Typhoid Fever

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Objectives

- At the end of the lecture, the student should be able to
  - Formulate and implement a multi-disciplinary and evidence-based approach in the diagnosis, treatment, as well as prevention of typhoid fever
  - Explain and interpret results of common laboratory tests related to common infectious and neglected tropical diseases
  - Design and employ a campaign on the prevention of typhoid fever, especially in high risk populations

Outline

- Organism
- Pathophysiology
- Mode of Transmission
- Risk Factors
- Epidemiology
- Clinical Manifestations
- Diagnosis and differentials
- Management

Some slides by Dr. J. Montoya.

Background

- *Salmonella enterica* serotype typhi has been a major human pathogen for thousands of years, thriving in conditions of poor sanitation, crowding, and social chaos.
- *S typhi* is derived from the ancient Greek *typhos,* an ethereal smoke or cloud that was believed to cause disease and madness (also a monstrous serpentine giant and the most deadly creature in Greek mythology).
- In the advanced stages of typhoid fever, the patient's level of consciousness is truly clouded.
- Although antibiotics have markedly reduced the frequency of typhoid fever in the developed world, it remains endemic in developing countries.

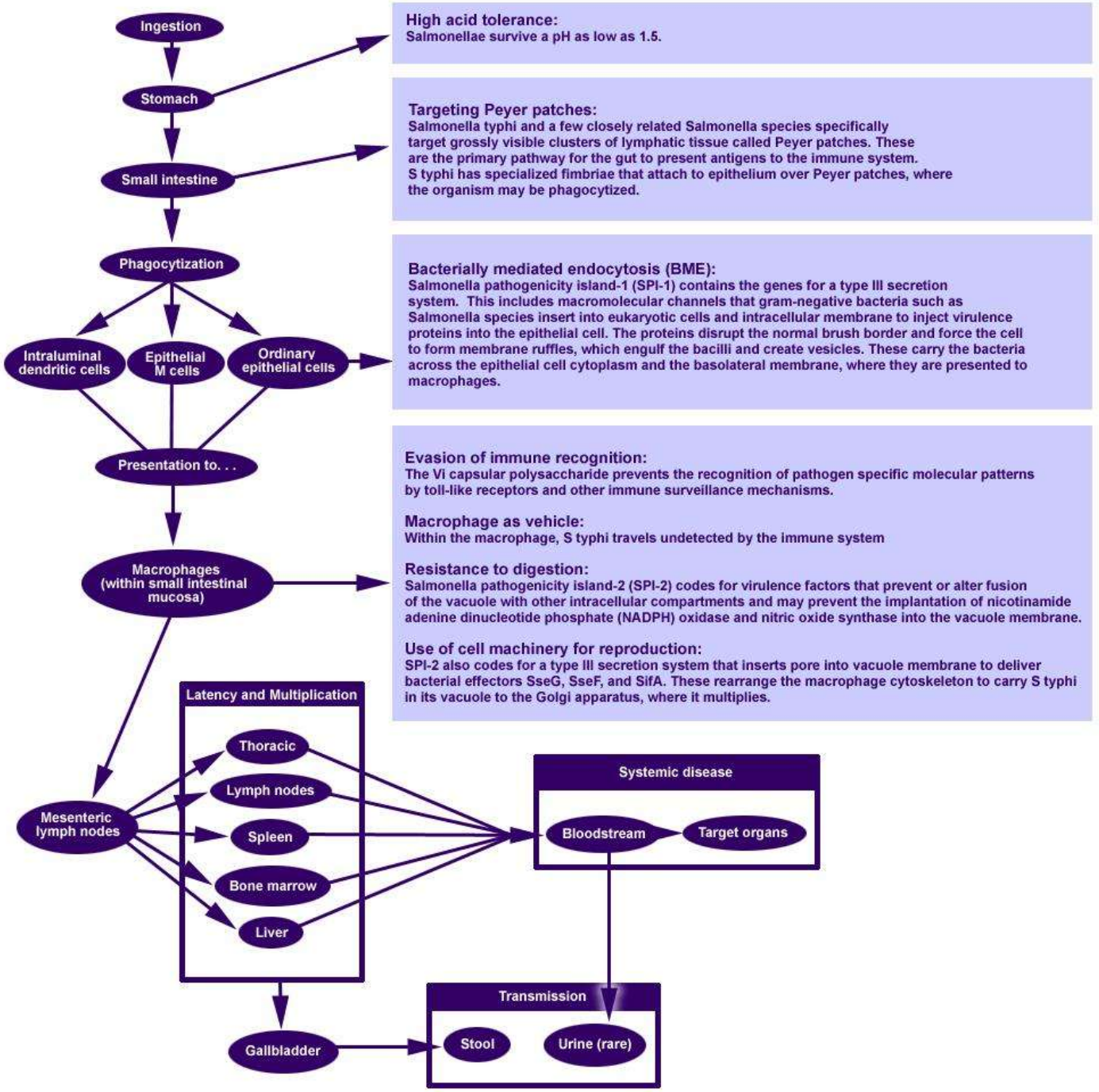
The Bacterium

- Typhoid (enteric) fever is a potentially fatal multisystemic illness caused primarily by *Salmonella enterica* subspecies *enterica* serovar *typhi* and, to a lesser extent, related serovars *paratyphi* A, B, and C.
- Characterized by polysaccharide capsule Vi, which is present in about 90% of all freshly isolated *S. typhi* and has a protective effect against the bactericidal action of the serum of infected patients.

The Bacterium

- Gram-negative, non-spore-forming, facultatively anaerobic bacilli
- Enterobacteriaceae
- Glucose fermenter, reduces nitrates, oxidase negative
- Motile
- Produces H_2S on sugar fermentation

