Typhoid and paratyphoid fever

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Etiology – *Salmonella* sp.

- Nonencapsulated, G- bacilli, motile – peritrichous flagellae
- O antigens (somatic); H antigens (flagellar): > 2200 serotypes
- *S. typhi* and *S. paratyphi* A and B have no known hosts other than humans (in contrast to other Salmonella serotypes)
- *S. typhi* causes the most severe and *S. paratyphi* B the mildest disease, *S. paratyphi* A and C intermediate
- Most cases of disease result from ingestion of contaminated food or water
- Transmitted through close contact with acutely infected individuals or chronic carriers also – isolation of patients
- Health care workers occasionally acquire enteric fever after exposure to infected patients
- Laboratory workers can acquire the disease after laboratory accidents

Typhoid fever distribution

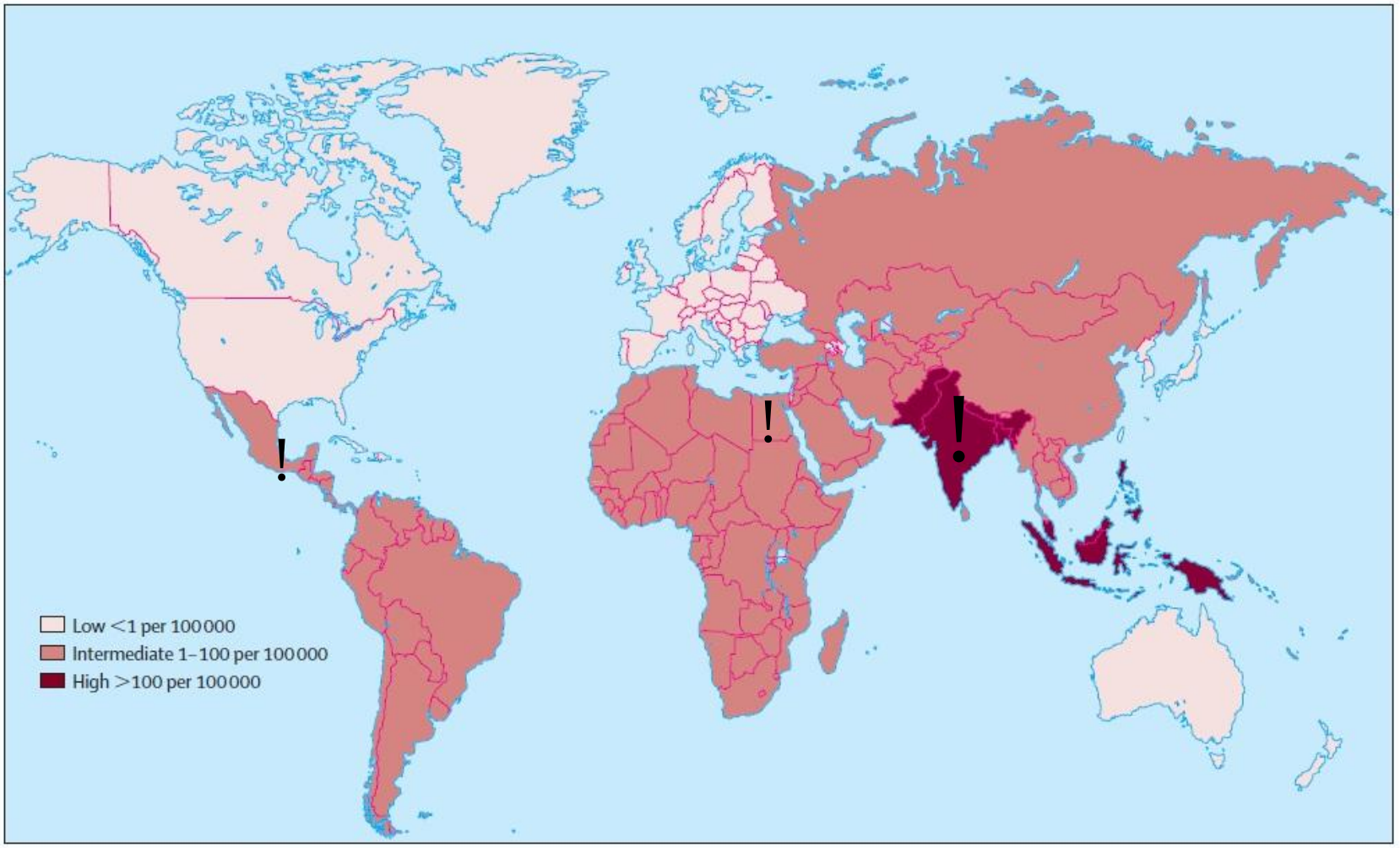


Figure 1: Annual incidence of enteric fever worldwide

