TYPHOID FEVER

THOSE WHO FORGOT THE PAST ARE CONDEMNED TO REPEAT IT
Background

• Typhoid fever is caused by Salmonella typhi and serotypes paratyphi A, B & C
• Challenging to diagnose due to its variable manifestations
• Incidence of 540 cases / 100,000 population in developing countries
• In developed countries, proper sanitation has successfully diminished this infection
Here We Are!

Map showing the geographic distribution of typhoid. The map highlights regions with a high, medium, or low incidence of typhoid. The area of interest is circled and labeled as 'Here We Are!'
Typhoid Outbreak in Kelantan (2005)

“From April to June 2015, there were 735 cases of typhoid & 2 deaths.”

Typhoid Mary

"Typhoid Mary"

The Extraordinary Predicament of Mary Mallon, a Prisoner on New York's Quarantine Island.

By Dr. Wm. H. Park, New York Board of Health.
• Mary Mallon, a cook identified as an asymptomatic carrier of typhoid, infected 51 people (3 of whom died)

• 2X forcibly isolated by public health authorities

• Died after a total of nearly 30 years in isolation
The Culprit
Salmonella typhi

- Rod-shaped, flagellated, aerobic, Gram –ve bacterium
- Name is derived from ancient Greek “typhos” - an ethereal smoke that was believed to cause disease & madness
- Thrives in areas of poor sanitation, crowding & social chaos
- Salmonella paratyphi causes the same disease, but is a relatively newcomer.
Pathophysiology

1. S. typhi & paratyphi have specialised fimbriae which adhere to epithelium over clusters of lymphoid tissue in the ileum (Peyer patches)

2. They co-opt the macrophages’ cellular machinery for their own reproduction

3. They are then carried through mesenteric lymph nodes -> thoracic duct -> lymphatics -> reticuloendothelial tissues (liver, spleen, bone marrow)
4. Once there, they continue to multiply until some critical density is reached -> induced macrophage apoptosis, breaking out into bloodstream -> invade the rest of body

5. Bacteria then infect gallbladder -> reenters GI tract in the bile -> reinfect Peyer patches

6. Some would be shed in stool & are available to infect other hosts

7. S. typhi has Vi capsular antigen that masks PAMPs* avoiding neutrophil-based inflammation, while S. paratyphi does not – the reason for greater infectivity of typhi as compared to paratyphi (ratio 10:1)

*pathogen-associated molecular patterns
Salmonella typhi

**Ingestion**

*S. typhi* passes through and between epithelial cells lining the ileocecal area

**Intraluminal multiplication**

Remains viable after engulfment by macrophage

**Mononuclear cell response**

Intracellular multiplication continues in the cells of reticuloendothelial system

**Hyperplastic changes in mesenteric lymphoid tissue**

Clinical signs of sepsis

**Necrosis**

**Hemorrhage**

**Perforation of intestinal wall**

Reenters bowel (liver to gall bladder to intestine) found in stool specimens
Modes of Transmission

• Oral transmission via food handled by asymptomatic carriers
• Hand-to-mouth transmission after using contaminated toilet & neglecting hand hygiene
• Oral transmission via sewage-contaminated water or shellfish (especially in developing world)
Various ways that typhoid bacteria can contaminate a water well (illustration from 1939)
Fimbriae of S. typhi bind to cystic fibrosis transmembrane regulator (CFTR) on gut membrane.

**Mutation** in CFTR leads to decreased susceptibility to typhoid fever.

Therefore, it is believed that typhoid fever may have contributed to the **evolutionary pressure** that maintains a steady occurrence of cystic fibrosis in the White population. *(Just like malaria maintains sickle cell disease in Africa)*
Presentation...
Severe non-specific febrile illness following exposure to typhoidal salmonella should always raise diagnostic possibility of typhoid fever.
Classic Typhoid Fever Syndrome

• Fever begins 1-2 weeks after ingestion of organism
• Fever pattern:
  – Stepwise
  – Rising T° over the course of the day which drops by subsequent morning
  – Peaks and troughs rise progressively over time
• 1st week of illness
  – GI manifestations: diffuse abdominal pain, tenderness
  – Inflamed Peyer patches narrow bowel lumen -> constipation
  – Dry cough, frontal headache, delirium, malaise
Pattern of Fever

