31 *Salmonella typhi*

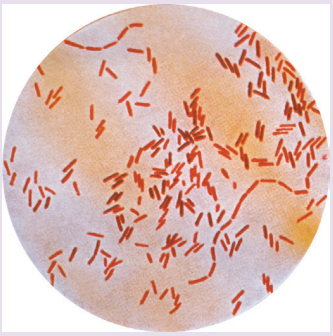


Figure 31.1 Gram-negative bacilli in a blood culture. *From the Centers for Disease Control & Prevention, Atlanta, Georgia. Image is found in the Public Health Image Library #2114.*

A 53-year-old woman returned from a visit to Lahore complaining of feeling generally unwell with a fever and a cough. She attended a clinic where she was seen by a doctor who confirmed a temperature of 38°C and he noticed a rash on the upper chest. She was admitted to hospital for investigation which included a thick and thin film for malaria, a full blood count, urea and electrolytes, a chest X-ray, and blood cultures. The malaria investigation was negative, the chest X-ray showed patchy basal consolidation, the full blood count revealed a relative **lymphocytosis** and gram-negative bacilli were seen in the blood culture (**Figure 31.1**). A provisional diagnosis of enteric fever was made and she was started on appropriate antibiotics. The diagnosis was confirmed by isolation of *Salmonella typhi* from the blood cultures.

1. WHAT IS THE CAUSATIVE AGENT, HOW DOES IT ENTER THE BODY AND HOW DOES IT SPREAD A) WITHIN THE BODY AND B) FROM PERSON TO PERSON?

CAUSATIVE AGENT

The nomenclature of the genus *Salmonella* has undergone a number of revisions leading to two systems of validly published names, the latest version of which (2005) has the disadvantage of not highlighting important human pathogens such as *Salmonella typhi* or *Salmonella enteritidis* by not giving them succinct names. In the current version of the nomenclature, the cause of enteric fever and the organism that is one of the important causes of gastroenteritis would be *S. enterica* subsp. *enterica* serovar Typhi and *S. enterica* subsp. *enterica* serovar Enteritidis, respectively. For pragmatic reasons, this nomenclature will not be used in this text but will be shortened to *Salmonella* Typhi. There are only two species in the genus: *S. enterica* and *S. bongori* of which *Salmonella enterica* is further subdivided into six subspecies: *S. enterica* (1531), *S. salamae*, (505) *S. arizonae*, (99) *S. diarizonae*, (336) *S. houtenae* (73) and *S. indica* (13) with the number of serovars in each group in brackets. New serovars are regularly being identified so these numbers are not constant.

Salmonella organisms are motile nonsporing gram-negative facultative anaerobic rods measuring 2–3×0.4–0.6 µm. The genome of *Salmonella* Typhi and *Salmonella* Typhimurium have both been sequenced and contain about 4.8 million base pairs with 4000–5000 coding sequences, of which 98% are homologous between the two serovars. *Salmonella* pathogenicity islands (SPIs) are gene sequences within the *Salmonella* genome that code for virulence characteristics. They usually have a GC content different from the host genome as they are acquired horizontally from other bacteria. The genus *Salmonella* has five SPIs. SPI-1 is involved in penetration of the intestinal epithelium. SPI-2 is involved with intracellular survival. Both SPI-1 and 2 code for a different Type III secretion system. SPI-3 carries virulence functions related to survival within macrophages. SPI-4 codes for a Type I secretion system and probably secretes toxin(s). SPI-5 mediates inflammation and chloride secretion which characterizes non-typhoid *Salmonella* (NTS) infection. SPI-6 codes for a Type VI secretion system and is found in SPI-7 and codes for the Vi antigen.