Connor BA, Schwartz E, 2005

Epidemiology

- Enteric fever has become a rare occurrence in developed nations (~400 cases of typhoid fever annually in the U.S.)
- Global health problem, with an estimated 13 to 17 million cases worldwide resulting in ~600,000 deaths per year.
- Children <1 year of age appear to be most susceptible to initial infection and to the development of severe disease.
- Enteric fever is endemic in most developing regions, especially the Indian subcontinent, South and Central America, and Asia
- Antibiotic resistance among salmonellae is also a rising concern:
  - plasmids encoding resistance to chloramphenicol, ampicillin, and trimethoprim)
  - resistance to ciprofloxacin (either chromosomally or plasmid encoded - India and Vietnam)

Number of notified cases of the typhoid fever to the CZ (CEM):

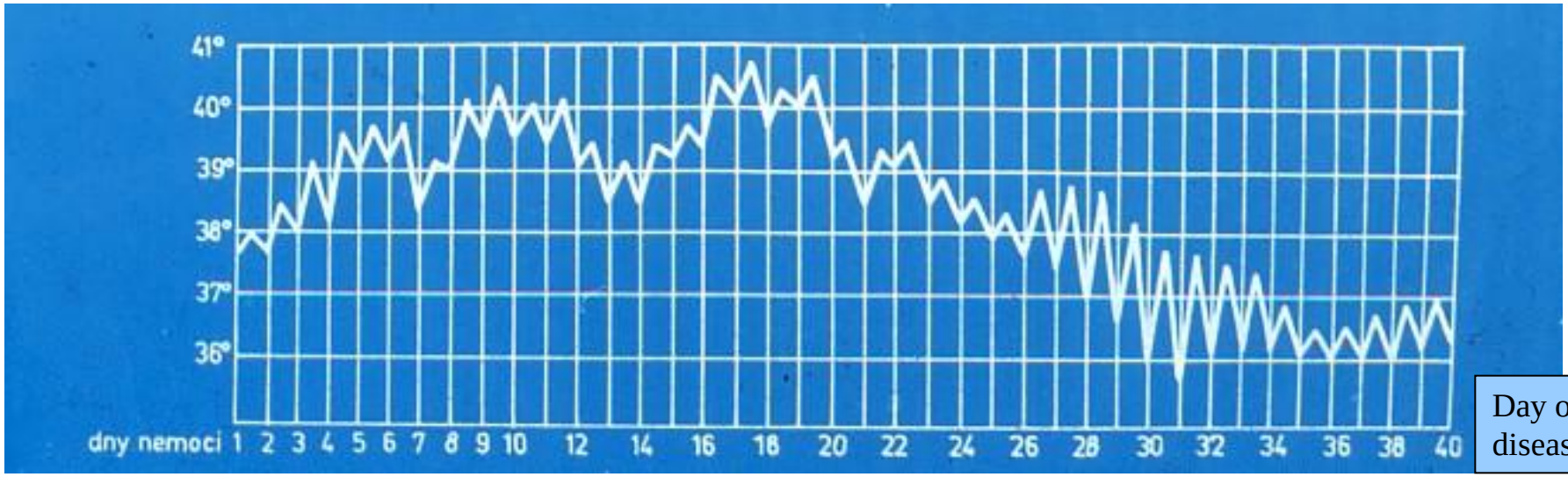
Year	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006
	6	5	5	1	1	0	1	1	2	4	3	6

