Life Science & BT Pre PhD Course Work 2022

Paper I- Advance Theory

Chhatrapati Shahu Ji Maharaj University Kanpur

Enteric Infections: Cross Talk between pathogen and intestinal epithelium and how it modulate host function for its survival

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Microbial Technology

- Host Microbe Interactions
- General Secretion systems bacteria employ for pathogenesis, Diversity observed in secretion systems
- Mechanisms of survival of *Mycobacterium*
- Enteric Infections: Cross Talk between pathogen and intestinal epithelium and how it modulate host function for its survival

Enteric disease

- Definition of **enteric disease** would include:

"≥3 or more unformed stools per day and any documented intestinal infection associated with disrupted intestinal absorptive and/or barrier function. This may impair growth in young children or cognitive function".

- An **enteric pathogen** may be classified as any microbe that is able to cause enteric "disease" as defined above.
- Microbial pathogenesis can involve direct invasion, signals triggering host inflammation or other changes, or secreted factors that damage the host directly (e.g., toxins), indirectly (e.g., microbial competition), and/or by exploiting other environmental host-associated factors to thrive.

Kolling G, Wu M, Guerrant RL. Enteric pathogens through life stages. Front Cell Infect Microbiol. 2012 Aug 25;2:114. doi: 10.3389/fcimb.2012.00114.

Terms used to describe GIT infections

- **Gastroenteritis**: a syndrome characterized by gastrointestinal symptoms including nausea, vomiting, diarrhea and abdominal discomfort
- **Diarrhoea:** Abnormal fecal discharge characterized by frequent stool/fluid; usually resulting from disease of small intestine, involves increased fluid and electrolyte loss
- **Dysentery**: an inflammatory disorder of GIT often associated with blood and pus in feces accompanied by symptoms of pain, abdominal cramps, usually disease of large intestine (colon)

- **Enterocolitis**: inflammation involving both small and large intestine

Enteric Pathogens

- Viruses: Rotavirus, Norovirus, Adenovirus, Torovirus, Corona virus, Astrovirus
- Bacteria: *Enteropathogenic E. coli, Shigella dysenteriae, Salmonella typhi, Vibrio cholerae, Campylobacter jejuni, Yersinia enterocolitica, Clostridium difficile*
- Food poisoning: *S. aureus, Bacillis*
- Protozoa: *Giardia lamblia, Entamoeba histolytica, crystosporidium parvum*,

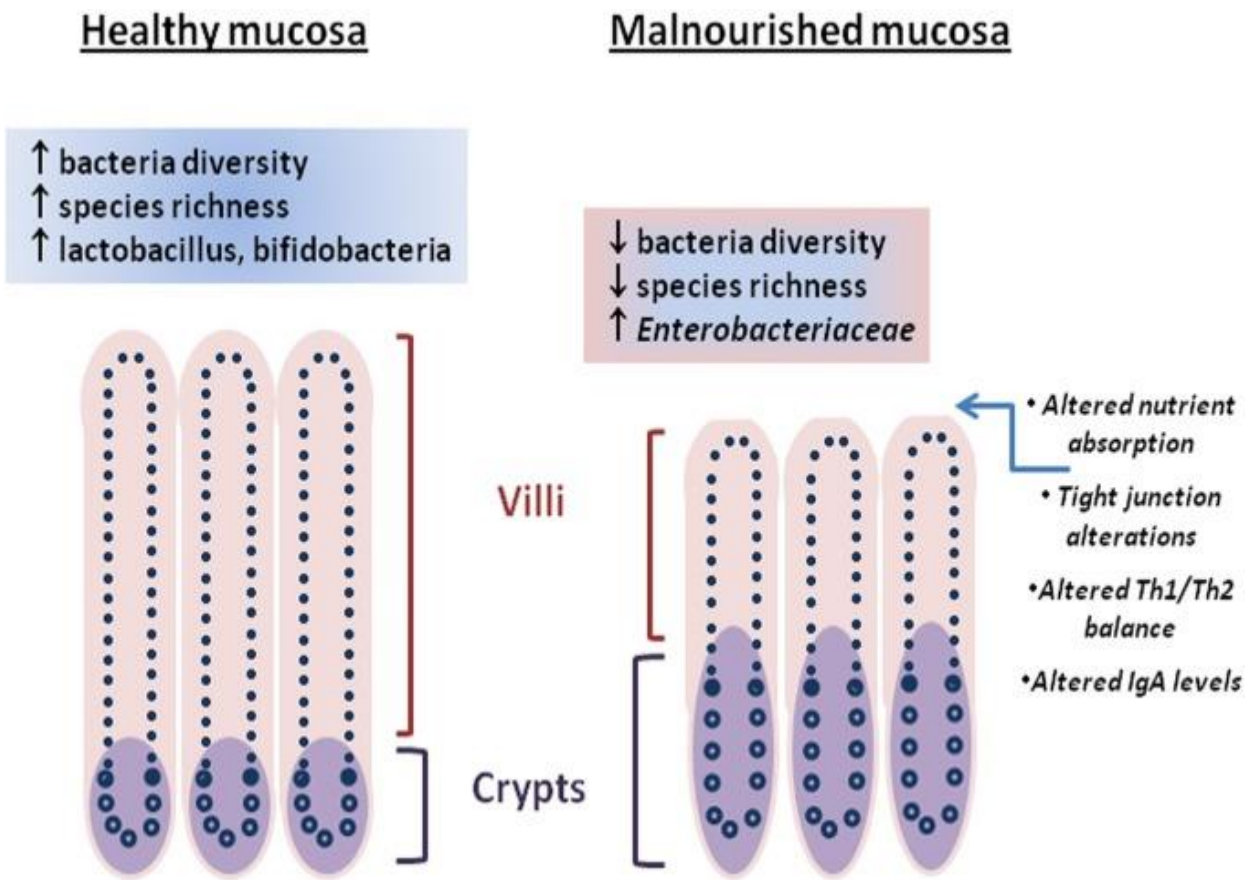
Enteric bacterial Pathogens

CLINICAL FEATURES OF BACTERIAL DIARRHEAL DISEASE						
pathogen	incubation period	duration	symptoms			
			diarrhea	vomiting	abdominal cramps	fever
Salmonella	6h–2 days	48h–7 days	++	+	–	+
Campylobacter	2–11 days	3 days–3 weeks	+++	–	++	++
Shigella	1–4 days	2–3 days	++/+++	–	+	+
Vibrio cholerae	2–3 days	up to 7 days	++++	+	–	–
Vibrio parahaemolyticus	8h–2 days	3 days	+/++	+	+	+
Clostridium perfringens	8h–1 day	12h–1 day	++	–	++	–
Bacillus cereus diarrheal emetic	8h–12h 15min–4h	12h–1 day 12h–2 days	++ +	– ++	++	–
Yersinia enterocolitica	4–7 days	1–2 weeks	++	–	++	+

https://www.uib.cat/depart/dba/microbiologia/ADSenfcomI/material_archivos/infeccion%20gastrointestinal.pdf

Intestinal Mucosa

- Differences between “healthy” and malnourished intestinal mucosa are represented by architectural changes (villi height/crypt depth, crypt hypertrophy), molecular changes (tight junction alteration, nutrient absorption), immune changes, and the intestinal microbiota.



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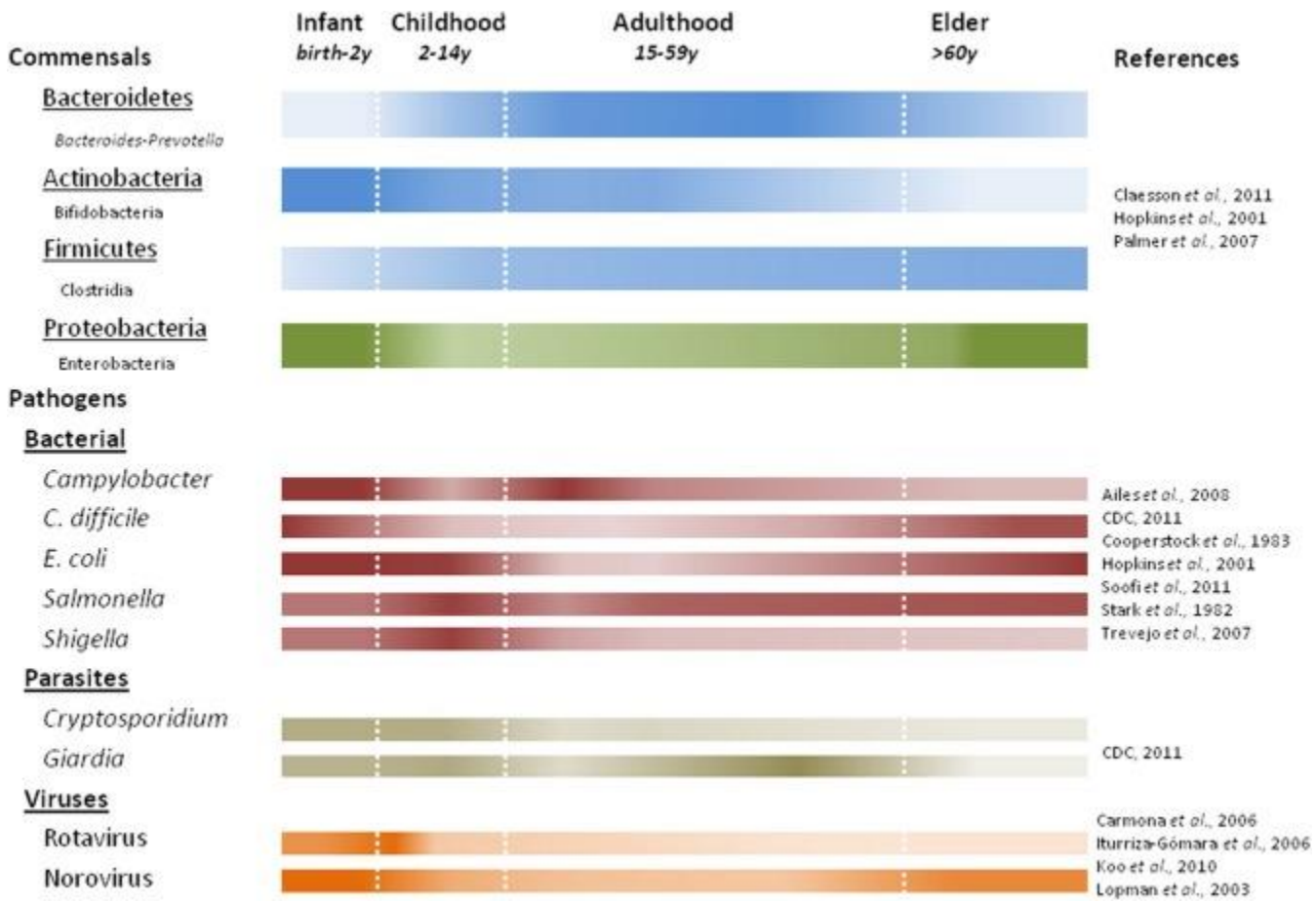
- **Predominant commensal and pathogenic microbes associated with human life stages.**
- Color intensity of each bar correlates with presence or absence of commensal bacteria at the phylum (underlined) with examples listed below using noted references. Studies characterizing fecal microbiota prior to 2007 quantify the viable counts of bacteria, while later studies use DNA based methods.



