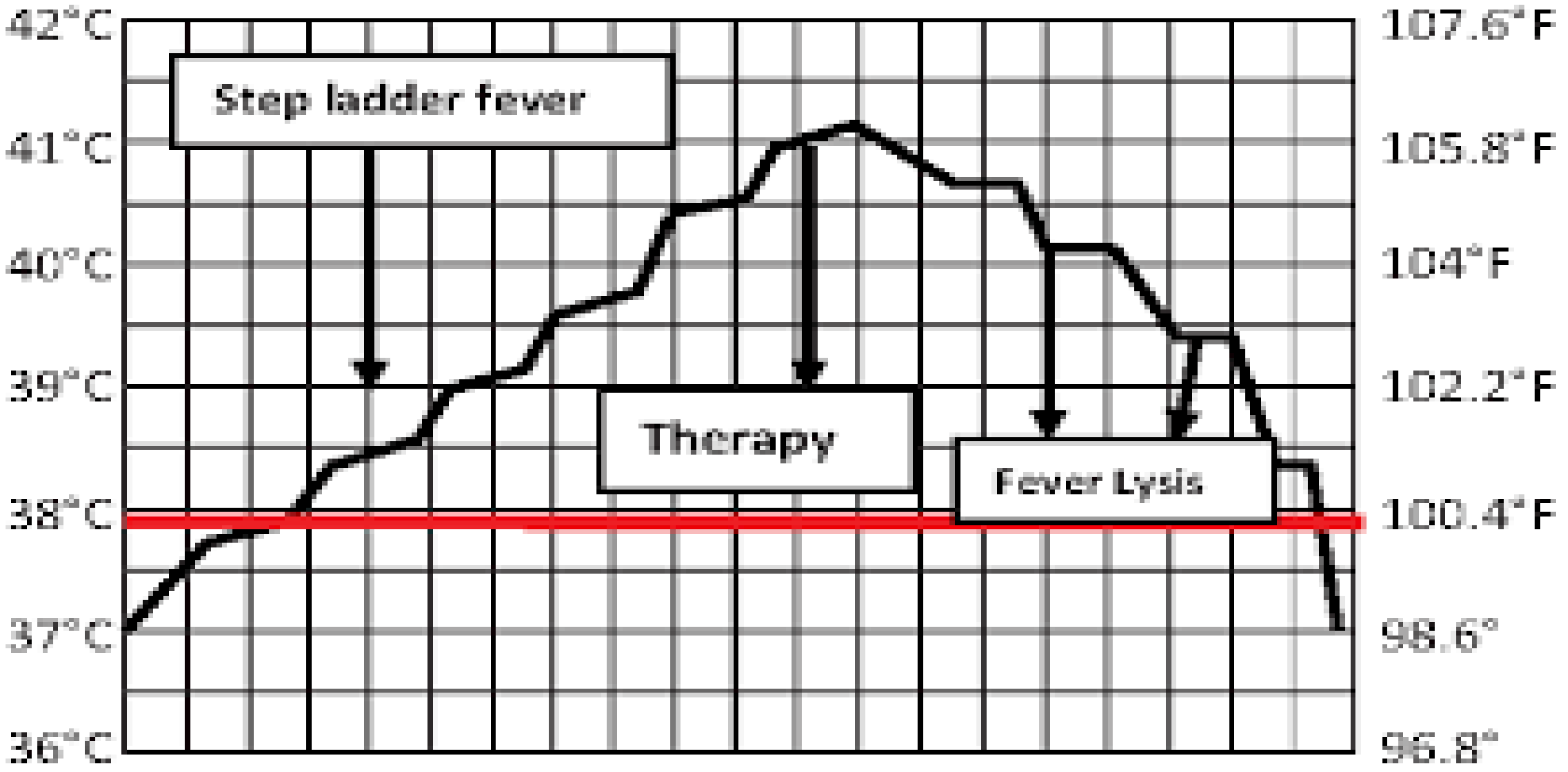
Modes of transmission

- Typhoid fever is transmitted via the faecal-oral route or urine-oral routes.
- This may take place directly through soiled hands contaminated with faeces or urine of cases or carriers, or indirectly by the ingestion of contaminated water, milk and/or food, or through flies.