Clinical manifestations of enteric fever I

- The illness typically lasts 4 weeks:
- 1st week: non-specific features of malaise, headache, rising remitting fever with mild cough, constipation
- 2nd week: patient becomes toxic and apathetic, sustained high fever with relative bradycardia rose spots, distended abdomen, splenomegaly
- 3rd week: increasing toxicity with persistent high temperature, the patient becomes delirious and weak with feeble pulse, tachypnea (+/- basal creps); abdominal distension ↑, bowel sounds↓, profuse pea soup diarrhea; neurological complication and death may accur during week 3 and 4.
- 4th week: if the patient suvives, GI complications may occur; fever, mental state, and abdominal distension improve over a few days

Clinical manifestations of enteric fever II

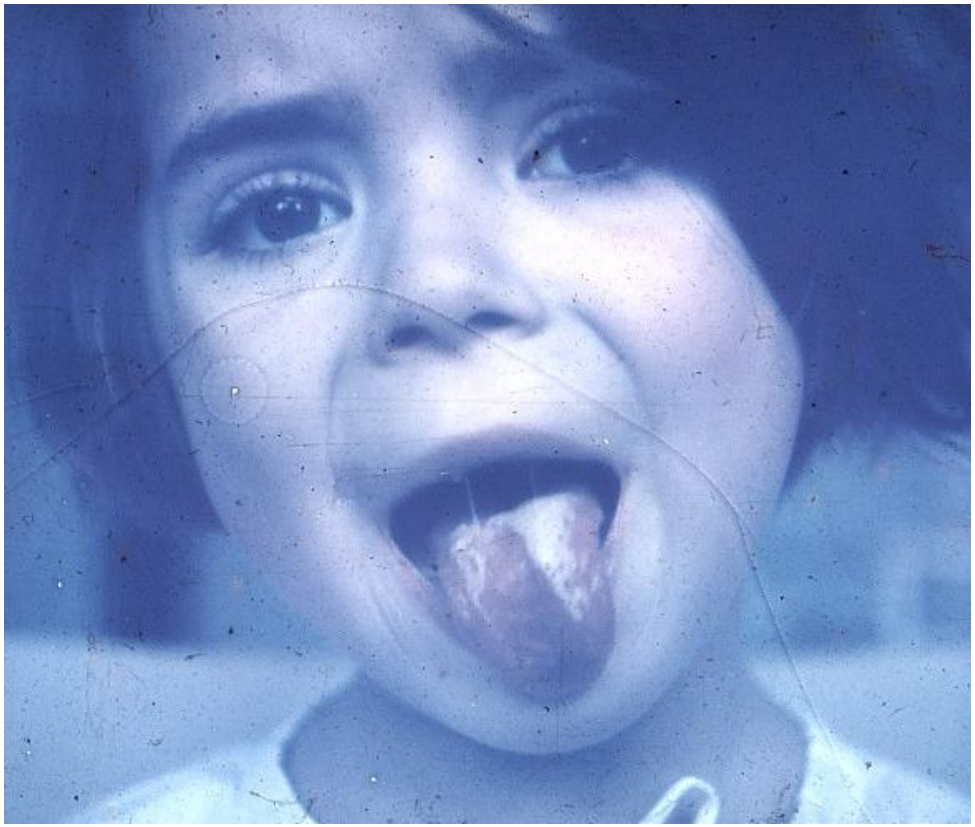
- The incubation period for S. typhi ranges from 3 to 21 days (10 – 20 days) - history of recent travel to a developing country:
  - this variability is most likely related to the size of the initial inoculum and the health and immune status
- A prodrome of nonspecific symptoms often precedes fever and includes chills, headache, anorexia, cough, weakness
- Fever is documented at presentation in more than 75% of cases; prolonged fever (38.8° to 40.5°C, or 101.8° to 104.9°F).