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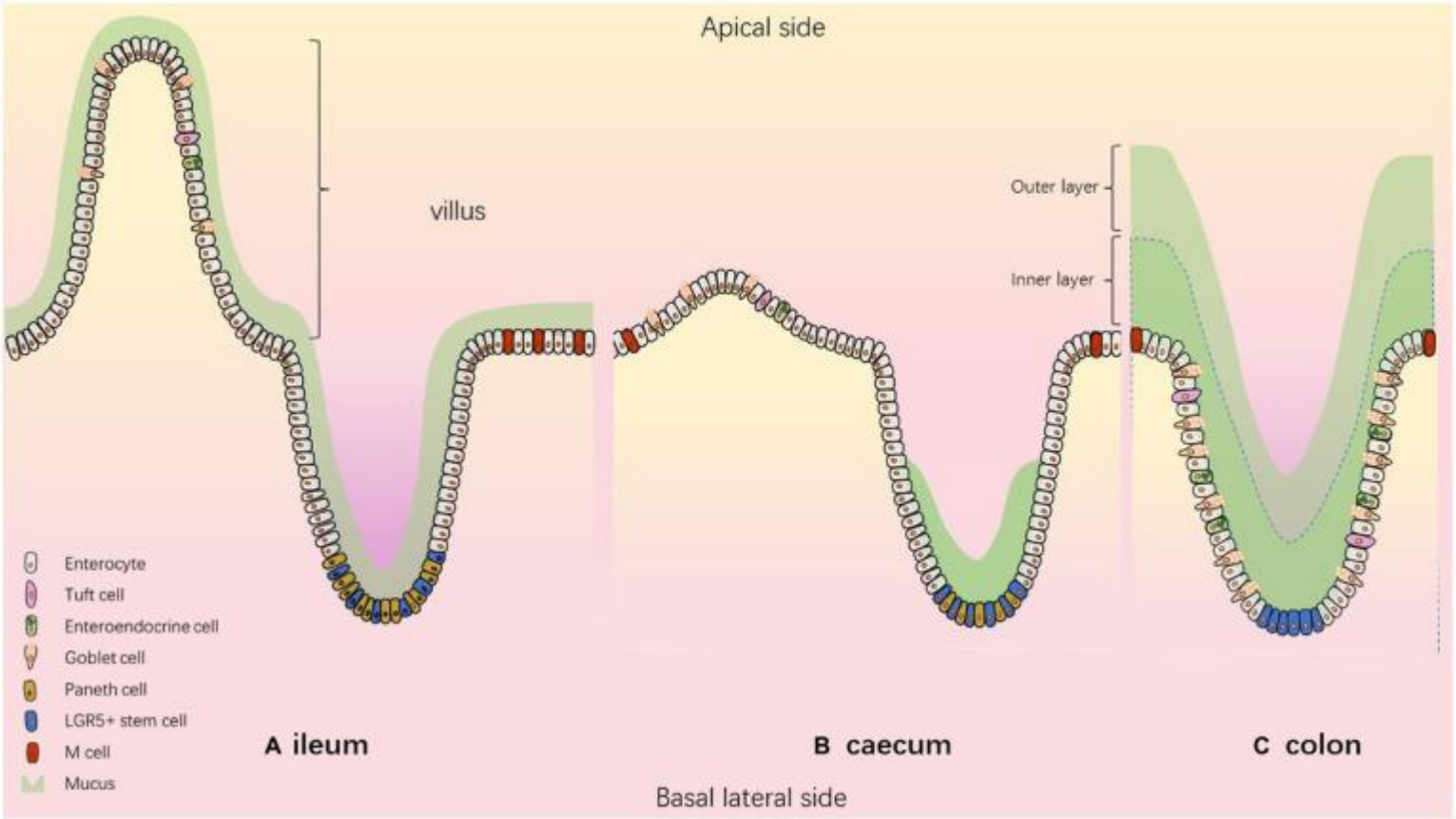
Enteric pathogens and Diseases

Organism	Disease	Mechanism
Shigella species	Shigellosis (bacillary dysentery)	Invasion of the large intestine
Non typhoidal Salmonella ssp	Salmonellosis/ Diarrhea	Invasion of the small intestine
Yersinia enterocolitica	Diarrhea	Invasion of the small intestine
Campylobacter jejuni	Diarrhea	Invasion of the small intestine
Escherichia coli	Diarrhea	Toxins
	Urinary tract infection	Pili
	Meningitis	K1 capsule
Vibrio cholerae	Diarrhea/ Cholera	Toxins
Vibrio parahemolyticus	Diarrhea	Toxins
Vibrio vulnificus	Septicemia	Capsullar polysaccharide
Salmonella Typhi	Enteric Fever	Capsullar polysaccharide
Helicobacter pylori	Gastritis/Ulcers	Invasion of stomach epithelium

https://quizlet.com/88254389/enteric-pathogens-flash-cards/

Cross talk between pathogen and intestinal epithelium



The composition of the intestinal epithelium according to the segment. Model describing (A) ileum (B) caecum (C) colon.

Ménard S, Lacroix-Lamandé S, Ehrhardt K, Yan J, Grassl GA, Wiedemann A. Cross-Talk Between the Intestinal Epithelium and Salmonella Typhimurium. Front Microbiol. 2022 Jun 6;13:906238. doi: 10.3389/fmicb.2022

Barrier Function of Intestinal EC

- intestinal epithelium represents a barrier between luminal antigens and the underlying immune system. Intestinal passage occurs *via* para- or trans-cellular permeability.
- Paracellular permeability is a passive transport allowing passage of small molecules and ions and is dependent on the highly regulated network of tight and adherens junctions and desmosomes
- Transcellular permeability is an active transport occurring for large molecules, antigens and bacteria and involves endocytosis and receptor-mediated transport
- Proteases/ toxins can affect the barrier permeability- damage