Ingestion of contaminated food or water
Salmonella bacteria
Invade small intestine and enter the bloodstream
Carried by white blood cells in the liver, spleen, and bone marrow
Multiply and reenter the bloodstream
Bacteria invade the gallbladder, biliary system, and the lymphatic tissue of the bowel and multiply in high numbers
Then pass into the intestinal tract and can be identified for diagnosis in cultures from the stool tested in the laboratory

Clinical features(1st week)

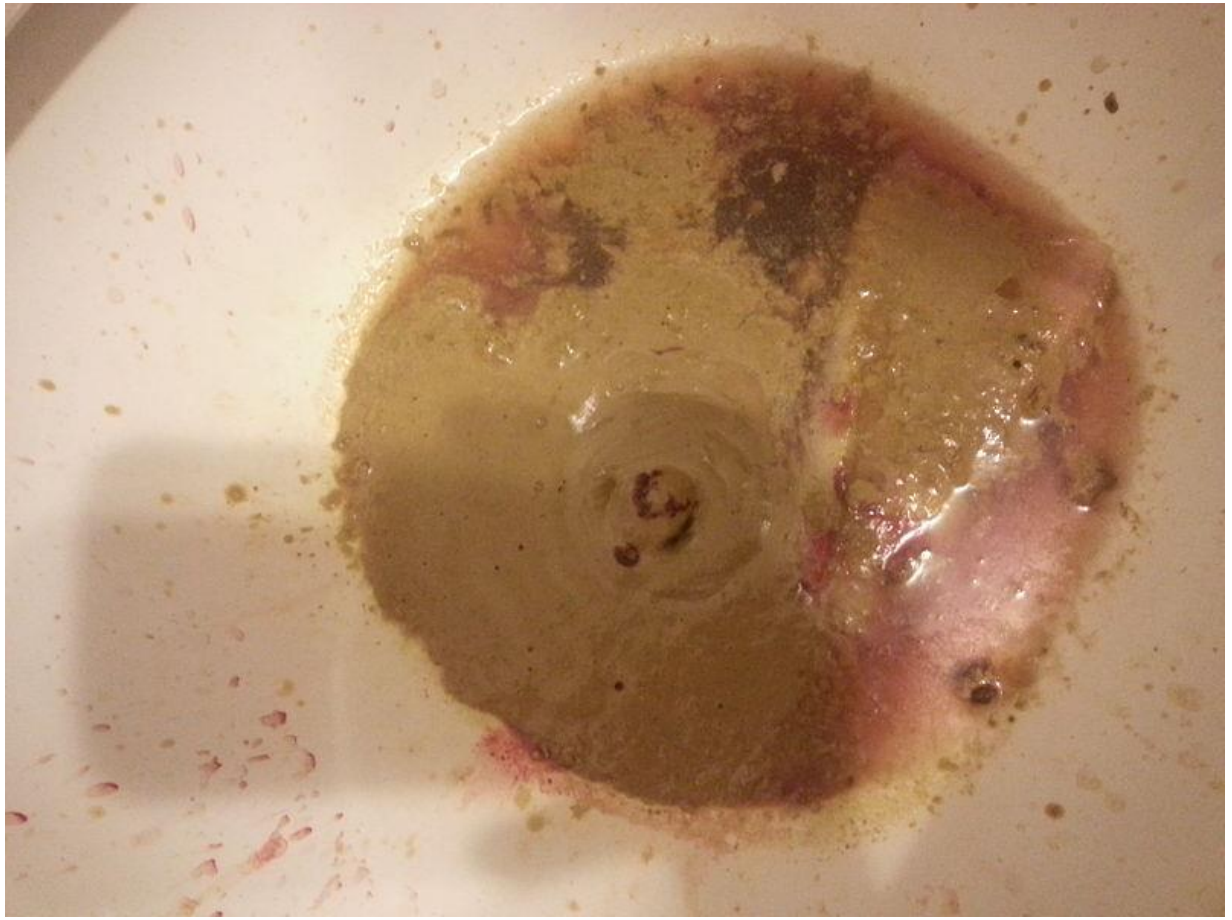
- The onset is usually insidious but in children may be abrupt, with chills and high fever.
- During the prodromal stage, there is malaise, headache, cough and sore throat, often with abdominal pain and constipation.
- The fever ascends in a step-ladder fashion.
- After about 7-10 days, the fever reaches a plateau and the patient looks toxic, appearing exhausted and often prostrated.