Frequent genome rearrangements associated with the SPIs lead to outgrowth of strains that are better adapted to different environmental circumstances. Horizontal gene transfer is also an important factor in the evolution of the genus. A large plasmid is carried in *Salmonella* Typhi (pHCM1) that encodes drug resistance. **Virulence** plasmids are also carried in non-typhoidal serovars. There are over 2500 serovars in the genus

and they are grouped according to the possession of somatic O antigens, flagellar H antigens, and surface virulence (Vi) antigens in the Kauffman-White scheme. K (capsular) antigens are also present (**Figure 31.2**). Most *Salmonella* spp. express two types of flagella made up of different proteins (H antigen) and they switch from one phase to the next at characteristic frequencies. Thus, the H antigens occur in two phases: phase I and II. The O antigens are designated by arabic numerals, the phase I antigens by letters a–z, and the phase II antigens by arabic numerals. Thus, a specific serovar may be designated [9,12,Vi/d/–] = *Salmonella* Typhi (*Salmonella* Typhi does not have a phase II antigen) or [1,4,5,12/i/1,2] = *Salmonella* Typhimurium. For epidemiologic purposes, a number of typing methods have been used. These include **phage typing**, plasmid profiling, **ribotyping**, **pulse field gel electrophoresis** (**PFGE**), variable number of tandem repeats (VNTR), enterobacterial repetitive intergenic consensus-**polymerase chain reaction** (ERIC-**PCR**), and whole genome sequencing (WGS).

ENTRY AND SPREAD WITHIN THE BODY

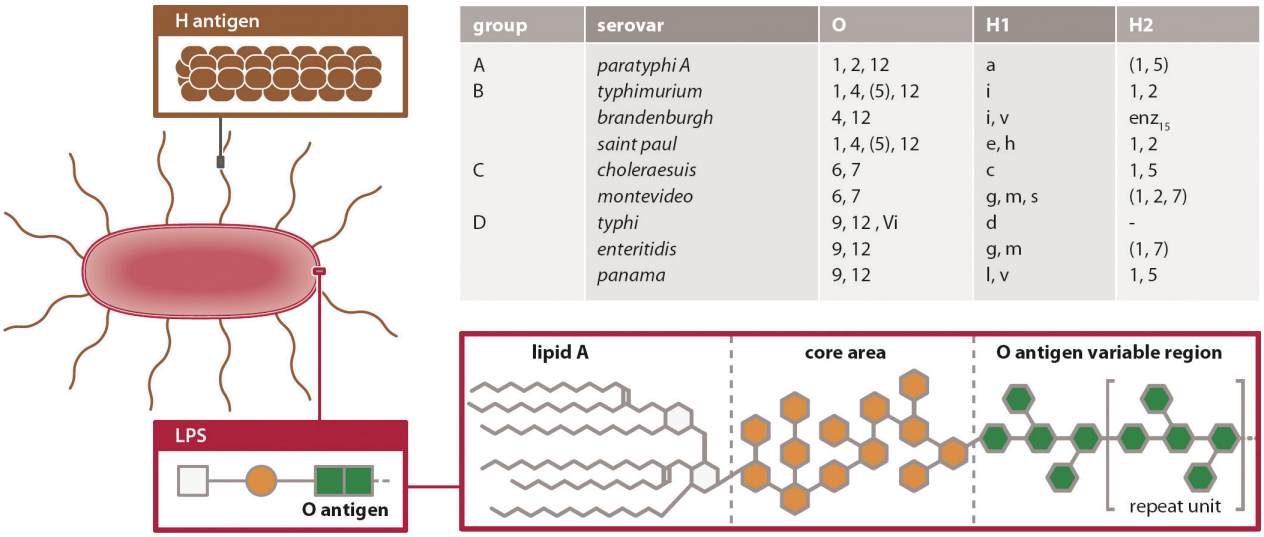
Salmonella are ingested in food or water. The infecting dose is uncertain but has been reported to vary between 10^2 and 10^6 cells. Reduced gastric acidity is a predisposing risk factor and colonization by *Helicobacter pylori* may be an important co-morbidity through its reduction in acid output in cases of pan-gastritis.

Entry into the body is a complex process with sequential expression of various virulence modalities at each stage.