Pathophysiology

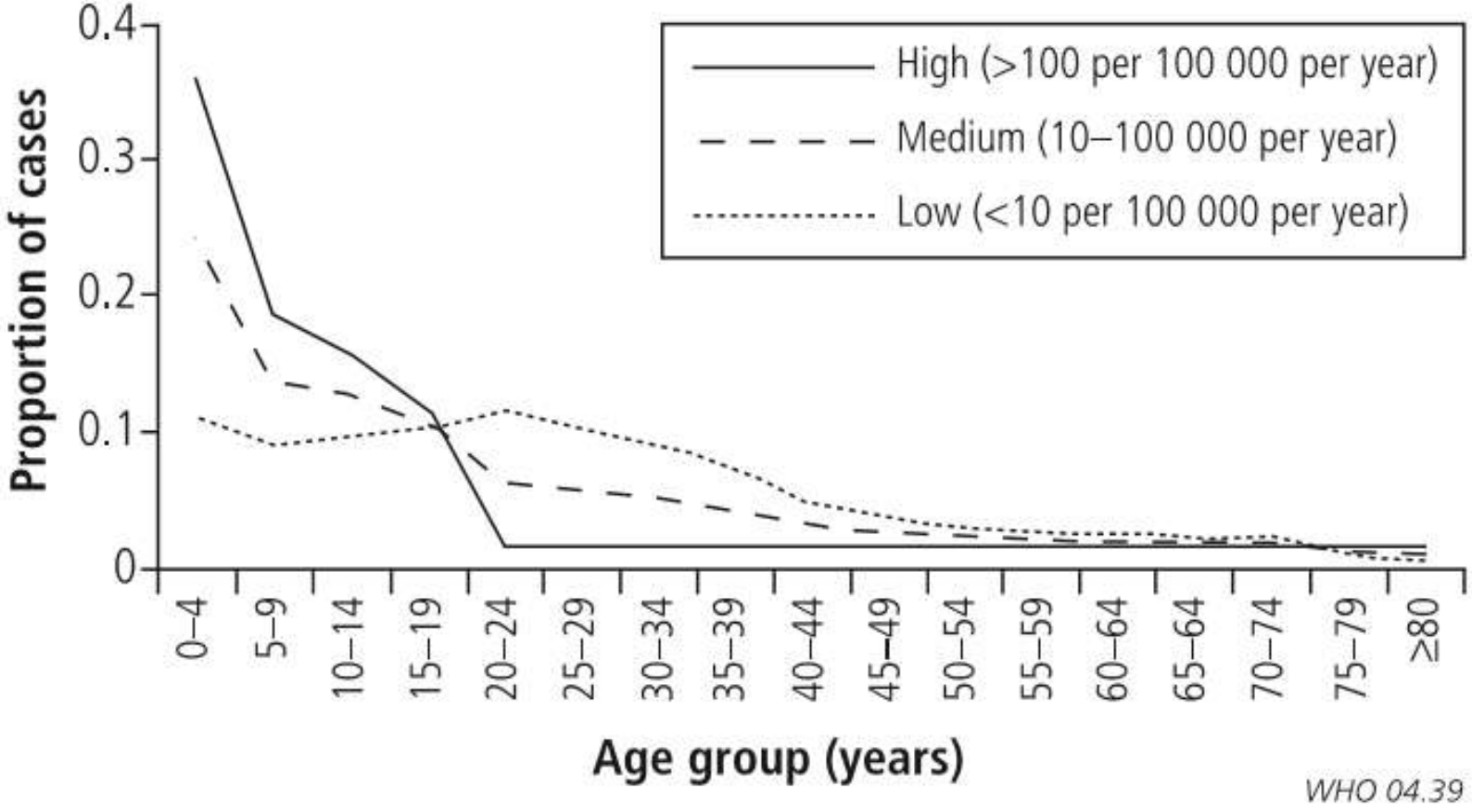


Brusch JL. https://emedicine.medscape.com/article/231135-overview#a5

Fig. 2. **Geographical distribution of typhoid fever**

Crump JA et al. Bulletin WHO. 2004;82:346-53.

Fig. 1. **Distribution of typhoid fever, by age group, at various incidences**



Crump JA et al. Bulletin WHO. 2004;82:346-53.

Mode of Transmission

- Typhoidal *salmonella* have no nonhuman vectors.
- An inoculum as small as 100,000 organisms of typhi causes infection in more than 50% of healthy volunteers.
- *Paratyphi* requires a much higher inoculum to infect, and it is less endemic in rural areas. Hence, the patterns of transmission are slightly different.

Levine MM et al. Microbes Infect. 2001;3(14-15):1271-9.

Mode of Transmission

- Oral transmission via food or beverages handled by an often asymptomatic individual—a carrier—who chronically sheds the bacteria through stool or, less commonly, urine
- Hand-to-mouth transmission after using a contaminated toilet and neglecting hand hygiene
- Oral transmission via sewage-contaminated water or shellfish (especially in the developing world).

Earampamoorthy S, Koff RS. Ann Intern Med. 1975;83(1):107-10.
Ali S et al. Clin Exp Immunol. 2006;144(3):425-31.
Ram PK et al. Epidemiol Infect. 2007;135(3):458-65

Risk Factors

- Travel to endemic areas
- Poor hygiene habits
- Poor sanitation conditions
- Achlorhydria
- Immunosuppression, e.g. AIDS
- Healthcare workers
- Clinical microbiologists
- Recent contact with a patient with typhoid fever
- Protection: hemochromatosis, CFTR polymorphism

Epidemiology

- Typhoid fever occurs worldwide, primarily in developing nations whose sanitary conditions are poor. Typhoid fever is endemic in Asia, Africa, Latin America, the Caribbean, and Oceania, but 80% of cases come from Bangladesh, China, India, Indonesia, Laos, Nepal, Pakistan, or Vietnam.
- Within those countries, typhoid fever is most common in underdeveloped areas. Typhoid fever infects roughly 21.7 million people (incidence of 3.6 per 1,000 population) and kills an estimated 217,000 people every year.

Crump JA et al. Bulletin WHO. 2004;82:346-53.
Crump JA et al. CID. 2010;50:241-6.