Wunderlich temperature chart – the illness typically lasts 4 weeks

Clinical manifestations of enteric fever III

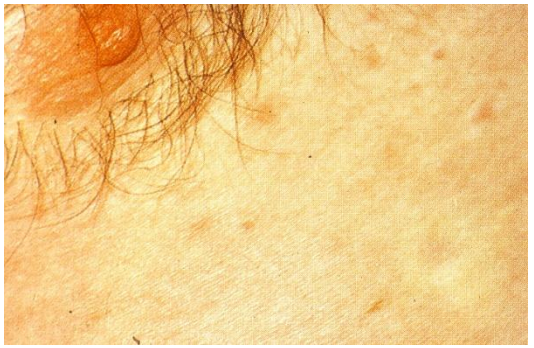
- Gastrointestinal symptoms are quite variable:
  - abdominal pain is reported in only 20 to 40%
  - the majority have abdominal tenderness
  - diarrhea or constipation
    - diarrhea more common among patients with AIDS and children <1 year of age.
- Sore throat, dizziness, and muscle pains



Clinical manifestations of relapsing fever IV

Early physical findings of enteric fever include rash ("rose spots"), hepatosplenomegaly, epistaxis, and relative bradycardia.

- Rose spots make up a faint, salmon-colored, blanching, maculopapular rash (2 – 4 mm) located primarily on the trunk and chest, fading on pressure.
- The rash is evident in ~30-50% of patients at the end of the first week and resolves after 2 to 5 days without leaving a trace.
- Patients can have two or three crops of lesions, and Salmonella can be cultured from punch biopsies of these lesions. The faintness of the rash makes it difficult to detect in dark-skinned patients.



Clinical manifestations of relapsing fever V

- Patients who remain toxic manifest neuropsychiatric symptoms described as a "muttering delirium" or "coma vigil," with picking at bedclothes or imaginary objects
- Late complications, occurring in the third and fourth weeks of infection, are most common in untreated adults and include intestinal perforation and/or gastrointestinal hemorrhage (result from necrosis at the initial site of Salmonella infiltration at the Peyer's patches of the small intestine)
- Both complications are life-threatening and require immediate medical and surgical interventions:
  - broadened antibiotic coverage for polymicrobial peritonitis
  - treatment of gastrointestinal hemorrhages, including bowel resection
- Rare complications include pancreatitis, hepatic and splenic abscesses, endocarditis, pericarditis, orchitis, hepatitis, meningitis, nephritis, myocarditis, pneumonia, arthritis, osteomyelitis, and parotitis
- Despite prompt antibiotic treatment, relapse rates remain at ~10% in immunocompetent hosts
- Approximately 1 to 5% of patients with enteric fever become long-term, asymptomatic, chronic carriers who shed S. typhi in either urine or stool for >1 year
- The incidence of chronic carriage is higher among women and among persons with biliary abnormalities (e.g., gallstones, carcinoma of the gallbladder) and gastrointestinal malignancies

Laboratory manifestations of enteric fever

- Elevated erythrocyte sedimention rate.
- Blood count
  - leukopenia and neutropenia (in 15 to 25% of cases) with monocytosis
  - leukocytosis can develop in typhoid fever (especially in children) during the first 10 days of the illness
  - In the majority of cases, the white blood cell count is normal despite high fever
- Moderately elevated values in liver function tests (aminotransferases, alkaline phosphatase, and lactate dehydrogenase).
- Nonspecific ST and T wave abnormalities can be seen on electrocardiograms