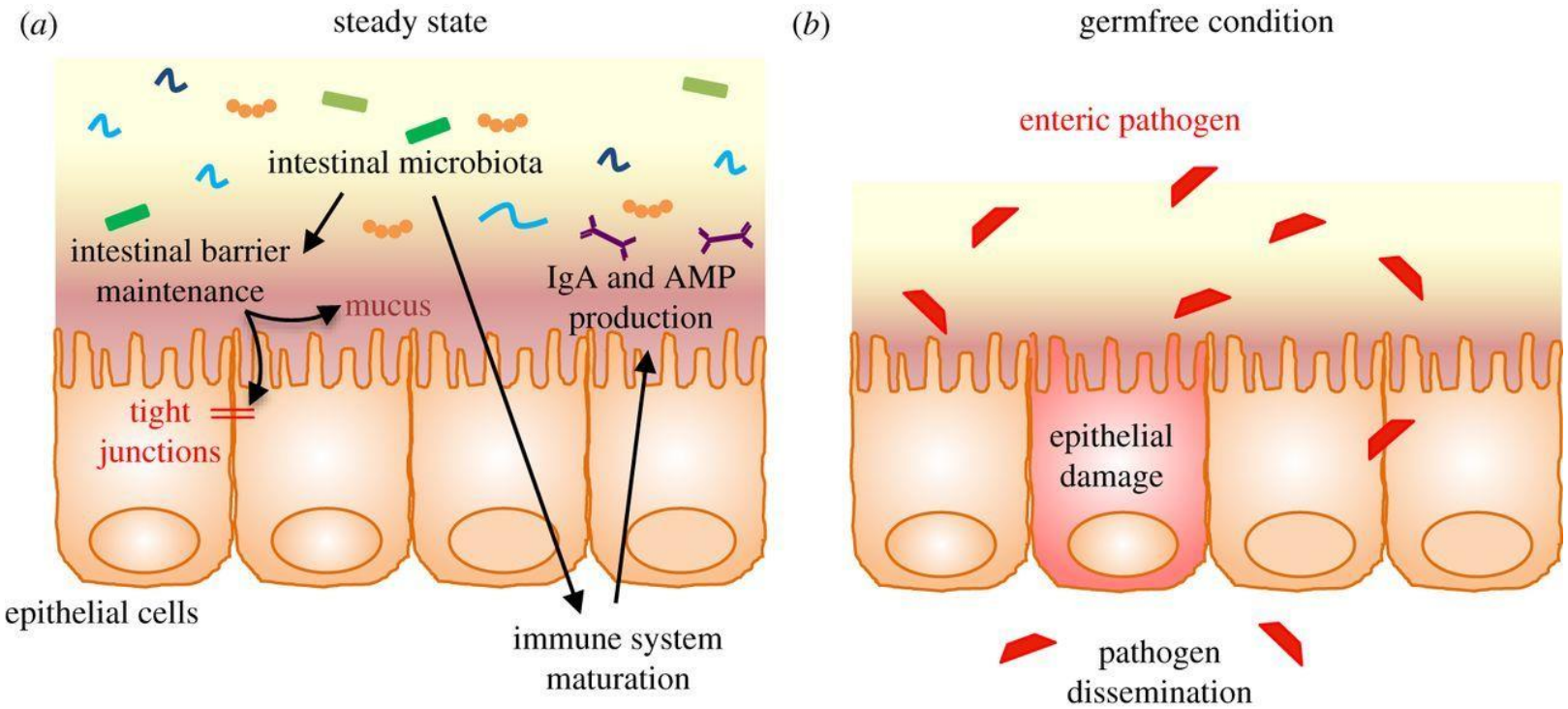
Host Epithelium

- The intestinal mucus layer, for example, plays a key role in limiting invasion by commensal bacteria of the microflora or by foodborne pathogenic bacteria
- This mucus is mainly composed of glycoproteins called mucins, digestive enzymes, antimicrobial peptides and immunoglobulins. Bacteria are often found at the top of this intestinal mucus layer, where they interact with mucins, whereas the inner layer of mucus, where the concentration of antimicrobial compounds is high, is normally devoid of bacteria- Mucins are produced and secreted in the intestine by goblet cells, a specialized cell-type of the intestinal epithelium. Their production can be modulated in response to microbial products or inflammation
- The level of antimicrobial peptides, predominantly secreted by Paneth cells from intestinal crypts, can also be regulated by the presence of microorganisms. Indeed, whereas a-defensins are constitutively expressed, other antimicrobial peptides such as REG3g (Regenerating islet-derived protein 3g) or cryptdins are produced in response to the detection of pathogen-associated molecular patterns (PAMPs) that activates TLR (Toll-like receptors) or NOD (nucleotidebinding oligomerization domain-containing protein) signaling pathways

Host Epithelium

- Mucosal IgA can prevent bacterial pathogens
- shedding of mucus can be another mechanism to prevent bacterial adhesion to epithelial surface, as reported in the case of gastric mucus colonized by the pathogenic bacterium Helicobacter pylori
- epithelial cell renewal plays an important role in the control of bacterial colonization- very high turnover rate tight balance between the self-renewal of cells and their elimination that is crucial to homeostasis and epithelium integrity. Induction of epithelial cell death has been characterized as a defensive mechanism used by the host to limit infection by enteric pathogens
- Microbiota

Microbiota



Microbiota: commensal bacteria living on human mucosal surfaces. In the human intestine, this microbiota plays fundamental roles in digestion, as well as in intestinal epithelial metabolism and proliferation. In addition, it plays a key role in the resistance to foodborne infections by directly competing with enteric pathogens

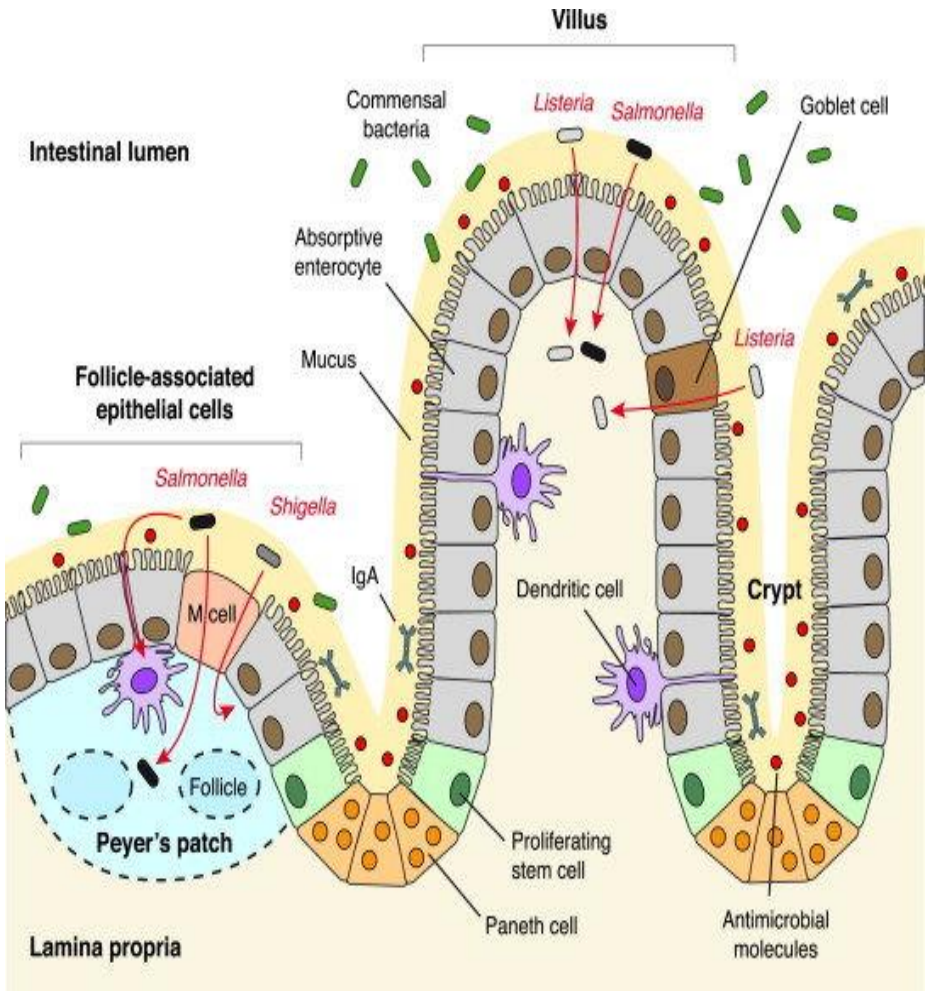


Fig. 1. Routes of invasion by enteric pathogens in the human small intestine.

The epithelium of the small intestine is composed of absorptive enterocytes, mucus producing goblet cells, M cells, as well as proliferating stem cells and Paneth cells located in intestinal crypts. The intestinal epithelium is covered by a mucus layer containing secreted IgA, antimicrobial peptides and other types of antimicrobial compounds that limit the colonization by commensal bacteria or foodborne pathogens.

Listeria monocytogenes can cross the host intestinal barrier at sites of cell extrusion at the tip of the villi or at junctions between goblet and absorptive epithelial cells.

Salmonella typhimurium can cross the intestinal epithelium by targeting absorptive cells, M cells of Peyer's patches or dendritic cells sampling the intestinal lumen.

Shigella flexneri also target M cells for crossing the intestinal barrier and then reinfect epithelial cells basolaterally

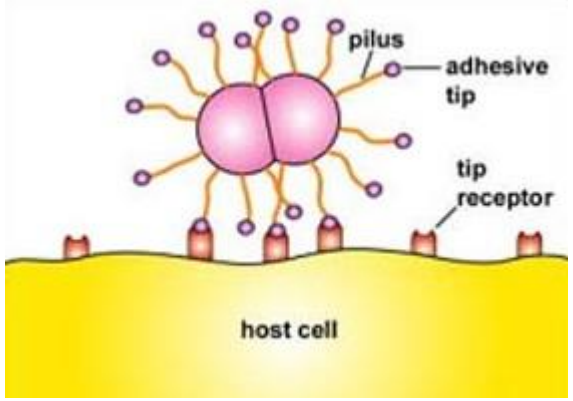
Enteric pathogens strategies

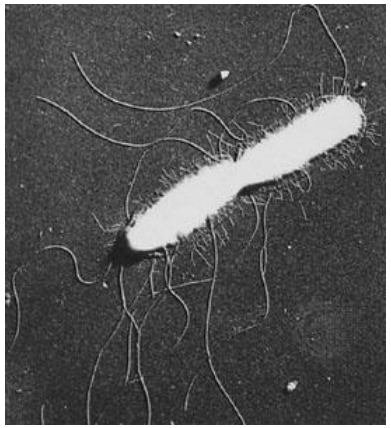
Invasion into the gut tissue is intimately linked to

- diarrhea and
- gut inflammation: Inflammation provides pathogens with a competitive advantage to outcompete the gut resident microbiota and to establish its niche in the gut lumen