- The initial site is in the stomach where the organism expresses an acid tolerance response.
- Penetration of the mucus layer in the small intestine and adhesion to enterocytes and M cells in Peyer's patches.
- Penetration of cells with bacteria enclosed in a vacuole.
- Disruption of normal endocytic pathway to avoid fusion with the lysosome.
- Penetration of basement membrane and release of bacteria into lamina propria.
- Activation of the innate immune system.
- Uptake by neutrophils, macrophages, and dendritic cells with bacteria in a vacuole.
- Disruption of endocytic pathway again.
- Infected cells enter lymph system then enter bloodstream.
- Relocation to various other organs: liver, spleen, bone marrow.
- Disease onset with clinical symptoms.

Non-Typhoid *Salmonella*

NTS penetrate intestinal epithelial cells but rarely disseminate throughout the body by the bloodstream and are more prone to cause local disease. Co-infection with HIV is a risk factor



group	serovar	O	H1	H2
A	*paratyphi A*	1, 2, 12	a	(1, 5)
B	*typhimurium*	1, 4, (5), 12	i	1, 2
	brandenburgh	4, 12	i, v	enz_{15}
	saint paul	1, 4, (5), 12	e, h	1, 2
C	*choleraesuis*	6, 7	c	1, 5
	montevideo	6, 7	g, m, s	(1, 2, 7)
D	*typhi*	9, 12 , Vi	d	-
	enteritidis	9, 12	g, m	(1, 7)
	panama	9, 12	l, v	1, 5

key

H haunch (breath) bacteria which produce a thin film on the growth medium similar to the effect of breath on a glass, only motile bacteria do this because they have flagellae, H antigens can occur as two types, H1 and H2

O ohne (without) that is without breath i.e. do not produce a thin film on the growth medium because they do not have flagellae and are nonmotile

Vi virulence

Figure 31.2 The relationship between the O (cell wall) and H (flagella) antigens and the Kaufmann-White serotyping scheme.

for severe non-typhoidal infection and is a significant cause of mortality.

PERSON-TO-PERSON-SPREAD

Salmonella Typhi

Salmonella Typhi and *Salmonella* Paratyphi are strictly human pathogens and are **endemic** in several countries (see below). Endemicity of typhoid fever is associated with a poor social hygiene infrastructure (inadequate sewage disposal, inadequate potable water supplies, and inadequate food hygiene practices) and social upheaval.

Salmonella Typhi is acquired either directly or indirectly from another human or carrier by ingestion. Direct acquisition from a person is uncommon but can occur associated with certain sexual practices. More usually, infection is acquired from fecally contaminated water or food and less commonly in laboratories handling clinical specimens. Outbreaks have been linked to food-handlers who are carriers of the organism – the most notorious being "Typhoid Mary". Mary Mallon was a cook for a New York banker, who infected most of his family with typhoid because she was a healthy carrier excreting *Salmonella* Typhi. Investigations by a civil engineer employed by the banker to identify the source revealed that outbreaks of typhoid had occurred in seven families for whom Mary had been the cook.

An important virulence characteristic is the ability to form biofilms. The main factors in biofilm formation are curli fimbriae and exopolysaccharide cellulose. Biofilm is important in maintaining viability under adverse environmental circumstances making the food chain susceptible as a source of infection.

The organism is endemic in India, Africa, South America, and South-East Asia. In Africa, the incidence is about 900/100 000 population. In Indonesia, enteric fever is one of the commonest causes of death in children, with 20 000 deaths each year. In nonendemic countries such as the UK and the US, the incidence is about 0.2/100 000 population. In the UK, the number of cases in 2000 was 331 (caused by *Salmonella* Typhi, *Salmonella* Paratyphi A and B) and in 2012 the number of cases was 430.

A significant proportion of cases of typhoid in industrialized countries are acquired abroad.

Non-Typhoid *Salmonella*

NTS are found in a variety of animal species. Infection is acquired by ingestion from contaminated food, particularly eggs, poultry, and dairy produce. The sudden increase in *Salmonella* Enteritidis PT4 in the UK was linked to contaminated eggs. Since 2018, a pan-European outbreak of *Salmonella* Enteritidis sequence type 11, associated with breaded chicken, has affected people in Britain, Denmark, Finland, France, Germany, Ireland, the Netherlands, Poland, and Sweden, with 120 infections thus far in the UK. In 2021, five clusters of *Salmonella* Braenderup in the UK are being investigated. The source is currently unknown. Infection may also be acquired from direct contact with infected animals, particularly exotic pets, for example, snakes.