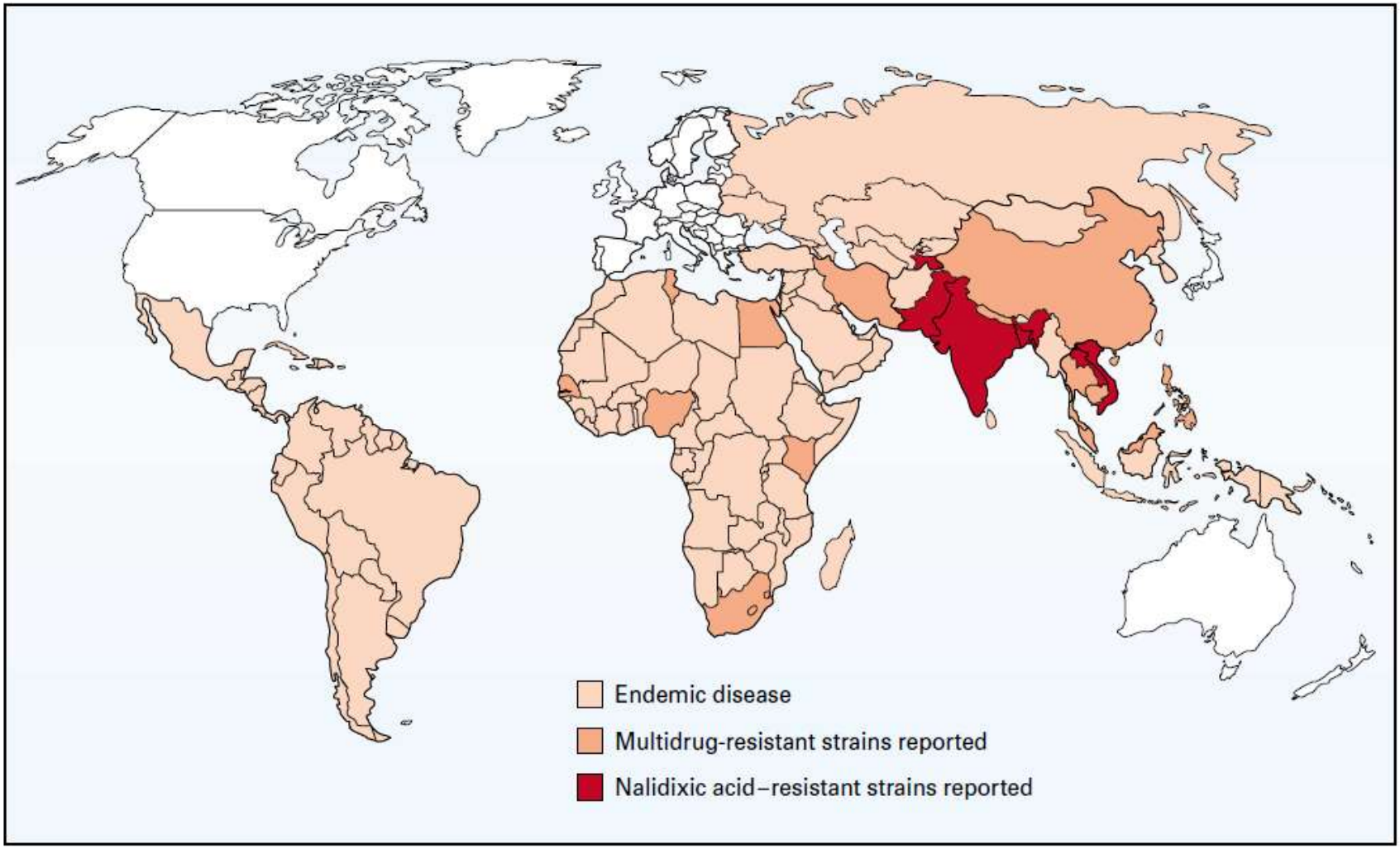


Figure 2. Global Distribution of Resistance to *Salmonella enterica* Serotype Typhi, 1990 through 2002. All shaded areas are areas of endemic disease.

Parry CM et al. NEJM. 2002;347(22):1770-82.

Clinical Features

- Asymptomatic/incubation period 7-14 days (range 3 to 60 days)
- Onset of bacteremia is marked by fever and malaise
- The fever pattern is stepwise, characterized by a rising temperature over the course of each day that drops by the subsequent morning. The peaks and troughs rise progressively over time. (This pattern appears in as few as 12% of cases)

Clinical Features

- Over the course of the first week of illness, the notorious gastrointestinal manifestations of the disease develop. These include diffuse abdominal pain and tenderness and, in some cases, fierce colicky right upper quadrant pain.
- Monocytic infiltration inflames Peyer patches and narrows the bowel lumen, causing **constipation** that lasts the duration of the illness. (Young children, patients with AIDS, and 1/3 of immunocompetent adults will develop diarrhea)
- The individual then develops a dry cough, dull frontal headache, delirium, and an increasingly stuporous malaise.