Mechanisms of bacterial adhesion to host cells

- adhesion represents a crucial step for extracellular bacteria that facilitates their persistence in the host. For intracellular bacteria, it is a first essential step that precedes their internalization within host cells
- Pili are adhesive hair-like organelles that protrude from the surface of bacteria. Since pili can be used as appendages for transfer of genetic material during bacterial conjugation, the term “fimbria” is more commonly used to describe pili, whose function is devoted to attach bacteria to a surface.
- The base of these structures, initially discovered in gram-negative bacteria, is anchored to the bacterial outer membrane, whereas the tip is usually an adherence factor conferring the binding specificity of these structures



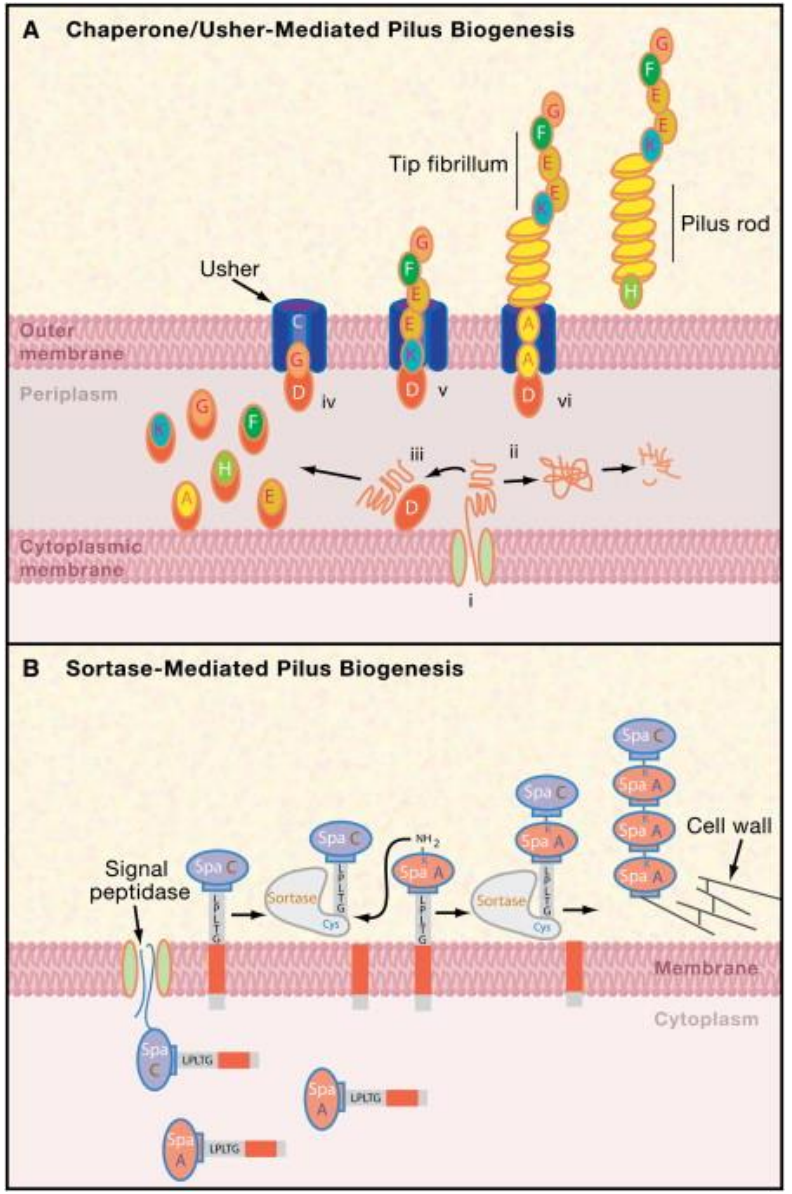


Electron micrograph of Salmonella showing both flagella and pili from the Wiki Biodiversityserene.

- Type 1 fimbriae: They contain FimH adhesins at the "tips". The chaperone-usher pathway is responsible for moving many types of fimbriae out of the cell, including type 1 fimbriae and the P fimbriae eg pathogenic *E. coli*
- Type 4 pili:The external ends of the pili adhere to a solid substrate, either the surface to which the bacterium is attached or to other bacteria. Then, when the pili contract, they pull the bacterium forward like a grappling hook. Movement produced by type IV pili is typically jerky, so it is called twitching motility

EPEC, EHEC, *Salmonella enterica* serovar Typhi, *Pseudomonas aeruginosa, Legionella pneumophila, Neisseria gonorrhoeae*, *Neisseria meningitidis,* and *Vibrio cholerae*

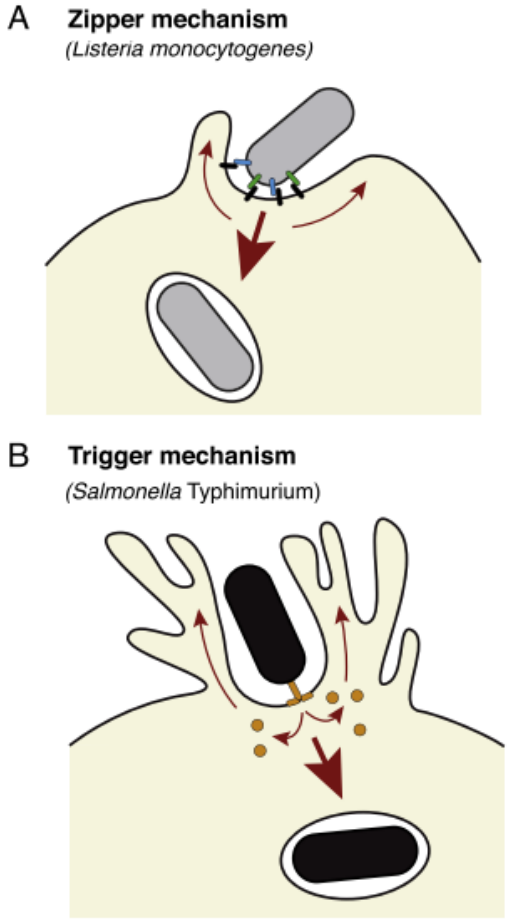
- Gram-negative bacteria assemble functional amyloid surface fibers called curli. Curli are composed of proteins called curlins.[19] Some of the genes involved are CsgA, CsgB, CsgC, CsgD, CsgE, CsgF, and CsgG.



- EPEC (Entero-Pathogenic E. coli) and EHEC (Entero-Hemorragic E. coli) pathogens: they inject an effector, called Tir, that inserts into the host cell plasma membrane and serves as an “exogenous” receptor for the bacterial surface protein intimin
- Tir is delivered into the host cell cytoplasm via EPEC or EHEC type III secretion system (T3SS), a complex of proteins forming a needle-like structure that traverses the bacterial cell wall and the hostcell plasma membrane
- Binding of bacterial intimin to the extracellular domain of Tir is followed by the recruitment of host cell cytoskeleton regulators such as the WiskottAldrich syndrome protein (N-WASP) and the actin-related protein 2/3 (Arp2/3) complex that locally remodels the actin cytoskeleton
- . This remodeling leads to the retraction of the host cell absorptive microvilli and to the creation of a pedestal under the attached bacterium, thereby creating the characteristic “attaching and effacing” lesions induced by this pathogen.
- Tir thereby tethers the bacteria to the host epithelial cell surface and provides a direct connection between the bacteria and the host's cytoskeleton.
- These bacterial factors are essential for pathogenesis as mutants of intimin/Tir interaction do not colonize the intestine and are avirulent in animal models of infection

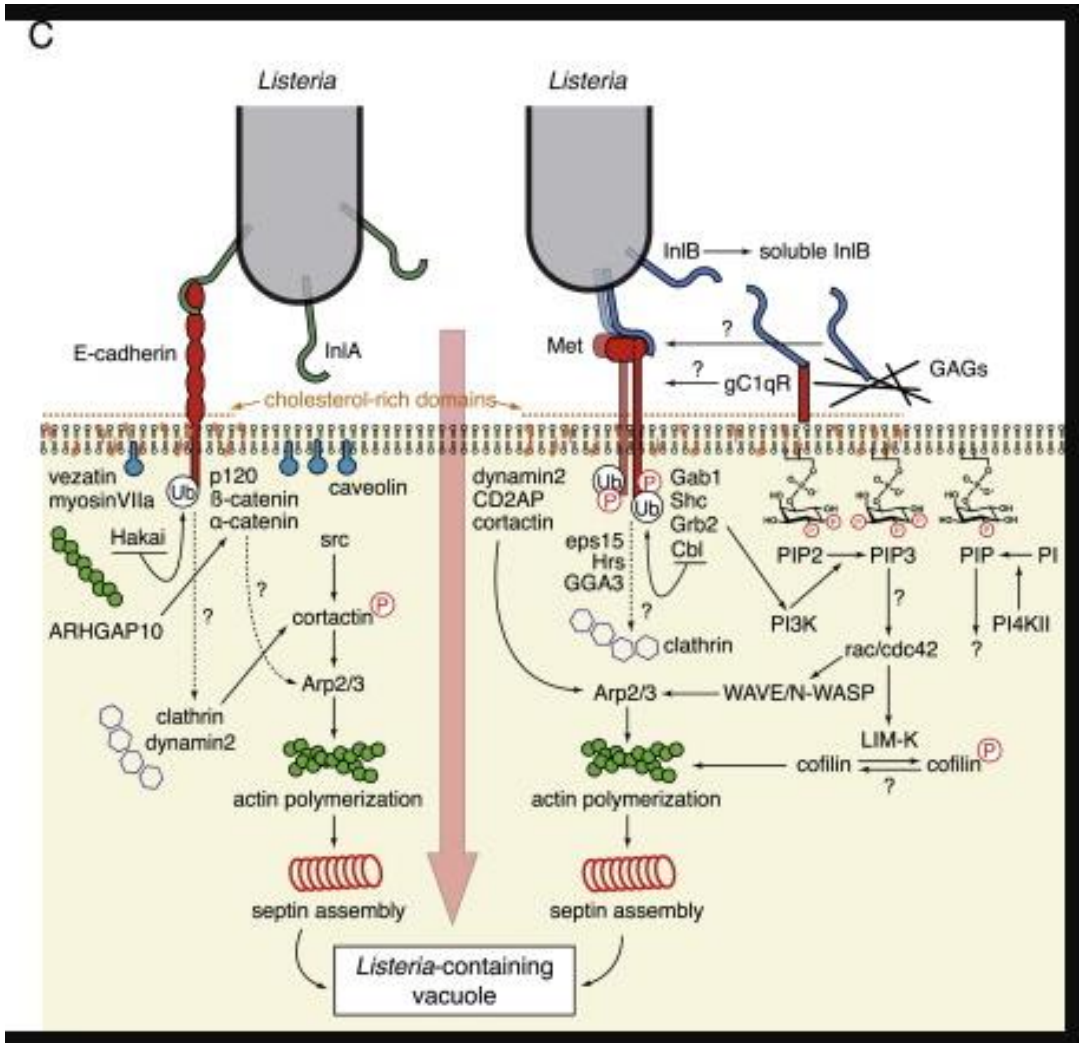
Establishment as intracellular pathogens