EPIDEMIOLOGY

The number of cases of gastroenteritis caused by the 2500 different serovars of salmonella (e.g. *Salmonella* Enteritidis, *Salmonella* Typhimurium, etc.) has increased over the years. In the US, about 1.4 million cases occur annually with an incidence of 17/100 000 population, with *Salmonella* Typhimurium and *Salmonella* Enteritidis being the most common serovars causing infection. In the UK, the incidence of *Salmonella* [Enteriditis, Typhimurium, Typhi, other non-typhoidal salmonellae (NTS)] in 2000 was 15 435 [8616, 2688, 331, 3798], which decreased to 8355 [2169, 1902, 430, 3854] in 2012. The most frequent serovar causing disease was *Salmonella* Typhimurium, until 1988 when there was a sudden increase in *Salmonella* Enteritidis, which became the predominant serovar. The predominant strain of *Salmonella* Enteritidis causing disease is phage type 4 (PT4) and in 2000, *Salmonella* Enteritidis accounted for 8616 cases, outnumbering all other *Salmonella* types combined. The age of infection (per 100 000 population) in 2000 [<1yr, 1–9yr, 15–64yr, >64] was 104, 91, 54, 34, respectively and in 2012, this had decreased to 79, 58, 30, 21, respectively. Globally, NTS is estimated (WHO) that 500 million persons are infected annually with 3 million deaths and in 2017 this had decreased to 21.7 million cases and 217 000 deaths.

2. WHAT IS THE HOST RESPONSE TO THE INFECTION AND WHAT IS THE DISEASE PATHOGENESIS?

Low gastric acid, immunosuppression, and certain polymorphisms predispose to infection, for example Toll-like receptor (TLR) 4, interleukin (IL-) 4, and HLA class II and class III.

INNATE IMMUNITY

Infection with *Salmonella* Typhi induces a monocytic response with little diarrhea, due in part to the immunosuppressive effect of the **Vi antigen**. On the other hand, NTS induces an acute inflammatory reaction with the secretion of **interleukin** (**IL**)-8, the recruitment of neutrophils, and pronounced diarrhea. The diarrhea is induced in part by translocated proteins and in part by disruption of the epithelial barrier.

In the lamina propria, salmonella enter epithelial cells and macrophages by bacteria-mediated endocytosis or **phagocytosis**, respectively. Once inside the macrophage, the bacterium is protected from the humoral immune system and it survives intracellular killing by the macrophage by up-regulating numerous genes required for intracellular survival and replication, including the Vi antigen, which is principally anti-phagocytic. Changes occur in the cell wall of *Salmonella* making it resistant to bactericidal peptides and

reactive oxygen species (**ROS**) and causing less inflammation. Additionally, products coded by the pathogenicity island SPI-2 are secreted into the macrophage cytoplasm, which inhibit phagolysosome fusion by modulation of the actin cytoskeleton surrounding the vacuole and by incorporating proteins into the membrane of the vacuole.

In response to bacterial invasion, **microbe-associated molecular patterns** (**MAMPs**) are recognized by **Toll-like receptors** (TLR2, lipoprotein; TLR4, **lipopolysaccharide** (**LPS**); TLR5, flagellin) and initiate an inflammatory response in the GI tract. Pro-inflammatory **cytokines** are induced by the *Salmonella*, particularly IL-1, **interferon** (IFN-β and γ), IL-2, IL-6, and the **chemokine** IL-8, which recruits neutrophils. The epithelial monolayer is an important target and mainly secretes the IL-8 in response to the bacterium. The production of IL-8 is a result of the activation of NFκB within the epithelial cells and is dependent on the type III secretion system in the bacterium, which injects bacterial proteins into the cells thereby inducing the cytokine response. Killing by macrophages is also important as defects in macrophage function, for example, lack of IFN-γ, leads to severe disease.