The fever goes up a little each day.
Bull Market
– At the end of 1st week of illness, fever plateaus at 39-40°C and rose spots develops

– Rose spots are caused by bacterial emboli to dermis
  • Salmon-coloured
  • Blanching
  • Truncal
  • Maculopapules (1-4cm wide, < 5 in numbers)
  • Resolves within 2-5 days
• **2nd week of illness**
  – GI signs and symptoms progress
  – Abdomen distended, soft splenomegaly
  – Relative bradycardia
  – Dicrotic pulse
    • double beats
    • the second beat weaker than the first
• **3rd week of illness**
  – Significant weight loss
  – Tachypnoiec with thready pulse and crackles bibasally
  – Pea-soup diarrhoea (foul, green-yellow)
  – Typhoid state: apathy, confusion & psychosis
  – Necrotic Peyer patches -> bowel perforation & peritonitis
  – At this point, overwhelming toxaemia, myocarditis, intestinal haemorrhage may cause death
  – Some survivors become asymptomatic carriers & have the potential to transmit bacteria indefinitely
Various Presentations

• Clinical course may deviate from the classic description of typhoid fever
• Immunocompromised children may develop diarrhoea instead of constipation
• Atypical manifestations:
  – Isolated severe headaches
  – Acute lobar pneumonia
  – Isolated arthralgias
  – Urinary symptoms
  – Severe jaundice
  – Fever alone
Treated Typhoid Fever

If appropriate treatment is initiated within 1st few days of full-blown illness, disease begins to remit after about 2 days and markedly improve within 4-5 days.
Investigations

1. FBC
2. Urea & electrolytes
3. LFT
4. ESR
5. Blood C&S
6. Urine FEME
7. Urine C&S
8. Stool C&S
Culture

- Criterion standard for diagnosis is culture isolation of organism (100% specific)
- Bone marrow aspirate culture is 90% sensitive until at least 5 days after commencement of abx
  - This technique is painful, which may outweigh its benefits
- Blood, intestinal secretions (vomitus or duodenal aspirate), stool culture are positive in 85-90% of patients within 1st week of onset
- Multiple blood cultures (>3) yield a sensitivity of 73-97%
- Stool culture alone yields a sensitivity of < 50%
More on Culture....

- Reasons of failure to isolate the organism:
  - Presence of abx
  - Volume of specimen cultured
    - to achieve optimal isolation rate: 2-4ml from toddlers & preschool children; 10-15ml from schoolchildren & adults
  - Timing of collection
    - h/o 7-10 days of fever being more likely to have a +ve blood culture
## Sensitivities of Culture

<table>
<thead>
<tr>
<th>Sample Type</th>
<th>Incubation</th>
<th>Week 1</th>
<th>Week 2</th>
<th>Week 3</th>
<th>Week 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone marrow aspirate (0.5-1 mL)</td>
<td>90% (may decrease after 5 d of antibiotics)</td>
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<tr>
<td>Blood (10-30 mL), stool, or duodenal aspirate culture</td>
<td>40%-80%</td>
<td>~20%</td>
<td>Variable (20%-60%)</td>
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<tr>
<td>Urine</td>
<td>25%-30%, timing unpredictable</td>
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</tbody>
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Other Serological Tests

- Elevated ESR
- Anaemia, thrombocytopenia, neutropenia
- Liver transaminase & serum bilirubin rise to 2X the reference range
- Ratio of serum ALT to LDH of < 9:1 supports typhoid hepatitis rather than viral hepatitis
- Typhidot-M test uses 50kDa antigen to detect specific IgM & IgG antibodies to S. typhi
  - Speedy (takes 3 hours)
  - Specificity (73%)
  - Sensitivity (95%)
  - High negative predictive value (useful in endemic areas)
Management