42°C
41°C
40°C
39°C
38°C
37°C
36°C
107.6°F
105.8°F
104°F
102.2°F
100.4°F
98.6°
96.8°
Step ladder fever
Therapy
Fever Lysis

Clinical features

- There may be marked constipation, especially in early stage or "pea soup" diarrhoea.
- There is marked abdominal distention.
- There is leukopenia and blood, urine and stool culture is positive for · salmonella.
- If there are no complications the patient's condition improves over 7-10 days.
- However, relapse may occur for up to 2 weeks after termination of therapy.

PEA SOUP STOOL



Clinical features(2nd week)

- During the early phase, physical findings are few.
- Later, :
- splenomegaly,
- abdominal distension and tenderness,
- relative bradycardia,

Temperature	Appropriate pulse response (beats/min)	Relative bradycardia If pulse (beats/min)
106 °F (41.1 °C)	150	<140
105 °F (40.6 °C)	140	<130
104 °F (40.7 °C)	130	<120
103 °F (39.4 °C)	120	<110
102 °F (38.9 °C)	110	<100

[a] Relative bradycardia refers to heart rates that are inappropriately slow relative to body temperature (pulse must be taken simultaneously with temperature elevation). Applies to adult patients with temperature ≥102 °F; does not apply to patients with second/third-degree heart block, pacemaker-induced rhythms, or those taking beta-blockers, diltiazem, or verapamil.

CLINICAL FEATURES

- dicrotic pulse((double beat, the second beat weaker than the first),
- and occasionally meningismus appear.

- The rash (rose spots) commonly appears during the second week of disease.
- The individual spot, found principally on the trunk, is a pink papule 2-3 mm in diameter that fades on pressure.
- It disappears in 3-4 days.

Complications(3rd week)

- Serious complications occur in up to 10% of typhoid fever patients, especially in those who have been ill longer than 2 weeks, and who have not received proper treatment.
- Intestinal haemorrhage is manifested by a sudden drop in temperature and signs of shock, followed by dark or fresh blood in the stool.
- Intestinal perforation is most likely to occur during the third week.

- Less frequent complications are:
- Urinary retention,
- Pneumonia.
- Thrombophlebitis,
- Myocarditis,
- Psychosis ,
- Cholecystitis ,
- Nephritis and
- Osteomyelitis .

CFR

- Estimates of case-fatality rates of typhoid fever range from 1%- 4%.
- Fatality rates in children aged less than 4 years being 10 times higher (4.0%) than in older children (0.4%).
- In untreated cases, the fatality rates may rise to 10-20 per cent.

Laboratory diagnosis of typhoid

- (a) MICROBIOLOGICAL PROCEDURES : The definitive diagnosis of typhoid fever depends on the isolation of S. typhi from blood, bone marrow and stools.
- Blood culture is the mainstay of diagnosis of this disease.