Both Type I and Type II interferons (IFN) are important in infection with *Salmonella* Typhi and NTS. Type II interferon (IFN-γ) promotes phagocytosis and activates macrophages to kill intracellular bacteria. IFN-γ acts in two ways to eradicate *Salmonella* spp. It induces the production of guanylate binding proteins which lyse the vacuole wall protecting the organism, releasing it into the cytoplasm of the cell leading to pyroptotic cell death. The second method by which IFN-γ is involved is activation of the macrophage leading to ROS that kill the *Salmonella* and induce a pro-inflammatory response.

Type I interferons (IFN-β) are protective of *Salmonella* as they have an anti-inflammatory action via IL-10 which diminishes the TLR-inflammosome response and inhibits a pro-inflammatory environment.

ADAPTIVE IMMUNITY

Eradication of the infection and the production of immunity require **CD4**+ helper T cells and the production of specific antibodies by B cells. The role of cytotoxic CD8 cells in effective eradication of the organism is less clear.

PATHOGENESIS

NTSs induce a secretory diarrhea with a Th-1 pro-inflammatory response. MAMPs on the organism for example LPS and flagellin bind to TLR4 and 5 respectively, activating the Th-1 response by stimulating the production of IL-8 and recruiting neutrophils to the local area causing inflammation.

With *Salmonella* Typhi, adhesion to epithelial cells occurs via **fimbriae**. *Salmonella* Typhi enter via the M cells and/or **dendritic cells** and enterocytes; *Salmonella* Typhi adheres to the **cystic fibrosis transmembrane conductance receptor** (**CFTM**) on GI epithelial cells. Mutations in this protein may lead to lack of adhesion and thus resistance to infection. Once adherent, the bacteria invade by a process called bacteria-mediated **endocytosis** where the type III secretion system is involved. Adhesion of the bacterium induces cytoskeletal changes in the epithelial cell with membrane ruffling that encloses the organism into a vacuole.

Once inside the intestinal epithelial cells of the host, the organism produces a multi-subunit toxin, B (typhoid toxin TT). The toxin consists of three subunits, one of which is similar to that of cytolethal distending toxins and has DNase activity. The toxin induces single-strand breaks in host DNA and replication stress with accumulation of damaged replication forks. Damage to DNA leads to the DNA damage response (DDR). The regulators of DDR are ataxia telangiectasia mutated kinase (ATM) and ATM and rad3-related kinase (ATR). ATM is involved with resolution of double-stranded breaks (dsDNA) and ATR with replication stress involving single-stranded DNA (ssDNA). Single-stranded DNA binds to the replication protein A complex (RPA) which activates ATR and the cell cycle is stalled in order to repair the replication fork. A link between ATM and ATR is phosphorylation of the H2AX histone which co-ordinates the repair process.

The action of the typhoid toxin is to overload the repair pathway with ssDNA eventually leading to senescence of the cell. This state of senescence is transmitted to adjacent cells by an as yet unidentified factor. Induction of cell senescence allows chronic carriage of the organism making the host a typhoid carrier.

Once endocytosed, a proportion of **vesicles** will fuse with the basolateral membrane and enter the **lamina propria**. During adhesion, *Salmonella* Typhi induces up-regulation of the host CFTM receptor and an increased level of translocation to the lamina propria. Here, the organism enters macrophages and dendritic cells where it survives and replicates. *Salmonella* Typhi surviving and replicating within the monocytic lineage are released and pass to the mesenteric lymph nodes and via the thoracic duct to the general circulation where they localize in the cells of the **mononuclear phagocyte system** (in the liver, spleen, and bone marrow). The bacteria continue to replicate and are shed into the bloodstream with the onset of clinical illness and are circulated in the blood to all body organs and induce organ-specific signs and symptoms. Movement of *Salmonella* Typhi from the GI tract may also occur when dendritic cells and macrophages carrying the intracellular organisms migrate to mesenteric lymph nodes.