• Supportive:
  – Oral or iv hydration
  – Antipyretics

• Patients with persistent vomiting, severe diarrhoea, abdominal distension would require hospitalisation & parenteral abx therapy
<table>
<thead>
<tr>
<th>Infection/Condition &amp; Likely Organism</th>
<th>Suggested Treatment</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. Typhoid Fever</strong></td>
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<td></td>
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<tr>
<td><em>Salmonella Typhi</em></td>
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<tr>
<td>Stable Case</td>
<td></td>
<td></td>
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<tr>
<td>Fully sensitive</td>
<td></td>
<td></td>
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<tr>
<td><strong>1st line if admitted to hospital</strong></td>
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<tr>
<td>Pefloxacin 400mg PO q12h for 5-7 days</td>
<td>Alternative</td>
<td>Fever clearance is faster with Quinolones</td>
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<tr>
<td>OR</td>
<td></td>
<td>Reference: WHO, 2003</td>
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<tr>
<td>OR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ofloxacin 400mg PO q12h for 5-7 days</td>
<td>Alternative</td>
<td></td>
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<tr>
<td>OR</td>
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<tr>
<td>Trimethoprim/ Sulfamethoxazole 160/800mg PO q12h for 14 days</td>
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<tr>
<td>Ceftriaxone 60mg/kg/day for 10-14 days</td>
<td>Preferred</td>
<td>Reference: WHO, 2003</td>
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<td>OR</td>
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<tr>
<td>Ciprofloxacin 400mg IV q12h for 10-14 days</td>
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<tr>
<td>Azithromycin 500mg PO q24h for 7 days</td>
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<tr>
<td>Quinolone resistance</td>
<td>Ceftriaxone 60mg/kg/day for 10-14 days</td>
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<tr>
<td>Unstable or complicated cases</td>
<td>Ceftriaxone 60mg/kg/day for 10-14 days</td>
<td>Indication of dexamethasone: (discuss with physician)</td>
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<td></td>
<td>OR</td>
<td>i) Typhoid psychosis</td>
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<tr>
<td></td>
<td>OR</td>
<td>ii) Septic shock</td>
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<tr>
<td></td>
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<td>Dose: 3mg/kg loading, then 1mg/kg q6h for 2 days</td>
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</tbody>
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From “National Antibiotic Guideline 2014”
On the Use of Dexamethasone...

“Dexamethasone may decrease mortality in severe typhoid fever cases complicated by delirium, obtundation, stupor, coma or shock.”

Stool Clearance

- A case may be released from supervision only after 3 consecutive negative stool specimens are submitted; these specimens should be collected at least 24 hours apart, at least 48 hours after discontinuation of antibiotics, and at least 1 month after onset of illness.

- If any of the clearance specimens are positive, at least 3 consecutive negative stool specimens at one-month intervals within the 12 months following onset shall be required for release from supervision.

- If a person continues to excrete S. Typhi at 12 months, he/she should be considered a chronic carrier of S. Typhi and followed as such.

Source: WHO Guidelines for Management of Typhoid Fever, July 2011
Management of Carriers

- Amoxicillin or ampicillin (100mg/kg/day) plus probenecid (1g orally or 23mg/kg for children)
- Should be excluded from food preparation and serving
- Food handlers should not resume duties until 3 negative stool cultures at least one month apart
# Vaccines

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Indication/Dose</th>
<th>Contraindication</th>
<th>Possible Side Effects</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typhoid (Typhim Vi)</td>
<td>Single dose. Seroconversion in 85-95% of recipients; confers 60-80% protection beginning 2 wks after vaccination. Boosters every 3 yrs.</td>
<td>Children &lt; 2yrs. (Immunogenicity &lt; 2 yrs of age has not been established)</td>
<td>Local reactions. Myalgia, malaise, nausea, headaches and fever in 3% of recipients.</td>
<td>Intramuscular. Polysaccharide vaccine</td>
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A Notifiable Disease

(2) Every medical practitioner who treats or becomes aware of the existence of any infectious disease in any premises shall, with the least practicable delay, give notice of the existence of the infectious disease to the nearest Medical Officer of Health in the form prescribed by regulations made under this Act.

Typhoid and paratyphoid fever are listed under first schedule [Section 2, Part 1] of Prevention and Control of Infectious Diseases Act 1988
Prevention

1. Safe water
2. Food safety
3. Sanitation
4. Health education
5. Vaccination
Take Home Messages

• Typhoid fever can have variable manifestations

• Late treatment can lead to serious complications and even death (mortality rate 10-20%)

• It is a notifiable disease by law

• Prevention of the infection is possible as demonstrated by developed countries
References