- Two main mechanisms of entry are involved in this case, namely the zipper and the trigger mechanisms. Both of them rely on the activation of signaling cascades leading to the reorganization of the actin cytoskeleton at the level of the host plasma membrane
- In the “zipper” mechanism, engagement of bacterial surface proteins with host proteins induce cytoskeleton and membrane rearrangements, leading to the internalization of the bacterium. In the “trigger” mechanism, injection of effectors by the bacterium in the host cell cytoplasm triggers large-scale cytoskeletal rearrangements and ruffles formation allowing the bacterium to be engulfed and internalized.



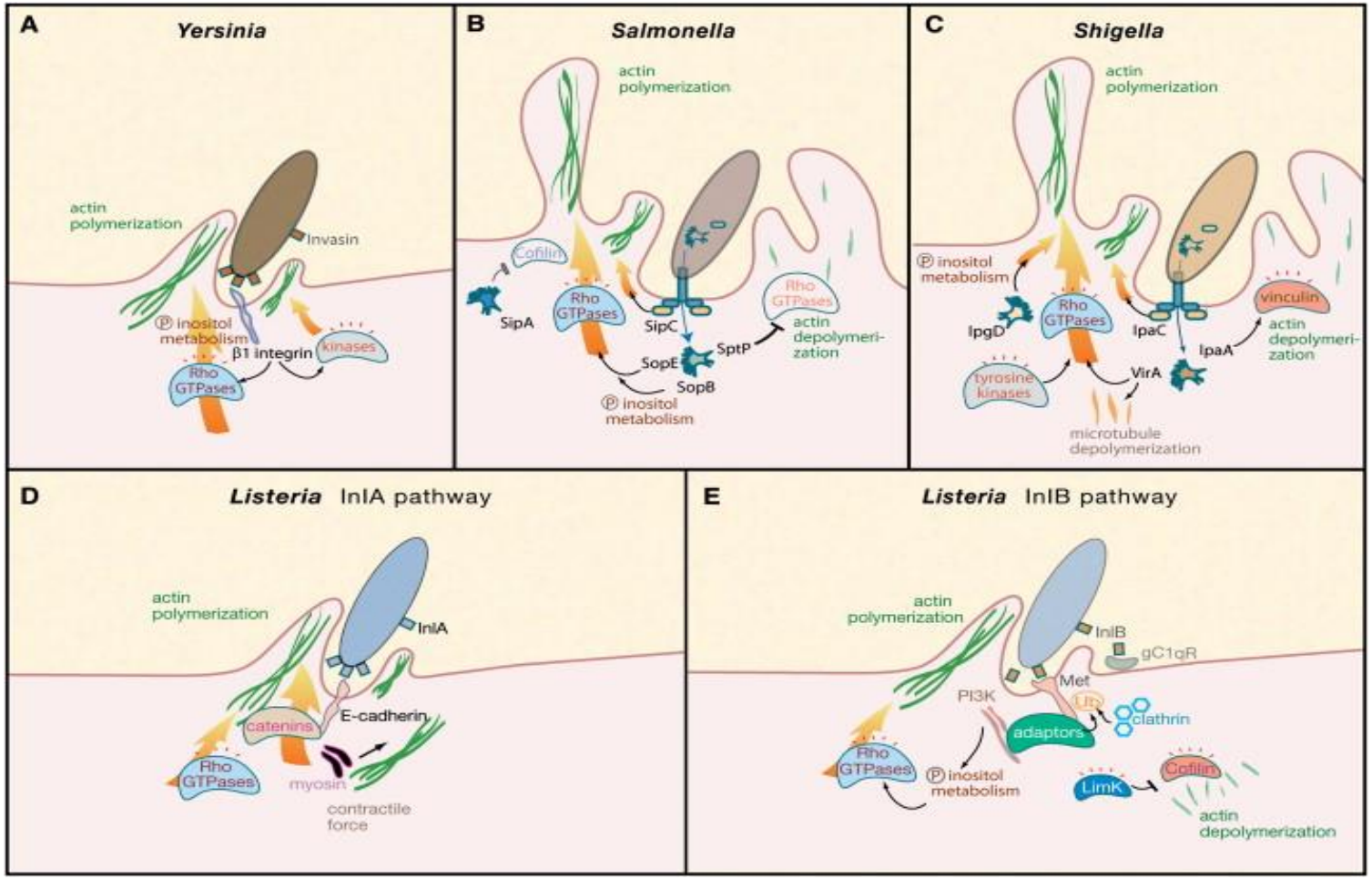
Ribert, Cossart, How bacterial pathogens colonize their hosts and invade deeper tissues Microbes and Infection Volume 17, Issue 3, March 2015, Pages 173-183

Schematic representation of the multiple molecular pathways activated by bacterial surface proteins (in this case, InlA and InlB from *Listeria monocytogenes)* leading to the internalization of bacteria by a “zipper” mechanism



Ribert, Cossart, How bacterial pathogens colonize their hosts and invade deeper tissues Microbes and Infection Volume 17, Issue 3, March 2015, Pages 173-183

Invasins



https://doi.org/10.1016/j.cell.2006.02.012

Enterotoxins

- Protein exotoxin that targets the intestinal epithelium. Can be chromosomally or extra chromosomally encoded
- Action of enterotoxins leads to increased chloride ion permeability of the apical membrane of intestinal mucosal cells. These membrane pores are activated either by increased cAMP or by increased calcium ion concentration intracellularly.
- The pore formation has a direct effect on the osmolarity of the luminal contents of the intestines. Increased chloride permeability leads to leakage into the lumen followed by sodium and water movement. This leads to a secretory diarrhea within a few hours of ingesting enterotoxin. Several microbial organisms contain the necessary enterotoxin
- ***Staphylococcus aureus*: Food poisoning caused by 6** characterized staphylococcal enterotoxins based on serological groups: staphylococcal enterotoxin types A, B, C, D, E, and H
- ***Bacillus cereus***: opportunistic pathogen causing gastroenteritis due to HBL, Nhe and CytK enterotoxins