Organs particularly affected (through the cells of the mononuclear phagocytic system) are the liver and spleen, bone marrow, gallbladder, and importantly, the Peyer's patches in the intestine. **Kupffer cells** in the liver are a major defense mechanism of the host but surviving *Salmonella* that invade hepatocytes induce **apoptosis** of the cells. At this stage, the patient will show systemic signs of inflammation: fever, **jaundice**, hepatosplenomegaly, **myalgia**, headache, and, in some cases, mental confusion. Later on in the infection, **rose spots** may appear and, if left untreated by the third week, there is an intense monocytic infiltration of Peyer's patches, which may rupture leading to signs of perforation of the small bowel.

3. WHAT IS THE TYPICAL CLINICAL PRESENTATION AND WHAT COMPLICATIONS CAN OCCUR?

SALMONELLA TYPHI

Enteric (or typhoid) fever is a serious infection with an appreciable mortality, if left untreated. It is caused by *Salmonella* Typhi or *Salmonella* Paratyphi. The incubation period is from 5 to 21 days depending on the size of the ingested inoculum and host co-morbidity, for example, immunosuppression. In adults, the disease may present as a nonspecific **febrile** illness (**pyrexia of unknown origin – PUO**) or it may present with fever and GI symptoms. In children, there may be a much more nonspecific presentation. Typical symptoms include fever, headache, abdominal pain, and tenderness, constipation or diarrhea, and delirium. On examination, there may be a relative **bradycardia** (where the pulse rate is less than expected from the temperature of the patient), a pinkish **maculopapular rash** found on the trunk (rose spots – **Figure 31.3**), and hepatosplenomegaly. Laboratory investigations (see later) demonstrate **anemia**, **leukopenia**, classically, but not always, with a relative lymphocytosis, abnormal LFTs, and elevated creatine phosphokinase (CPK). Risk factors for infection include immunosuppression and sickle cell anemia. Complications include **cholecystitis**, intestinal perforation and hemorrhage, **osteomyelitis**, and **endocarditis**. *Salmonella* Paratyphi (paratyphoid fever) causes a milder form of the illness compared with *Salmonella* Typhi. Following infection, about 1–5% of patients may become long-term GI carriers of the organism. These individuals are at greater risk of developing hepatobiliary and intestinal carcinoma.

NON-TYPHOID *SALMONELLA*

NTS is one cause of a self-limiting gastroenteritis that is indistinguishable from other bacterial causes. The incubation period is from 12 to 48 hours following ingestion of contaminated food. It presents with fever, abdominal pain, and diarrhea, which may occasionally be bloodstained. Complications include **paralytic ileus** leading to **toxic megacolon**.

4. HOW IS THE DISEASE DIAGNOSED, AND WHAT IS THE DIFFERENTIAL DIAGNOSIS?

DIAGNOSTIC TESTS

Diagnosis of enteric fever is made by isolation of *Salmonella* Typhi or Paratyphi from a blood culture, feces, or bone marrow of a symptomatic patient. The specimen providing the highest diagnostic yield is the bone marrow. Sampling of duodenal secretions using the string test may add to the diagnostic yield. The organism may also be isolated from other specimens such as rose spots, urine, sputum, and cerebrospinal fluid (CSF). NTS are usually isolated from only the feces but occasionally may also be isolated from the blood.

One of a number of selective media may be used for fecal specimens, including xylose-lysine-deoxycholate (XLD), deoxycholate citrate agar (DCA), bismuth sulfite agar, *Salmonella Shigella* (SS) agar, and Hektoen agar. The general principle of these media is that they include sugars and a pH indicator to differentiate *Salmonella* spp. (and *Shigella* spp.) from non-enteric pathogens; a source of sulfur and iron as the *Salmonella* spp. generate hydrogen sulfide, which precipitates the iron to give black colonies; and a selective agent such as bile to which *Salmonella* spp. are resistant (**Figure 31.4**).

The organism is identified by **MALDI-TOF** or **WGS** (**whole genome sequencing**). The serovars are identified by slide agglutination with O and H antibodies and by reference to the Kaufmann-White scheme although this is being replaced by WGS. In the UK, enteric fever is a notifiable disease, as is food poisoning (of any microbiologic cause). Although most industrialized countries have a reporting system for infectious diseases, many countries do not.