1- Microbiological procedure
Blood Cultures

- Bacteremia occurs early in the disease
- Blood Cultures are positive in

1st week in 90%
2nd week in 75%
3rd week in 60%
4th week and later in 25%

(b) SEROLOGICAL PROCEDURE :

- Felix-WidaL test measures agglutinating antibody levels against 0 and H antigens.
- Usually, 0 antibodies appear on day 6-8 and H antibodies on day 10-12 after the onset of disease.
- The test is usually performed on an acute serum (at first contact with the patient).
- The test has only moderate sensitivity and specificity.

2- SEROLOGICAL PROCEDURE

FELIX-WIDAL TEST

Significant Titers helps in Diagnosis

- Serum agglutinins raise abruptly during the 2nd or 3rd week
- Following Titers of antibodies against the antigens are significant when single sample is tested

  O > 1 in 160

  H > 1 in 320
- Testing a paired sample (7-10 days) for raise of antibodies carries a greater significance

Limitations of Widal test

Classically, a four-fold rise of antibody in paired sera Widal test is considered diagnostic of typhoid fever. However, paired sera are often difficult to obtain and specific chemotherapy has to be instituted on the basis of a single Widal test. Furthermore, in areas where fever due to infectious causes is a common occurrence the possibility exists that false positive reactions may occur as a result of non-typhoid

(b) SEROLOGICAL PROCEDURE

- It can be negative in up to 30 per cent of culture -proven cases of typhoid fever.
- This may be because of prior antibiotic therapy that has blunted the antibody response.
- On the other hand, S. typhi shares 0 and H antigens with other salmonella serotypes and has cross-reacting epitopes with other Enterobacteriaceae, and this can lead to false-positive results.
- Such results may also occur in other clinical conditions, e.g. malaria, typhus, bacteremia caused by other organisms, and cirrhosis

3- NEW DIAGNOSTIC TESTS

- IDL Tubex detects IgM09 antibodies with in few minutes
- Typhidot test that detects presence of IgM and IgG in one hour (sensitivity>95%, Specificity 75%)
- Typhidot-M, that detects IgM only (sensitivity 90% and specificity 93%)
- Typhidot rapid (sensitivity 85% and Specificity 99%) is a rapid 15 minute immunochromatographic test to detect IgM.
- IgM dipstick test

CONTROL OF TYPHOID FEVER

- The control or elimination of typhoid fever is well within the scope of modern public health.
- This is an accomplished fact in many developed countries.
- There are generally three lines of defense against typhoid fever :
- 1. control of reservoir
- 2. control of sanitation,
- and 3. immunization.
- The weakest link in the chain of transmission is sanitation which is amenable to control.

1. Control of reservoir

- The usual methods of control of reservoir are their identification, isolation, treatment and disinfection.
- a.CASES
- (i) Early diagnosis : This is of vital importance as the early symptoms are non-specific.
- Culture of blood and stools are important investigations in the diagnosis of cases.
- (ii) Notification: This should be done where such notification is mandatory.
- (iii) Isolation . Since typhoid fever is infectious and has a prolonged course, the cases are better transferred to a hospital for proper treatment, as well as to prevent the spread of infection.
- As a rule, cases should be isolated till three bacteriologically negative stools and urine reports, are obtained on three separate days.

CASES

- (iv) Treatment :
- The fluoroquinolones are widely regarded as the drug of choice for· the treatment of typhoid fever.
- They are relatively inexpensive, well tolerated and more rapidly and reliably effective than the former first-line drugs, viz. chloramphenicol, ampicillin, amoxicillin and trimethoprim sulfamethoxazole (TMP-SMX).
- Patients seriously ill and profoundly toxic may be given an injection of hydrocortisone 100 mg daily for 3 to 4 days.

- (v) Disinfection:
- Stools and urine are the sole sources of infection.
- They should be received in closed containers and disinfected with 5 per cent cresol for at least 2 hours.
- All soiled clothes and linen should be soaked in a solution of 2 per cent chlorine and steam-sterilized.
- Nurses and doctors should not forget to disinfect their hands.