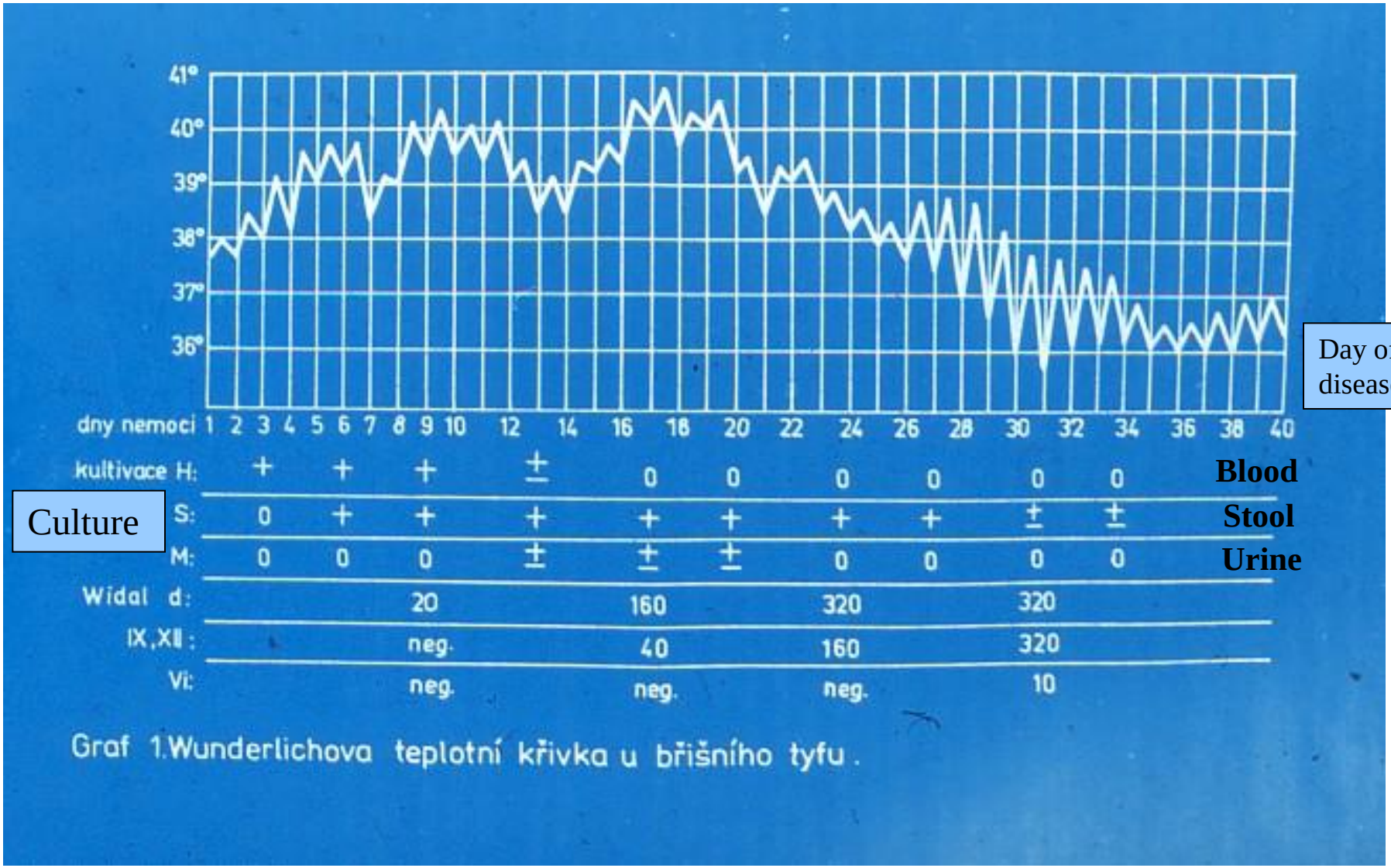
Differential diagnostics of enteric fever

- Malaria
- Rickettsial infections
- Leptospirosis
- Viral hepatitis
- Rat-bite fever
- Dengue
- Ehrlichiosis
- Acute HIV infection
- Bacterial enteritis
- Amebic liver abscess

Laboratory diagnostics of enteric fever I

- Febrile traveler returning from a developing country, especially the Indian subcontinent, the Philippines, or Latin America
- The diagnostic “gold standard” is a culture positive for S. typhi or S. paratyphi.
  - The yield of blood cultures is variable: it can be as high as 90% during the first week of infection and decrease to 50% by the third week.
  - Centrifugation to isolate and culture the buffy coat, which contains abundant blood mononuclear cells associated with the bacteria.
  - Stool: while negative in 60 to 70% of cases during the first week, can become positive during the third week of infection in untreated patients.
  - Urine,
  - Rose spots
  - Bone marrow: highly (90%) sensitive despite ≤5 days of antibiotic therapy
- If blood, bone marrow, and intestinal secretions are all cultured, the yield of a positive culture is >90%.
- Polymerase chain reaction and DNA probe assays are being developed.
- The majority of patients (90%) clear bacteria from the stool by the eighth week, some become chronic carriers and continue to have positive stool cultures for at least 1 year.

Laboratory diagnostics of enteric fever II



Day of disease

Culture

Blood

Stool

Urine

Laboratory diagnostics of enteric fever III

- Several serologic tests, including the classic Widal test for “febrile agglutinins,” are available; however, given high rates of false-positivity and false-negativity, these tests are not clinically very useful.