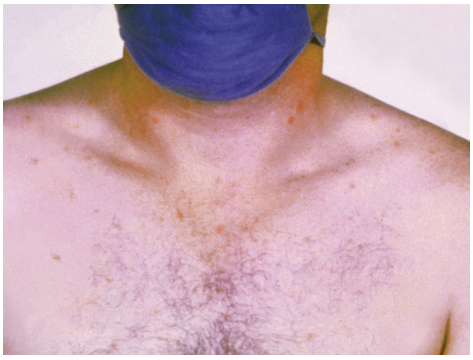


Figure 31.3 Rose spots on the upper trunk in a case of enteric fever. *From the Centers for Disease Control & Prevention, Atlanta, Georgia. Image is found in the Public Health Image Library #2215. Additional photographic credit is given to the Armed Forces Institute of Pathology and Charles N Farmer who created the image in 1964.*

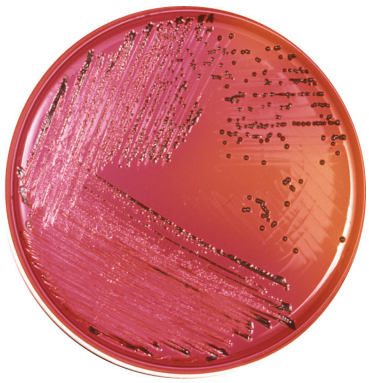


Figure 31.4 Growth of *Salmonella* on DCA medium. *Note the black center in some colonies indicating precipitation of FeS. From the Centers for Disease Control & Prevention, Atlanta, Georgia. Image is found in the Public Health Image Library #6619.*

Serologically, the **Widal test** has been used specifically for *Salmonella* Typhi but is not recommended for diagnosis (in the UK) as it does not have sufficient sensitivity; as many as 50% of patients with culture-confirmed enteric fever are negative in the Widal test. Serologic assays such as a dot **ELISA** test format (Typhidot, TpTest) and a latex agglutination inhibition test (Tubex-detecting IgM to 2009 only) detecting **IgG** and **IgM** in studies are available. In 2016, an comparative assay of TpTest, Tubex, Typhidot was assessed in culture positive cases versus healthy controls in Bangladesh. The sensitivity/specificity was TpTest (96%/96%), Tubex (60%/89%), and Typhidot (59%/80%). PCR and DNA probes are available but not currently in routine use, particularly in resource-poor countries.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis includes a wide range of causes of PUO such as brucellosis, malaria, typhus, and **Dengue fever** as well as causes of fever with intra-abdominal pathology such as **abscess**, amebic dysentery, and abdominal tuberculosis.

5. HOW IS THE DISEASE MANAGED AND PREVENTED?

MANAGEMENT

Salmonella Typhi and Paratyphi

Because of the increasing resistance to antibiotics including chloramphenicol, co-trimoxazole, ampicillin, and ciprofloxacin in India and South-East Asia, the treatment depends on the geographic location of the infecting strain and its susceptibilities. Similar antibiotic resistance also occurs in NTS spp. and, particularly in the UK, the emergence of resistance to ciprofloxacin was temporally associated with the use of a veterinary fluoroquinolone – enrofloxacin. An outbreak (2016) of a strain in Pakistan was resistant to chloramphenicol, amoxycillin, cotrimoxazole, ciprofloxacin, and ceftriaxone, moving the management of such strains to azithromycin/meropenem. The current recommended treatment in the UK in uncomplicated typhoid fever is either azithromycin or ciprofloxacin depending on the susceptibility. In severe enteric fever, either ceftriaxone, ciprofloxacin or meropenem is used, again depending on the susceptibility.

Enteric fever can be prevented by vaccination. Three main types of vaccine exist including an oral live attenuated strain (-Ty21a), a parenteral vaccine based on the Vi capsular polysaccharide antigen (ViCPS Vi), and a **conjugate vaccine** based on the Vi antigen and recombinant exotoxin A of *Pseudomonas aeruginosa* (Vi-rEPA). An acetone-inactivated parenteral vaccine also exists. The protection afforded by these vaccines ranges from 60% to 90%.

Non-Typhoid *Salmonella* spp.