Clinical Features

- At approximately the end of the first week of illness, the fever plateaus at 103-104°F (39-40°C).
- The patient develops **rose spots**, which are salmon-colored, blanching, truncal, maculopapules usually 1-4 mm wide; these generally resolve within 2-5 days.
- These are bacterial emboli to the dermis and occasionally develop in persons with shigellosis or nontyphoidal salmonellosis.

Clinical Features

- During the second week of illness, the signs and symptoms progress. The abdomen becomes distended, and soft splenomegaly is common. **Relative bradycardia** and dicrotic pulse (double beat, the second beat weaker than the first) may develop.
- Trivia: Faget’s sign vs Liebermeister’s rule

Clinical Features

- In the third week, the still febrile individual grows more toxic and anorexic with significant weight loss. The conjunctivae are infected, and the patient is tachypneic with a thready pulse and crackles over the lung bases. Abdominal distension is severe.
- Some patients experience foul, green-yellow, liquid diarrhea (pea soup diarrhea). The individual may descend into the typhoid state, which is characterized by apathy, confusion, and even psychosis.
- Necrotic Peyer patches may cause bowel perforation and peritonitis. This complication is often unheralded. At this point, overwhelming toxemia, myocarditis, or intestinal hemorrhage may cause death.

Clinical Features

- If the individual survives to the fourth week, the fever, mental state, and abdominal distension slowly improve over a few days. Intestinal and neurologic complications may still occur in surviving untreated individuals. Weight loss and debilitating weakness last months.
- Some survivors become asymptomatic *S typhi* carriers and have the potential to transmit the bacteria indefinitely.

Clinical Features

- Relapse occurs in 5-10% of patients, usually 2-3 weeks after resolution of fever. Relapse is usually milder and the isolate usually retains the same antibiotic susceptibility pattern
- Re-infection is also possible but can only be distinguished from relapse by molecular typing

Atypical Presentations

- Atypical manifestations of typhoid fever include isolated severe headaches that may mimic meningitis, acute lobar pneumonia, isolated arthralgias, urinary symptoms, severe jaundice, or fever alone.
- Some patients, especially in India and Africa, present primarily with neurologic manifestations such as delirium or, in extremely rare cases, parkinsonian symptoms or Guillain-Barré syndrome.
- Other unusual complications include pancreatitis, meningitis, orchitis, osteomyelitis, and abscesses anywhere on the body.

Suspect Typhoid when these are present

- Fever of more than 7 days
- Absence of leukocytosis
- Presence of rose spots (“ salmon pink”)
- Triad of fever, headache and GI disturbance
- Pulse-temperature dissociation
- (Retrospective) Fever lysis after at least 48 hours of appropriate antibiotics

Differential diagnosis

- Intra-abdominal abscess
- Hepatic abscess
- Appendicitis
- Brucellosis
- Dengue
- Influenza
- Leishmaniasis
- Malaria
- Rickettsial diseases
- Toxoplasmosis
- Tuberculosis
- Tularemia
- Typhus
- Encephalitis
- CTD

Diagnostics

- In endemic areas, a fever without evident cause that lasts more than a week should be considered typhoid fever until proven otherwise
- Blood cultures – standard diagnostic method
  - The larger the volume the better (~15 mL in adults)
  - Positive in 60-80% of cases
  - Sensitivity highest in the 1st week, reduced by prior antibiotic use, increased by larger volumes of blood
- Bone marrow cultures – more sensitive
  - Positive in 80-95% o patients, even in those who have been on antibiotics for several days, regardless of the duration of illness
- Stool cultures – positive in 30% of patients; increases with duration of illness

Diagnostics: Other Serologic Tests

- Assays that identify Salmonella antibodies or antigens support the diagnosis of typhoid fever, but these results should be confirmed with cultures or DNA evidence.
- Widal test measures agglutinating antibodies against H and O antigens of S typhi. Neither sensitive nor specific; no longer an acceptable clinical method.
- Indirect hemagglutination, indirect fluorescent Vi antibody, and indirect enzyme-linked immunosorbent assay (ELISA) for immunoglobulin M (IgM) and IgG antibodies to S typhi polysaccharide, as well as monoclonal antibodies against S typhi flagellin, are promising, but the success rates of these assays vary greatly in the literature.