https://en.wikipedia.org/wiki/Enterotoxin

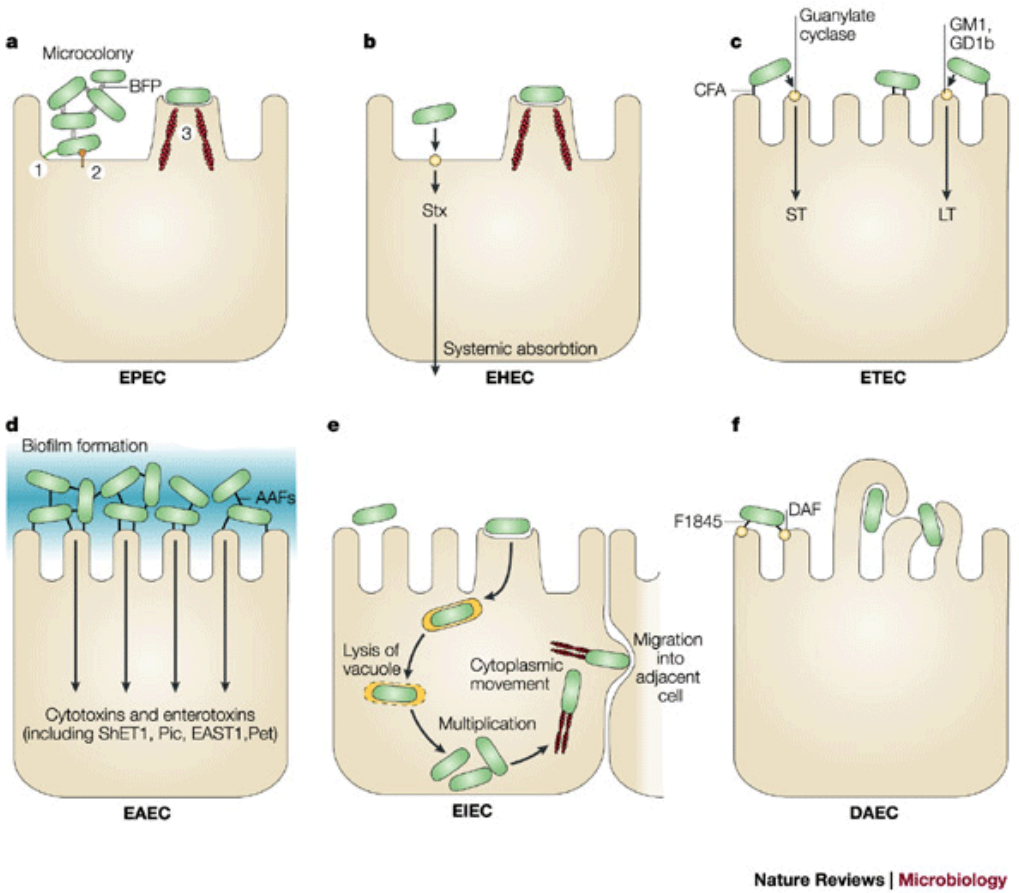
Viral Enterotoxins

- Rotaviruses are pathogens that infect the mature enterocytes of the villi in the intestine. Rotaviruses (of Reoviridae) have been found to contain an **enterotoxin** which plays a role in viral pathogenesis.
  - **NSP4**, is a protein that is made during the intracellular phase of the virion's life cycle and is known to have a primary function in intracellular virion maturation

Pathogenic E. coli

- Enteropathogenic *E. coli* (EPEC),
- Enterohaemorrhagic *E. coli* (EHEC),
- Enterotoxigenic *E. coli* (ETEC),
- Enteroaggregative *E. coli* (EAEC),
- Enteroinvasive *E. coli* (EIEC) and
- diffusely adherent *E. coli* (DAEC)

- The six recognized categories of diarrhoeagenic *E. coli* each have unique features in their interaction with eukaryotic cells.
- **a** | EPEC adhere to small bowel enterocytes, but destroy the normal microvillar architecture, inducing the characteristic attaching and effacing lesion. Cytoskeletal derangements are accompanied by an inflammatory response and diarrhoea. 1. Initial adhesion, 2. Protein translocation by type III secretion, 3. Pedestal formation.
- **b** | EHEC also induce the attaching and effacing lesion, but in the colon. The distinguishing feature of EHEC is the elaboration of Shiga toxin (Stx), systemic absorption of which leads to potentially life-threatening complications.
- **c** | Similarly, ETEC adhere to small bowel enterocytes and induce watery diarrhoea by the secretion of heat-labile (LT) and/or heat-stable (ST) enterotoxins.
- **d** | EAEC adheres to small and large bowel epithelia in a thick biofilm and elaborates secretory enterotoxins and cytotoxins.
- **e** | EIEC invades the colonic epithelial cell, lyses the phagosome and moves through the cell by nucleating actin microfilaments. The bacteria might move laterally through the epithelium by direct cell-to-cell spread or might exit and re-enter the baso-lateral plasma membrane.
- **f** | DAEC elicits a characteristic signal transduction effect in small bowel enterocytes that manifests as the growth of long finger-like cellular projections, which wrap around the bacteria. AAF, aggregative adherence fimbriae; BFP, bundle-forming pilus; CFA, colonization factor antigen; DAF, decay-accelerating factor; EAST1, enteroaggregative *E. coli* ST1; LT, heat-labile enterotoxin; ShET1, *Shigella* enterotoxin 1; ST, heat-stable enterotoxin.



Kaper, J., Nataro, J. & Mobley, H. Pathogenic *Escherichia coli*. *Nat Rev Microbiol* **2**, 123–140 (2004). https://doi.org/10.1038/nrmicro818

EPEC

- Enteropathogenic *Escherichia coli* (EPEC):watery diarrhea, sometimes accompanied by low-grade fever and vomiting
- Leading cause of infantile diarrhoeae
- Decrease in the number and height of microvilli, blunting of enterocyte borders, loss of glycocalyx and presence of a mucous pseudomembrane coating the mucosal surface
- EPEC induce attaching-and-effacing (A/E) histopathology:profound cytoskeletal alterations, disrupting the brush border cytoskeleton and leading to a proliferation of filamentous actin beneath adherent bacteria. Effacement of microvilli and intimate adherence between the bacterium and the epithelial cell membrane are also observed. The epithelial membrane beneath the adherent bacteria is raised locally in a characteristic pedestal shape which may extend up to 10 µm outwards from the cell to form pseudopod-like structures

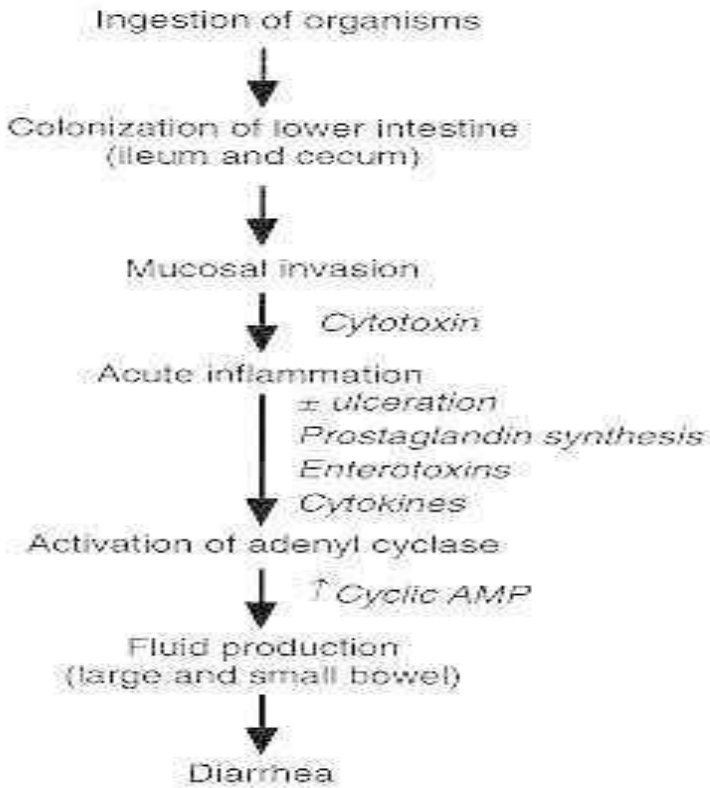
EPEC

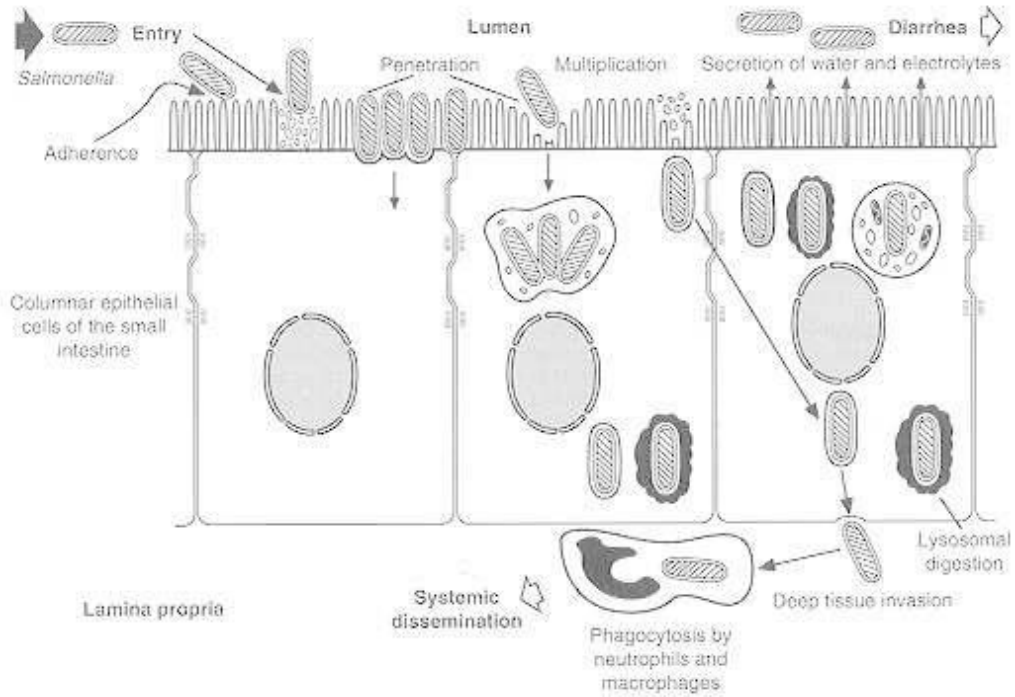
- First Stage: Adherence factor (BFP) :major pilin subunit of BFP (*bfp*A) was identified through the isolation of EPEC strain E2348/69 Tn*pho*A
- EPEC contains a 35.6 kb pathogenicity island called the locus of enterocyte effacement, LEE:-These genes are separated into three functional domains – a region encoding intimate adherence (Tir and intimin), a region encoding the EPEC secreted proteins (including EspA, EspB, EspD and EspF) and their putative chaperones and the region encoding a type III secretion system
- The second stage of EPEC infection is signal transduction. EPEC secreted a number of proteins (EPEC secreted proteins Esp) via a type III secretion pathway include Tir, EspA, EspB and EspD which are essential for the subversion of host cell signal transduction pathways and the formation of A/E lesions