Treatment

- In the preantibiotic era, the mortality rate from typhoid fever was 15%.
- The introduction of treatment with chloramphenicol in 1948 greatly altered the disease course, decreasing mortality to <1% and the duration of fever from 14–28 days to 3–5 days. Chloramphenicol remained the standard treatment for enteric fever until the emergence of plasmid-mediated resistance in the 1970s.
- Resistance to chloramphenicol and the rare chloramphenicol-induced bone marrow toxicity → ampicillin (1 g orally every 6 h) and trimethoprim-sulfamethoxazole (TMP-SMX; one double-strength tablet twice daily) became the mainstays of treatment.
- In 1989, MDR *S. typhi* emerged. These bacteria are resistant to chloramphenicol, ampicillin, trimethoprim, streptomycin, sulfonamides, and tetracycline. Like chloramphenicol resistance, resistance to ampicillin and trimethoprim is plasmid-encoded
  - In 1994, 12% of S. typhi isolates in the United States were MDR.
- Either quinolones or third-generation cephalosporins are currently recommended for empirical antibiotic treatment
  - Despite efficient in vitro killing of Salmonella, first- and second-generation cephalosporins and aminoglycosides are ineffective in treating clinical infections

Treatment

First-line	
Ciprofloxacin	500 mg PO bid for 10 days
Ceftriaxone	1–2 g IV or IM for 10–14 days
Alternative (NARST)	
Azithromycin	1 g PO daily for 5 days
Ciprofloxacin	10 mg/kg PO bid for 10 days

NARST: Nalidixic acid—resistant *S. typhi*.

Treatment II

- Quinolones are the only available oral antibiotics for the treatment of MDR S. typhi infections:
  - ciprofloxacin (500 mg orally twice a day for 10 days)
  - ofloxacin (10 to 15 mg/kg in divided doses twice daily for 2 to 3 days)

- Ceftriaxone (1 to 2 g intravenously or intramuscularly) for 10 to 14 days is equivalent to oral or intravenous chloramphenicol in the treatment of susceptible strains.

- In cases of severe typhoid fever (fever; an abnormal state of consciousness—i.e., delirium, obtundation, stupor, or coma—or septic shock; and a positive culture for S. typhi or S. paratyphi A), dexamethasone treatment should be considered:

- The 1 to 4% of patients who develop chronic carriage of Salmonella can be treated for 6 weeks with an appropriate antibiotic. Treatment with oral amoxicillin, TMP-SMX, ciprofloxacin, or norfloxacin has been shown to be ~80% effective in eradicating chronic carriage of susceptible organisms.

- In cases of anatomical abnormality (e.g., biliary or kidney stones), eradication of the infection often cannot be achieved by antibiotic therapy alone and requires surgical correction of the abnormalities.

TYPHOID FEVER VACCINES

- Whole-cell inactivated parenteral vaccines are not more used – severe side effects, low effectivity
- TYPHIM Vi (Aventis), TYPHERIX (SKB)
  - Inactivated polysacharide vaccine *S.typhi* Ty2; for persons older than 2 years
  - 1 dose, 0.5 ml i.m. or deep s.c. application, effective 1 - 2 weeks after vaccination
  - Immunity for 2 – 3 years (protection 60 - 80 %); booster after 3 years (at high risc after 1-2 years)
  - Well tolerated, around 1 % of side effects
- VIVOTIF (Berna), TYPHORAL L (Chiron)
  - Oral live attenuoated vaccine *S.typhi* Ty21a
  - 3-4 capseln every other day 1 hour before meal; liquid form for childern of 2 – 6 years
  - Effective 7 days after last dose
  - Immunity last for 1 - 3 years; (5 years after 4 doses)
  - Do not combine with mefloquine, antibiotics, chemotherapeutics

TYPHOID FEVER IMPORTED TO THE EUROPE

- TRENDS: Decreased number of imported cases to the Europe:
  - Indian subcontinent dominates
  - Decrease of cases from northern Africa and Peru
- Vaccination has 60-80% effectivity

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