Shigella Pathogenesis

Prof WWMaw
Pathogenesis & Pathology of Dysentery

Causal organisms

• *S. dysenteriae* (13 serotypes)
• *S. flexneri* (6 serotypes)
• *S. boydii* (18 serotypes)
• *S. sonnei*
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Causal organisms

• *S. dysenteriae*, *S. flexneri* and *S. boydii* cause severe infection

Reservoir

• Humans are only reservoir for these bacteria
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MOT

• Disease spread person to person by **fecal-oral route** (by “food, fingers, faeces, and flies”)
• less commonly in **water**
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Infective dose

• As few as 100 to 200 bacteria can establish disease

• highly infectious whereas it usually is $10^5$-$10^8$ for salmonellae and vibrios
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- Infections are almost always limited to the gastrointestinal tract
- invading and replicating in cells lining the colon
- Bloodstream invasion is quite rare
Pathogenesis

• CO; fecal-oral Route

1 Lipopolysaccharide - the irritation of the bowel wall.

2 Enterotoxins - ShET1 and ShET2 (80% of shigellae) - an early non-bloody, voluminous diarrhea and the

3 invasion of the large intestine - later dysentery with blood and pus in stools.
  • Invasion (M, Map)

A. induced phagocytosis ➔ type III secretion system ➔ IpaA, IpaB, IpaC, IpaD
membrane ruffling ➔ escape from the phagocytic vacuole ➔ multiply
spread within the epithelial cell cytoplasm, and ➔ passage to adjacent
cells.

B. inducing programmed cell death (apoptosis)

C. release of IL-1β, resulting in the attraction of polymorphonuclear leukocytes
into the infected tissues ➔
  • destabilizes the integrity of the intestinal wall and allows the bacteria to
reach the deeper epithelial cells.
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• First
• Upon autolysis,
• all shigellae release their toxic lipopolysaccharide
• the irritation of the bowel wall
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• Second
• Enterotoxins –
• ShET1 and ShET2 (80% of shigellae)
• produce an early non-bloody, voluminous diarrhea and
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• third
• the invasion of the large intestine result in

• later dysentery with blood and pus in stools
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- Shigellae invade the mucosal epithelial cells (e.g. M cells)
- by induced phagocytosis

- The type III secretion system mediates secretion of four proteins (IpaA, IpaB, IpaC, IpaD) into epithelial cells and macrophages
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- These proteins induce membrane ruffling on the target cell (M, Map), leading to engulfment of the bacteria
Contactin
Rho, cdc42
talin, vinculin
plastin
IL-8
Polymorphonuclear Leucocytes

MACROPHAGE APOPTOSIS
IpaB / Caspase 1
- BACTERIAL RELEASE
- INFLAMMATION (IL-1 β)
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- Shigellae escape from the phagocytic vacuole,
- multiplication and
- spread within the epithelial cell cytoplasm and
- passage to adjacent cells
Pathogenesis & pathology of dysentery

• Shigellae *survive phagocytosis* by
• inducing programmed cell death (apoptosis)

• This process also *leads to the release of IL-1β*,

• resulting in the attraction of polymorphonuclear leukocytes into the infected tissues
Pathogenesis & pathology of dysentery

• This in turn destabilizes the integrity of the intestinal wall and

• allows the bacteria to reach the deeper epithelial cells
Pathogenesis & pathology of dysentery

- Microabscesses in the wall of
- the large intestine and terminal ileum
  - lead to necrosis of the mucous membrane,
  - superficial ulceration,
  - bleeding and
  - formation of a "pseudomembrane" on the ulcerated area in the wall of the large intestine and terminal ileum
Pathogenesis & pathology of haemorrhagic colitis

- *S. dysenteriae* strains produce an exotoxin, Shiga toxin
- has one A subunit and five B subunits

- E coli - VT
Pathogenesis & pathology of haemorrhagic colitis

- The B subunits

- bind to a host cell glycolipid (GB3) and

- facilitate transfer of the A subunit into the cell
Pathogenesis & pathology of haemorrhagic colitis