- Third stage of EPEC infection is characterised by enterocyte effacement, pedestal formation at the apical enterocyte–cell membrane and intimate bacterial attachment to the host cell. This is mediated by a 94 kDa OMP, intimin.
- The binding of intimin to Tir focuses or clusters Tir beneath adherent EPEC, directly linking extracellular EPEC to the epithelial membrane and anchoring it to the host cell actin and cytokeratin cytoskeleton networks. EPEC can initiate pedestal formation and mediate its pathogenic effects on the host cell while remaining on the extracellular surface
- Dramatic loss of microvilli and the subsequent malabsorption due to brush border enzyme deficiency certainly contributes to diarrhoea. Alteration of epithelial cell integrity

S.typhimurium

Salmonella species are Gram-negative, flagellated facultatively anaerobic bacilli cause common Salmonella gastroenteritis (diarrhea, abdominal cramps, and fever) to enteric fevers (including typhoid fever)



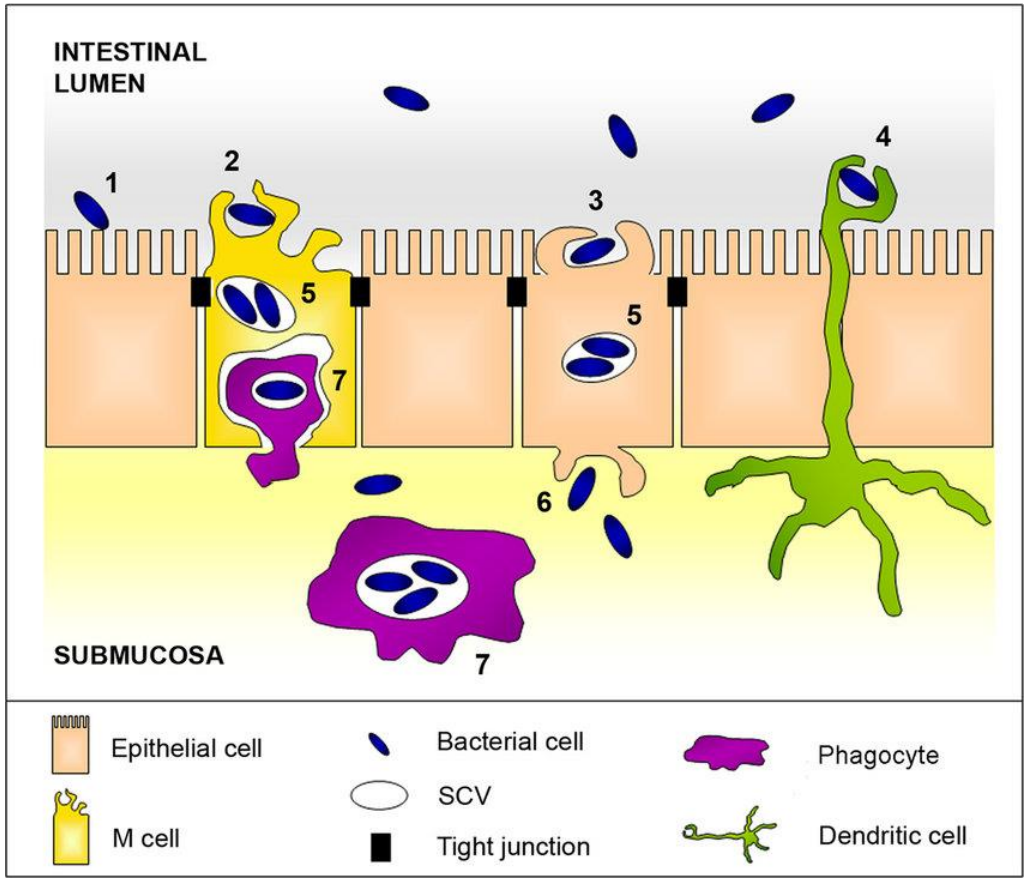


S.typhimurium

- *Salmonella* penetrate the intestinal epithelial cells but, unlike *Shigella* and invasive *E. coli*, do not escape the phagosome. Thus, the extent of intercellular spread and ulceration of the epithelium is minimal. *Salmonella* escape from the basal side of epithelial cells into the lamina propria. Systemic spread of the organisms can occur, giving rise to enteric fever. Invasion of the intestinal mucosa is followed by activation of mucosal adenylate cyclase; the resultant increase in cyclic AMP induces secretion.
- *Salmonella* strains elaborate one or more enterotoxin-like substances which may stimulate intestinal secretion

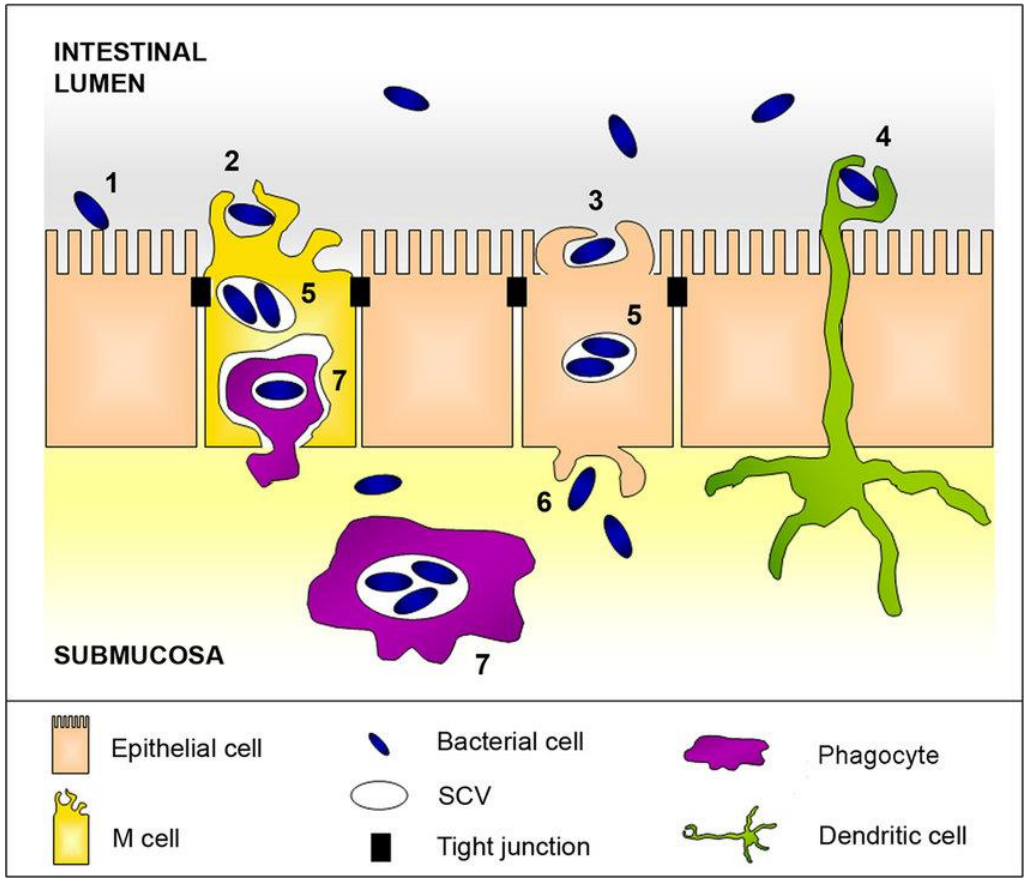
S.typhimurium

- Pathogenic salmonellae ingested in food survive passage through the gastric acid barrier and invade the mucosa of the small and large intestine and produce toxins.
- Invasion of epithelial cells stimulates the release of proinflammatory cytokines which induce an inflammatory reaction.
- The acute inflammatory response causes diarrhea and may lead to ulceration and destruction of the mucosa. The bacteria can disseminate from the intestines to cause systemic disease
- Pathogenic Salmonella species invade non-phagocytic intestinal epithelial cells by delivering a specialized set of effectors through the type 3 secretion system (T3SS),



S.typhimurium

- Two T3SSs encoded by Salmonella pathogenicity island 1 (SPI-1) and Salmonella pathogenicity island 2 (SPI-2)
- Many SPI-1 effector proteins have been identified in *Salmonella*. These effectors play a variety of roles during *Salmonella* infection, including taking part in rearrangement of the host cytoskeleton, immune cell recruitment, cell metabolism, fluid secretion, and regulation of the host inflammatory response