Typhidot

- Use of the 50 kD antigen to detect specific IgM and IgG antibodies to *S. typhi*
- Offers simplicity, speed, specificity (75%), economy, early diagnosis, sensitivity (95%) and high negative and positive predictive values.
- Detection of IgM reveals acute typhoid in the early phase of infection, while the detection of both IgG and IgM suggests acute typhoid in the middle phase of infection.

Table 2 Laboratory diagnosis of typhoid

Diagnostic test	Sensitivity range (%)	Specificity range (%)	Comments
Microbiological tests			
Blood culture	40-80	NA	Widely regarded as the gold standard, but sensitivity may be low in endemic areas with high rates of antibiotic use—hence true specificity is difficult to estimate
Bone marrow cultures	55-67	30	Greater sensitivity but invasive and thus of limited clinical value, especially in ambulatory management
Urine culture	0-58	NA	Variable sensitivity
Stool culture	30	NA	Sensitivity lower in developing countries and not used routinely for follow-up
Molecular diagnostics			
Polymerase chain reaction	100	100	Promising, but initial reports indicated similar sensitivity to blood cultures and lower specificity
Nested polymerase chain reaction	100	100	Promising and may replace blood culture as the new "gold standard"
Serological diagnosis			
Widal test (tube dilution and slide agglutination)	47-77	50-92	Classic and inexpensive. Despite mixed results in endemic areas, still performs well for screening large volumes. May need standardisation and quality assurance of reagents
Typhidot	66-88	75-91	Lower sensitivity than Typhidot-M
Typhidot-M	73-95	68-95	Higher sensitivity and specificity than classic Typhidot in some series, but other evaluations suggest that the performance may not be as robust in community settings as in hospital
Tubex	65-88	63-89	Promising initial results but has yet to be evaluated in larger trials in community settings
Others			
Urine antigen detection	65-95	NA	Preliminary data only

NA=Not available.

Bhutta ZA. BMJ. 2006;333:78-82.

Relapse

- After discharge, patients should be monitored for relapse or complications for 3 months after treatment has commenced.
- 5-10% of patients treated with antibiotics experience relapse of typhoid fever after initial recovery. Relapses typically occur approximately 1 week after therapy is discontinued, but relapse after 70 days has been reported.
- In these cases, the blood culture results are again positive, and high serum levels of H, O, and Vi antibodies and rose spots may reappear.
- A relapse of typhoid fever is generally milder and of shorter duration than the initial illness. In rare cases, second or even third relapses occur. Notably, the relapse rate is much lower following treatment with the new quinolone drugs, which have effective intracellular penetration.

Chronic Carriage

- Depending on the antibiotic used, between 0% and 5.9% of treated patients become chronic carriers.
- In some cases, the organism evades antibiotics by sequestering itself within gallstones or *Schistosoma haematobium* organisms that are infecting the bladder. From there, it is shed in stool or urine, respectively. If present, these diseases must be cured before the bacterium can be eliminated.
- Untreated survivors of typhoid fever may shed the bacterium in the feces for up to 3 months. Therefore, after disease resolution, 3 stool cultures in one-month intervals should be performed to rule out a carrier state.

Medical Therapy

- Treatment should not be delayed for confirmatory tests since prompt treatment drastically reduces the risk of complications and fatalities.
- Antibiotic therapy should be narrowed once more information is available.
- Compliant patients with uncomplicated disease may be treated on an outpatient basis.

Surgical Therapy

FIGURE 190-3 **Typical ileal perforation associated with *Salmonella typhi* infection.** *(From JM Saxe, R Cropsey: Is operative management effective in treatment of perforated typhoid? Am J Surg 189:342, 2005.)*

- Surgery is usually indicated in cases of intestinal perforation.
- Development of leukocytosis maybe an early sign
- Most surgeons prefer simple closure of the perforation with drainage of the peritoneum. Small-bowel resection is indicated for patients with multiple perforations.
- If antibiotic treatment fails to eradicate the hepatobiliary carriage, the gallbladder should be resected. Cholecystectomy is not always successful in eradicating the carrier state because of persisting hepatic infection.
- Mortality rates rise to 10-32% with perforations, and rise further with delays in surgery