- (vi) Follow-up :
- Follow-up examination of stools and urine should be done for S. typhi 3 to 4 months after discharge of the patient, and again after 12 months to prevent the development of the carrier state.
- With early diagnosis and appropriate treatment, mortality has been reduced to about 1%.

(b) CARRIERS

- Since carriers are the ultimate source of typhoid fever, their identification and treatment is one of the most radical ways of controlling typhoid fever.
- The measures recommended are :
- (i) Identification : Carriers are identified by cultural and serological examinations.
- Duodenal drainage establishes the presence of salmonella in the biliary tract in carriers.
- The Vi antibodies are present in about 80 per cent of chronic carriers.

- (ii) Treatment : The carrier should be given an intensive course of ampicillin or amoxycillin (4-6 g a day} together with Probenecid (2 g/day) for 6 weeks.
- These drugs are concentrated in the bile and may achieve eradication of the carrier state in about 70 per cent of carriers.

- (iii) Surgery : Cholecystectomy with concomitant ampicillin therapy has been regarded as the most successful approach to the treatment of carriers.
- Cure rate may be as high as 80 per cent.
- Urinary carriers are easy to treat, but refractory cases may need nephrectomy when one kidney is damaged and the other healthy.

- (iv) Surveillance :
- The carriers should be kept under surveillance.
- They should be prevented from handling food, milk or water for others.
- (v) Health education : Health education regarding washing of hands with soap, after defecation or urination, and before preparing food is an essential element.
- In short, the management of carriers continues to be an unsolved problem.
- This is the crux of the problem, in the elimination of typhoid fever.

2. Control of sanitation

- Protection and purification of drinking water supplies, improvement of basic sanitation, and promotion of food hygiene are essential measures to interrupt transmission of typhoid fever.
- For instance, typhoid fever is never a major problem where there is a clean domestic water supply.
- Sanitary measures, not followed by health education may produce only temporary results.
- However, when sanitation is combined with health education, the effects tend to be cumulative, resulting in a steady reduction of typhoid morbidity

3. Immunization

- While ultimately, control of typhoid fever must take the form of improved sanitation and domestic and personal hygiene, these are long-term objectives in many developing countries.
- A complementary approach to prevention is immunization, which is the only specific preventive measure, likely to yield the highest benefit for the money spent.
- Immunization against typhoid does not give 100 per cent protection, but it definitely lowers both the incidence and seriousness of the infection.

- It can be given at any age upwards of two years.
- It is recommended to :
- i) those living in endemic areas
- (ii} household contacts
- (iii) groups at risk of infection such as school children and hospital staff
- (iv) travelers proceeding to endemic areas,
- and (v} those attending FOOD FESTIVALS.

ANTI-TYPHOID VACCINES

- The old parenteral killed whole-cell vaccine was effective but produced strong side-effects, Two safe and effective vaccines are now licensed and available.
- One is based on defined subunit antigens, the other on whole-cell live attenuated bacteria.

The Vi polysaccharide vaccine

- This subunit vaccine .
- It is composed of purified Vi capsular polysaccharide from the Ty2 S. Typhi strain and elicits a T-cell independent IgG response that is not boosted by additional doses.
- The vaccine is administered subcutaneously or intramuscularly.
- The Vi vaccine does not elicit adequate immune responses in children aged less than 2 years.

Schedule

- The vaccine is licensed for individuals aged ≥ 2 years.
- Only 1 dose is required, and the vaccine confers protection 7 days after injection.
- To maintain protection, revaccination is recommended every 3 years.
- The Vi polysaccharide vaccine can be co-administered with other vaccines relevant for international travellers, such as yellow fever and hepatitis A, and with vaccines of the routine childhood immunization programmes.


TYPHIM Vi®
Sanofi Pasteur Europe
One dose = 0,5 ml


TYPHIM Vi
POLYSACCHARIDE TYPHOID VACCINE
SANOFI PASTEUR

Safety

- No serious adverse events and a minimum of local side effects are associated with Vi vaccination.
- There are no contraindications to the use of this vaccine other than previous severe hypersensitivity reaction to vaccine components.
- Although the Vi polysaccharide vaccine is safe for HIV-infected individuals, the induction of protective antibodies is directly correlated to the levels of CD4 positive T-cells.