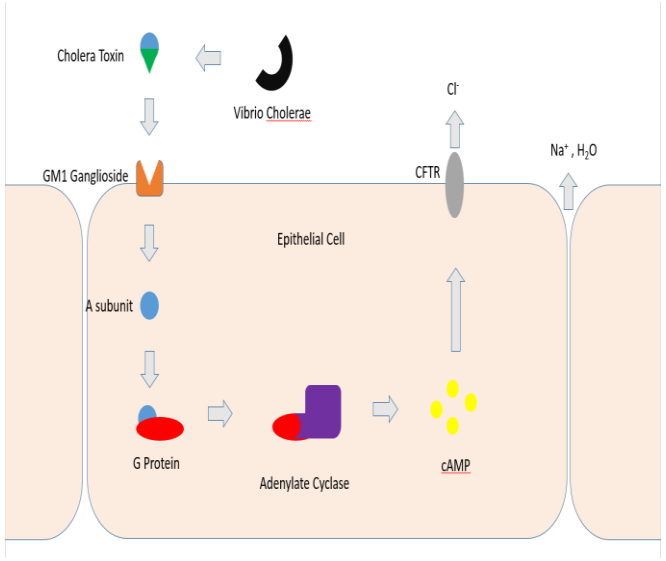


Vibrio cholerae

- Ggenome of one V. cholerae strain (El Tor N16961) has been completely sequenced - consists of two chromosomes.
- The larger of the two chromosomes includes genes encoding for two essential virulence factors, toxin-coregulated pilus (TCP) and CT.
- TCP is a type IV pilus required for intestinal colonization. The structural genes for TCP are encoded within a pathogenicity island
- CT is a potent enterotoxin required for the induction of secretory diarrhea. The structural genes for CT are encoded within a lysogenic phage (CTxϕ) integrated into the large chromosome

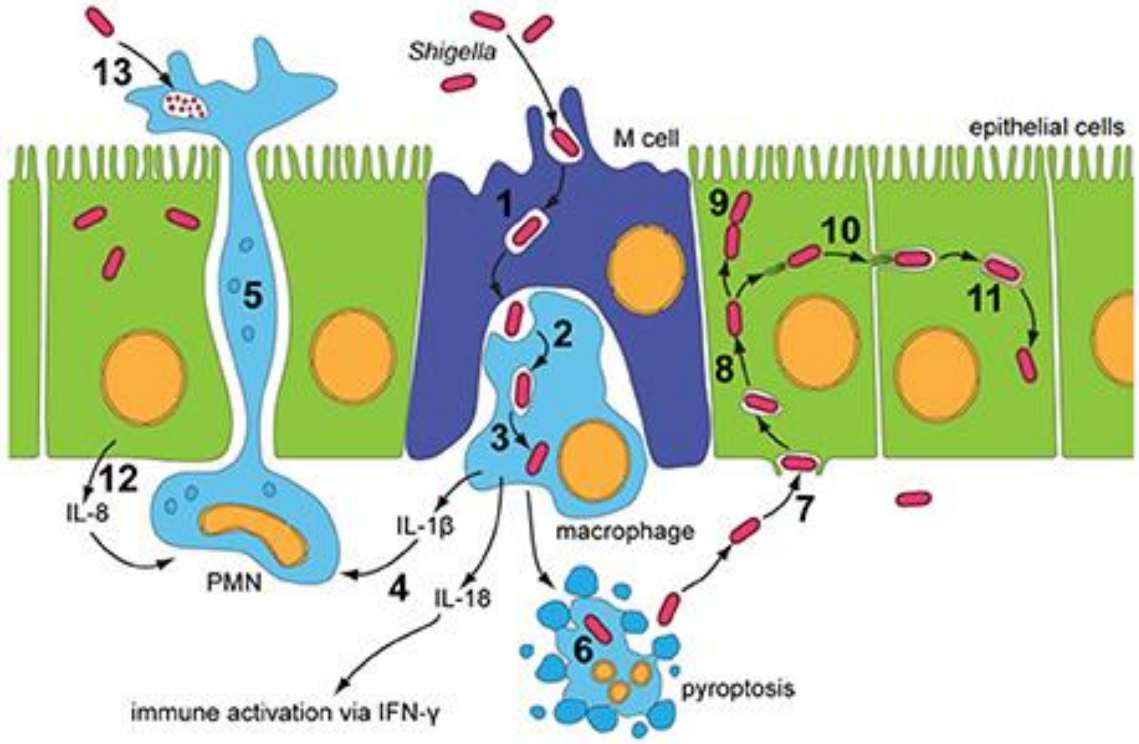
Vibrio cholerae

- CT released into the intestinal lumen must enter the intestinal epithelial cell at the apical membrane and eventually activate epithelial adenylyl cyclase at the cytoplasmic surface of the basolateral membrane.
- The CT holotoxin binds to G_{M1} in the apical membrane. After endocytosis, the CT-G_{M1} complex trafficks retrograde through Golgi cisternae into the lumen of the endoplasmic reticulum (ER), where the A_1 peptide is unfolded and dissociated from the B pentamer.
- The unfolded A_1 peptide is probably dislocated to the cytosol through the sec61p complex.
- The A_1 peptide may then gain access to ADP-ribosylate its substrate, the heterotrimeric GTPase Gsα on the cytoplasmic surface of the basolateral membrane, by diffusion through the cytosol (if the A_1 peptide breaks away from the membrane after translocation) or by membrane traffic back out the secretory pathway (if the A_1 peptide remains membrane associated).
- The B subunit is not unfolded in the ER, remains membrane associated (presumably bound to G_{M1}), and moves to the basolateral membrane by trafficking back out the secretory pathway in anterograde vesicles in a process we have termed indirect transcytosis.



Shigella dysenteriae

Entry into the colonic epithelium is mediated in two ways: M-cell membrane ruffling, and epithelial barrier destabilization. Entry via M-cells is achieved through membrane ruffling (1), and the bacillus is then transported to the M-cell pocket, where it is endocytosed by resident macrophages (2). Epithelial barrier destruction is mediated by pro-inflammatory (IL-1) and chemotaxic cytokines (IL-8). IL-8 produced by neighboring epithelial cells recruits PMN leukocytes (12), which travel from the basolateral to the apical colonic epithelium, destabilizing the junctions between the epithelial cells and allowing further invasion of Shigella (5). Induction of pyroptotic macrophage death occurs after Shigella escape from the phagocytic vacuole (3 and 6). Caspase-1, when activated, cleaves and activates IL-1β and IL-18, leading to the release of these pro-inflammatory cytokines (4) Uptake of Shigella is a macropinocytic process at the basolateral membrane of epithelial cells (7). Stimulation of Rho-family GTPases triggers actin polymerisation and then depolymerization, forming filopodial and lamellipodial extensions of the epithelial membrane, leading to engulfment of the bacilli. Lysis of the macropinocytic vacuole allows Shigella to gain access to the epithelial cytoplasm, where it rapidly multiplies, escapes autophagy and fragments the Golgi (8 and 9). Exploitation of the epithelial actin assembly machinery allows Shigella to move both intra- and intercellularly (10). Protrusions mediated by bacilli are actively endocytosed by the clathrin-mediated endocytic pathways at intercellular junctions, and the double membrane vacuole is lysed to give Shigella access to the neighboring cells cytoplasm (11). PMN leukocytes eventually eliminate Shigella infection from the colonic epithelium (13).



https://www.frontiersin.org/articles/10.3389/fcimb.2017.00064/full

Multiple serotypes

- A serotype is defined as a variation within a microbial species, distinguished by the humoral immune response.
- The serotype classification of bacteria or viruses is based on their surface antigens
- Eg. 19 **serotypes** of *S. flexneri*, based serologically on the major type-specific somatic antigen (I–VI)
- ~186 different Different *E. coli* O-groups and 53 H-types
- *Salmonella enterica* serotype Enteritidis and *Salmonella* enterica serotype *Typhimurium*, the two most important serotype

Summary

- As an initial step in the infection process, certain enteric pathogens target specific epithelial cell structures, including glycoproteins and glycolipids, which serve as receptors for bacterial attachment
- Invading enteric pathogens, such as *S. typhimurium* and *Shigella flexneri* have evolved a sophisticated strategy that directs the entry of the enteric pathogen into intestinal epithelial cells.
- This process requires the expression of a bacterial type III protein secretion system (TTSS), the function of which is to deliver a set of effector proteins into the host cell
  - rearrangement of the host cytoskeleton
  - direct cytotoxic injury, intracellular migration, disruption of the epithelial tight junctions, or indirectly by inducing neutrophil infiltration

- *Clostridium difficile* toxins A and B enhance epithelial cell permeability by disrupting actin microfilaments within the perijunctional ring
- Enteropathogenic *Escherichia coli* disrupt the epithelial barrier by the phosphorylation of myosin light chains
- *S. typhimurium*, *in vitro* models of infection have revealed an alteration of epithelial permeability and loss of barrier function, which involves rapid changes in both tight junction permeability and transcellular conductance
- *Salmonella* effector protein SigD (also called SopB), which is encoded in *Salmonella* pathogenicity island-1 (SPI-1), is able to elicit a reduction in epithelial barrier function, perhaps via activation of PKC . Also, the effector proteins SopB, SopE, SopE2, and SipA are necessary to disrupt the epithelial barrier and alter the distribution of at least some tight junction proteins
- the ability to regulate the molecular composition of the tight junctions facilitates the pathogenecity of *S. typhimurium* by fostering its uptake and distribution within the host

Reading Material

- Srikanth CV, McCormick BA. Interactions of the intestinal epithelium with the pathogen and the indigenous microbiota: a three-way crosstalk. Interdiscip Perspect Infect Dis. 2008;2008:626827. doi: 10.1155/2008/626827. Epub 2008 Oct 29. PMID: 19259328; PMCID: PMC2648619. https://textbookofbacteriology.net/pathogenesis_6.html
- https://www.oecd-ilibrary.org/docserver/9789264253018-4-en.pdf?expires=1662617862&id=id&accname=guest&checksum=B1021403A069F5C15BA5134B32B557A5
- Prescott Microbiology Book by Christopher J. Woolverton, Joanne Willey, and Linda Sherwood

- **THANK YOU**