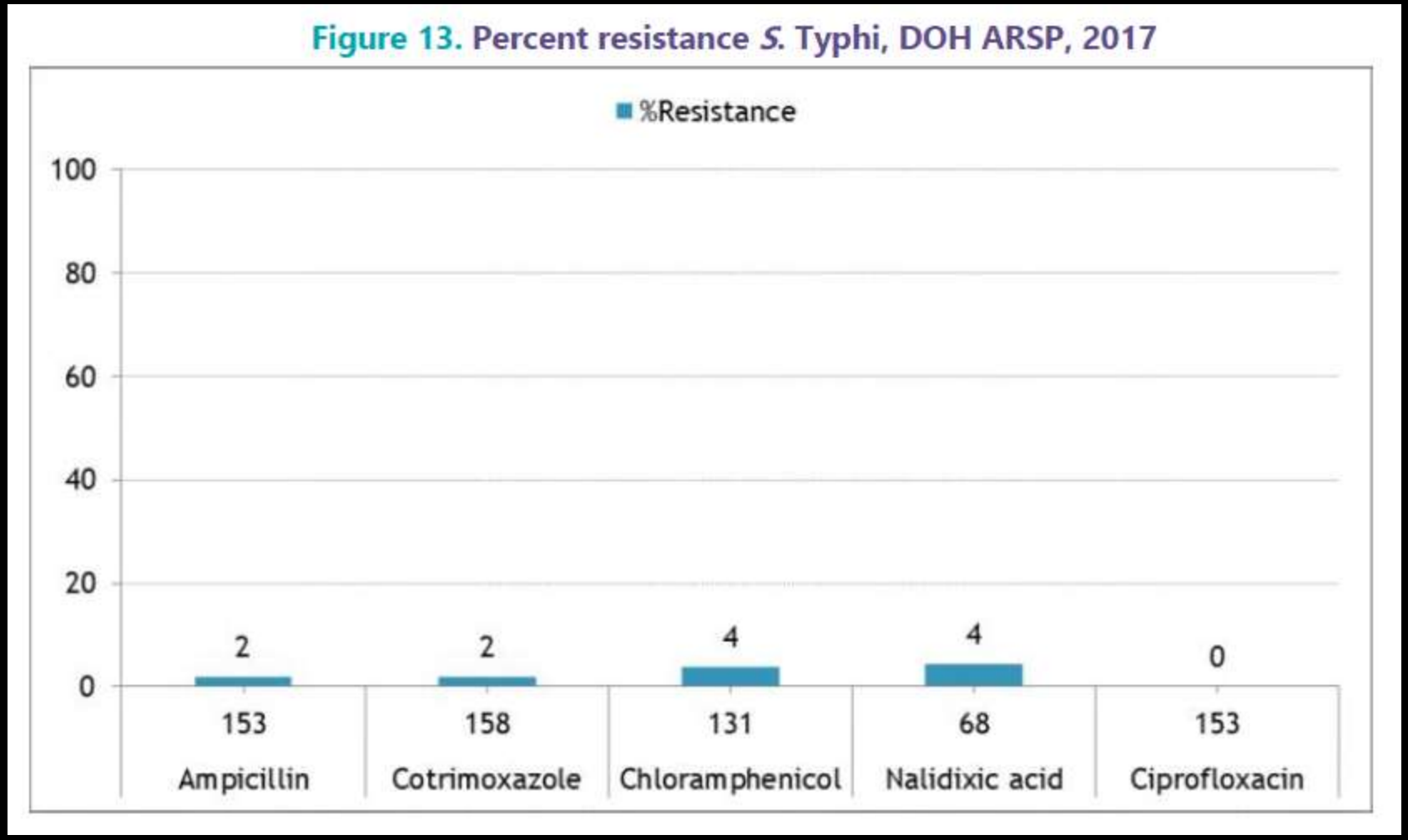


Figure 13. Percent resistance S. Typhi, DOH ARSP, 2017
%Resistance
100
80
60
40
20
0
2
2
4
4
0
153
158
131
68
153
Ampicillin
Cotrimoxazole
Chloramphenicol
Nalidixic acid
Ciprofloxacin

ARSP 2017.