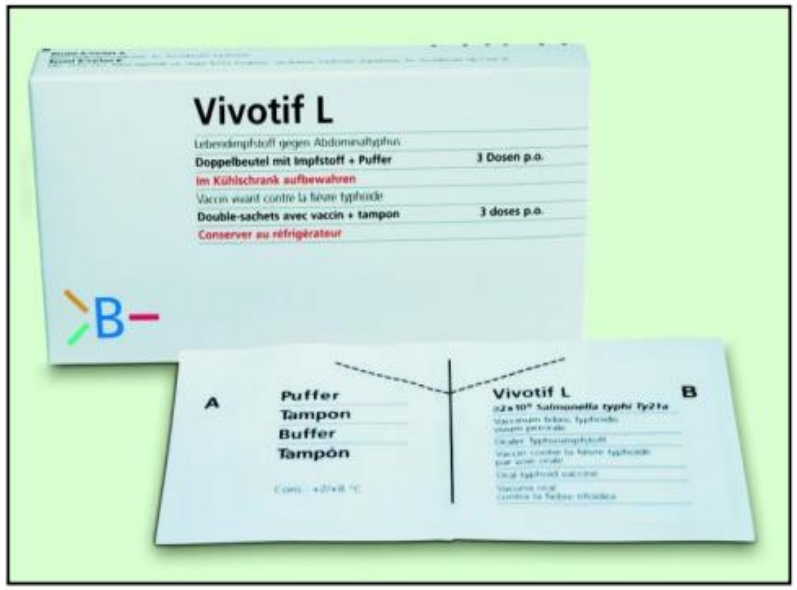
The Ty21a vaccine

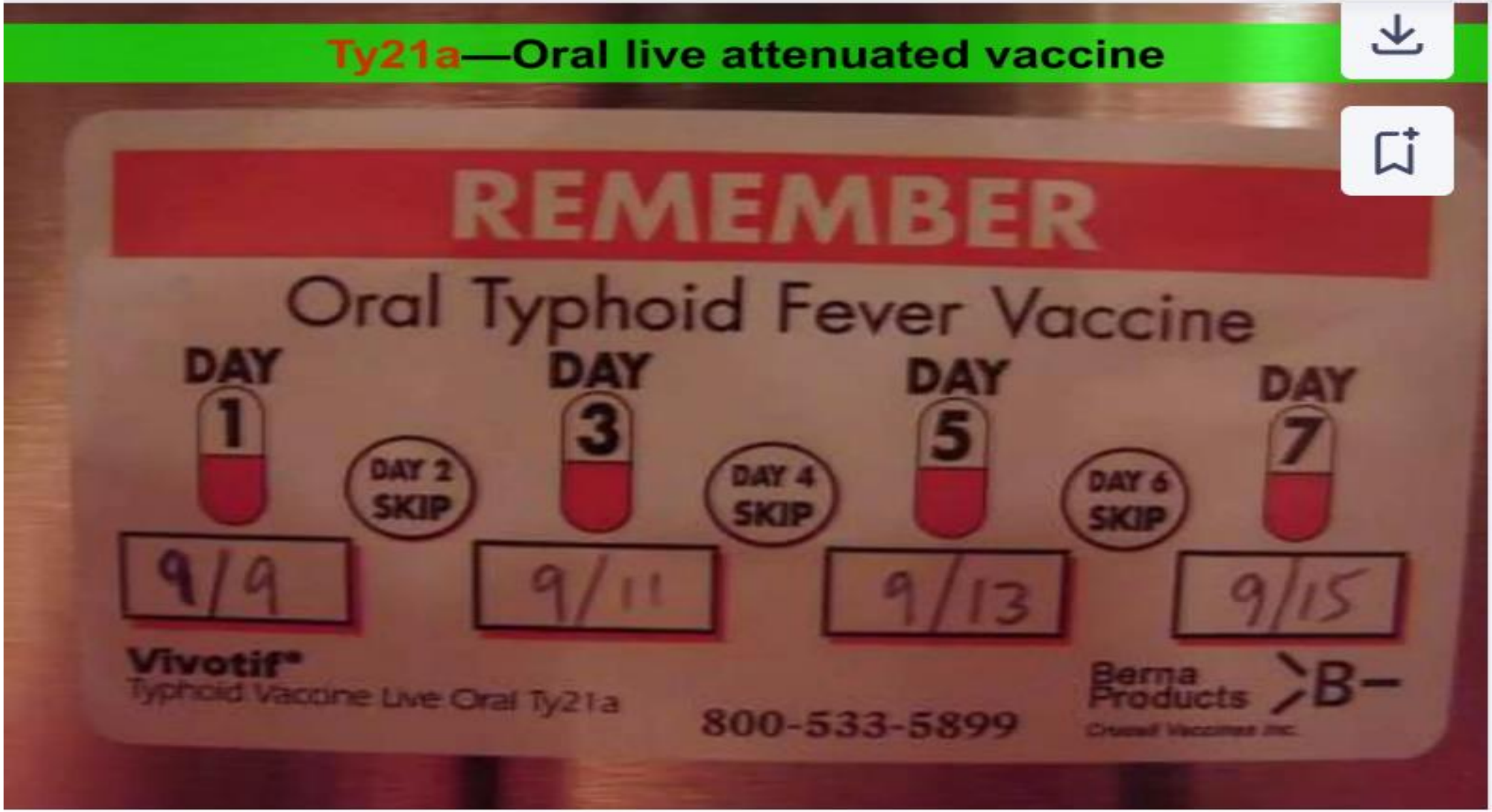
- live attenuated Ty2 strain of S. Typhi ..
- The lyophilized vaccine is available as enteric coated capsules.
- Protection is markedly influenced by the number of doses and their spacing.