Generally, gastroenteritis does not require antibiotic treatment as the illness is self-limiting. However, in severe disease, or if there is evidence of systemic spread, then depending on the sensitivities an appropriate antibiotic such as a cephalosporin or ciprofloxacin can be used. An unwanted effect of antibiotics is to increase the carriage rate of the organism.

PREVENTION

Prevention of gastroenteritis relies on control of critical points along the food chain from farm to dining room, which includes infection-free animals, sanitary animal transport, hygienic processes in abattoirs, and correct storage and cooking conditions in the kitchen.

SUMMARY

1. WHAT IS THE CAUSATIVE AGENT, HOW DOES IT ENTER THE BODY, AND HOW DOES IT SPREAD A) WITHIN THE BODY AND B) FROM PERSON TO PERSON?

- *Salmonella* spp. are motile gram-negative rods.
- There are over 2500 serovars; they are grouped in the Kauffman-White scheme based upon the O and H antigens.
- *Salmonella* Typhi is a strictly human pathogen and is acquired from food or water contaminated with organisms from another case or a carrier.
- Non-typhoid *Salmonella* spp. are found in animals and infection is acquired from contaminated food or pets.
- *Salmonella* Typhimurium and *Salmonella* Enteritidis are the two most frequent causes of non-typhoid *Salmonella* spp. gastroenteritis.
- *Salmonella* Typhi penetrates the gastrointestinal epithelium and is disseminated by the bloodstream.
- Non-typhoid *Salmonella* spp. generally remain within the gastrointestinal tract, although some serovars may disseminate in the blood.

2. WHAT IS THE HOST RESPONSE TO THE INFECTION AND WHAT IS THE DISEASE PATHOGENESIS?

- Low gastric acid, immunosuppression, and certain polymorphisms including TLR4 and HLA predispose to infection.
- Survival in macrophages occurs by modulating phagolysosome fusion and the bacterial cell wall to resist inimical bactericides.

Continued...

...continued

- *Salmonella* Typhi induces a monocytic response with few gastrointestinal symptoms.
- Non-typhoid *Salmonella* spp. induce a granulocyte response with pronounced gastrointestinal symptoms.
- *Salmonella* Typhi localizes to cells of the monocyte/macrophage system where it replicates.
- *Salmonella* Typhi is distributed to all body organs by the blood, giving rise to organ-specific disease.

3. WHAT IS THE TYPICAL CLINICAL PRESENTATION AND WHAT COMPLICATIONS CAN OCCUR?

- Enteric fever presents as a PUO and abdominal symptoms.
- The incubation period is 5–21 days.
- A rash (rose spots) may be present.
- There may be a relative bradycardia and a leukopenia.
- Hepatosplenomegaly may be present.
- Complications include cholecystitis, intestinal perforation, endocarditis, and osteomyelitis.
- Non-typhoidal gastroenteritis is self-limiting.
- The incubation period is 12–48 hours.
- It presents with fever, abdominal pain, and diarrhea.

4. HOW IS THE DISEASE DIAGNOSED, AND WHAT IS THE DIFFERENTIAL DIAGNOSIS?

- Enteric fever is diagnosed by isolation and identification of the organism.
- The highest yield of organism is from the bone marrow.
- Identification of *Salmonella* spp. is based on MALDI-TOF, WGS or serologic reactions using the Kaufmann-White scheme.
- In many countries, including the UK, food poisoning and enteric fever are notifiable diseases.

5. HOW IS THE DISEASE MANAGED AND PREVENTED?

- There are increasing levels of antibiotic resistance in *Salmonella*.
- Treatment is with azithromycin/ceftriaxone/meropenem in patients from India and South-East Asia.
- Treatment is with ciprofloxacin in patients from other areas.
- Protection from enteric fever is provided by vaccination.
- Antibiotics are not usually required in cases of gastroenteritis caused by non-typhoid *Salmonella*.
- Prevention of gastroenteritis is by adequate hygiene standards at all points in the food chain.

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Students can test their knowledge of this case study by visiting the Instructor and Student Resources: [www.routledge.com/cw/lydyard] where several multiple choice questions can be found.