TABLE 190-1 ANTIBIOTIC THERAPY FOR ENTERIC FEVER IN ADULTS

Indication	Agent	Dosage (Route)	Duration, Days
Empirical Treatment			
	Ceftriaxone[a]	2 g/d (IV)	10–14
	Azithromycin[b]	1 g/d (PO)	5
Fully Susceptible			
Optimal treatment	Ciprofloxacin[c]	500 mg bid (PO) or 400 mg q12h (IV)	5–7
	Azithromycin	1 g/d (PO)	5
Alternative treatment	Amoxicillin	1 g tid (PO) or 2 g q6h (IV)	14
	Chloramphenicol	25 mg/kg tid (PO or IV)	14–21
	Trimethoprim-sulfamethoxazole	160/800 mg bid (PO)	7–14
Multidrug-Resistant			
Optimal treatment	Ceftriaxone[a]	2 g/d (IV)	10–14
	Azithromycin	1 g/d (PO)	5
Alternative treatment	Ciprofloxacin	500 mg bid (PO) or 400 mg q12h (IV)	5–14
Quinolone-Resistant			
Optimal treatment	Ceftriaxone	2 g/d (IV)	10–14
	Azithromycin	1 g/d (PO)	5
Alternative treatment	High-dose ciprofloxacin	750 mg bid (PO) or 400 mg q8h (IV)	10–14

[a]Or another third-generation cephalosporin (e.g., cefotaxime, 2 g q8h IV; or cefixime, 400 mg bid PO). [b]Or 1 g on day 1 followed by 500 mg/d PO for 6 days. [c]Or ofloxacin, 400 mg bid PO for 2–5 days.

Abx: Fluoroquinolones

- Most effective drugs for the treatment of typhoid fever
- Average fever-clearance: 4 days
  - Cure rate: 96%
  - Fecal carriage: <2%
  - Relapse: <2%
- 3 main issues against: potential toxic effects on children, cost, and emergence of resistance
- Usually given for 5-7 days
- Given for at least 10 days in severe typhoid

Abx: Second Choices

- 3rd generation cephalosporins (ceftriaxone, cefixime)
  - Average fever-clearance: 7 days
  - Cure rate: 90-95%
  - Fecal carriage: <3%
  - Relapse: 3-6%
- Azithromycin
  - Average fever-clearance: 4-6 days
  - Cure rate: 95%
  - Fecal carriage: <3%
  - Relapse: <3

Abx for Chronic Carriers

- Cure rates of ~80% with prolonged antibiotics, provided there are no gallstones
- Amoxicillin or ampicillin 100 mg/kg PO + Probenecid x 3 months
- TMP-SMX DS 1 tabs x 3 months
- Ciprofloxacin 750 mg BID x 28 days

Prognosis

- Prognosis among persons with typhoid fever depends primarily on the speed of diagnosis and initiation of correct treatment.
- Generally, untreated typhoid fever carries a mortality rate of 10%-20%. In properly treated disease, the mortality rate is less than 1%.
- An unspecified number of patients experience long-term or permanent complications, including neuropsychiatric symptoms and high rates of gastrointestinal cancers.

Prevention

- Travelers to endemic countries should avoid raw unpeeled fruits or vegetables since they may have been prepared with contaminated water and should not buy food from street vendors; in addition, they should drink only boiled water or bottled water.
- In endemic countries, the most cost-effective strategy for reducing the incidence of typhoid fever is the institution of public health measures to ensure safe drinking water and sanitary disposal of excreta. The effects of these measures are long-term and reduce the incidence of other enteric infections.

Vaccines

Vaccine	Age	Route	Dosage	Revaccination
Vi capsular polysaccharide (Typhim Vi)	2 years	SC or IM	0.5 mL 1 dose >2wks before expected exposure	3 years
Ty21a (Vivotif) Live, attenuated (NOT available)	6 years	Oral	0.5 ml One capsule every other day, total of 3 capsules	5-7 years

Main References

- HPIM 19th edition, Chapter 190.
- Wain J et al. Lancet. 2015;385:1136-45.
- Parry CM et al. NEJM. 2002;347(22):1770-82.
- Bhutta ZA. BMJ. 2006;333:78-82.
- ARSP 2017