• The A subunit
• cleaves the 28S rRNA in the 60S ribosomal subunit,

• thereby preventing the binding of aminoacyl-transfer RNA and

• disrupting protein synthesis
Pathogenesis & pathology of haemorrhagic colitis

• The primary manifestation of toxin activity is damage to the intestinal epithelium
• (Haemorrhagic colitis)
Pathogenesis & pathology of haemolytic uraemic syndrome (HUS)

- However, in a small subset of patients, the Shiga
- toxin can mediate damage to the glomerular endothelial cells,
- resulting in renal failure (HUS)
Pathogenesis & pathology of haemolytic uraemic syndrome (HUS)

- During pathogenesis, **the release of the inflammatory mediators** tumour necrosis factor (TNF) and interleukin -1 (IL-1)

• **increase the number of Gb3 receptors on the surface of eukaryotic cells,**

• **increasing the binding of toxin to these cells**
Pathogenesis & pathology of haemolytic uraemic syndrome (HUS)

• Shiga toxin has also been shown to have neurotoxic properties
Figure 1. Invasion of submucosa by trophozoites. The lesion spreads out laterally, creating the flask-shaped amebic ulcer. (Histopathology, UFPA, Araújo R.).
Pathology of Amebiasis
Clinical findings of dysentery

- Short incubation period (1-2 days)
  - A sudden onset of
  - abdominal pain,
  - fever, and
  - watery diarrhea
- A day or so later, as the infection involves the ileum and colon
Clinical findings of dysentery

• The number of stools increases (>10 times)
• They are less liquid but often contain mucus and blood
Clinical findings of dysentery

• Each bowel movement is accompanied by

• straining and tenesmus (rectal spasms),

• with resulting lower abdominal pain

• In more than half of adult cases,

  fever and diarrhea subside spontaneously in 2-5 days
Clinical findings of dysentery

• However, in children and the elderly,

• loss of water and electrolytes may lead to

• dehydration, acidosis and even death
Clinical findings of dysentery

• The illness due to *S. dysenteriae* may be particularly severe

• On recovery,
• most persons *shed* dysentery bacilli for *only a short period*,
• but a *few remain chronic intestinal carriers* and may have *recurrent bouts of the disease*
Clinical findings of dysentery

• Upon recovery from the infection, most persons
devlop circulating antibodies to shigellae,

• but these do not protect against re-infection
Clinical findings of haemorrhagic colitis

• Bloody diarrhoea
Clinical findings HUS

- The condition, with its triad of:
  - haemolytic anaemia
  - thrombocytopenia
  - acute renal failure
Pathogenesis

- CO; fecal-oral Route
1. **Lipopolysaccharide** - the irritation of the bowel wall.
2. **Enterotoxins** - ShET1 and ShET2 (80% of shigellae) - an early non-bloody, voluminous diarrhea and the
3. **invasion of the large intestine** - later dysentery with blood and pus in stools.
   - Invasion (M, Map)
   - A. **induced phagocytosis**
     - membrane ruffling → escape from the phagocytic vacuole, multiply
     - type III secretion system → passage to adjacent cells
     - IpaA, IpaB, IpaC, IpaD

B. **inducing programmed cell death** (apoptosis)
C. **release of IL-1β**, resulting in the attraction of polymorphonuclear leukocytes into the infected tissues
   - destablizes the integrity of the intestinal wall and allows the bacteria to reach the deeper epithelial cells

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Prof WWM
$Shigella$

actin tail

Host cell
• Microabscesses in the wall of the large intestine and terminal ileum

• lead to necrosis of the mucous membrane,

• superficial ulceration,

• bleeding, and

• formation of a "pseudomembrane" on the ulcerated area in the wall of the large intestine and terminal ileum.
1. Shigella enters an epithelial cell.

2. Shigella multiplies inside the cell.

3. Shigella invades neighboring epithelial cells, thus avoiding immune defenses.

4. An abscess forms as epithelial cells are killed by the infection. The bacteria rarely spread in the bloodstream.