SAFETY

- The capsules are licensed for use in individuals aged >: 5 years.
- The vaccine is administered every other day; on 1, 3, and 5th day; a 3-dose regimen is recommended.
- With the 3-dose regimen, protective immunity is achieved 7 days after the last dose-.

- **Ty21a live oral strain**
  - 3 doses (most countries) or 4 doses (USA & Canada)




Ty21a—Oral live attenuated vaccine
REMEMBER
Oral Typhoid Fever Vaccine
DAY 1
DAY 2 SKIP
DAY 3
DAY 4 SKIP
DAY 5
DAY 6 SKIP
DAY 7
9/9
9/11
9/13
9/15
Vivotif®
Typhoid Vaccine Live Oral Ty21a
800-533-5899
Berna Products
>B–

- The recommendation is to repeat this series every 3 years for people living in endemic areas, and every year for individuals travelling; from non-endemic to endemic countries.
- The Ty21 a vaccine may be given simultaneously with other vaccines, including live vaccines against polio, cholera, and yellow fever, or the measles, mumps and rubella (MMR) combination.

Safety and precautions

- Proguanil and antibacterial drugs should be stopped from 3 days before until 3 days after giving Ty2la, as such drugs may harm live bacterial vaccines.
- The vaccine is unlikely to be efficacious if administrated at the time of ongoing diarrhoea.
- It is not known whether this live attenuated vaccine may cause foetal harm when administered to pregnant women.

- Ty21a can be administered to HIV-positive, asymptomatic individuals as long as the T-cell count (CD4) is >200/mm3 .
- Ty21a is remarkably well tolerated and has low rates of adverse events.
- The vaccine is not recommended in congenital or acquired immunodeficiency including treatment with immuno-suppressive and antimitotic drugs, acute febrile illness and acute intestinal infection

REFERENCE :park's textbook of preventive and social medicine 23rd edition