Typhoid fever and other salmonellosis

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Summary

- Typhoid: important disease in terms of frequency and mortality.
- Over and under diagnosis are common
- *Salmonella typhi :* Human reservoir, causing systemic illness, hotspot Asia
- Non-typhoid *Salmonellae*: zoonosis , causing enteritis (and invasive disease), hotspot Africa
- Typhoid fever: fever, abdominal pain, diarrhoea/constipation, dry cough, splenomegaly, relative bradycardia, rarely roseola typhosa
- Complications: ileal perforation, organ abscesses
- Clinical diagnosis: leukopenia, faeces/urine/blood/bone marrow cultures
- Widal test : serology has lack of specificity and sensitivity
- Treatment: (quinolones), ceftriaxone, azithromycin. Resistance is increasing worldwide.
- Importance of relapse, antibiotic resistance, chronic carriers, gallstones, schistosomiasis.

General

Typhoid fever is caused by infection with *Salmonella typhi*, a Gram-negative facultative intracellular bacterium. The genus is named after the American physician Daniel Salmon. Recently the bacterium has been named *Salmonella enterica subsp. enterica* serotype Typhi. However, the older name will be used in this text. It causes disease only in humans and has no animal reservoir, unlike non-Typhi *Salmonella* spp.

“Typhos” means smoke, obscurity, stupor in Greek and refers to the apathy, confusion, stupor and neuropsychiatric symptoms which are often seen in severe infection. The word also reflects the earlier belief that illnesses were caused by all kinds of emanations (miasmas). The disease is sometimes difficult to differentiate from spotted fever, caused by Rickettsiae (in typhus the rash is more pronounced).

Paratyphoid fever is infection with the closely related bacteria *Salmonella paratyphi* A, B and C. Clinically the course of these is similar although rather milder. Gastro-enteritis caused by other animal *Salmonella* species should not be given the name paratyphoid. *Salmonella paratyphi* A and B have humans as their reservoir. The term “enteric fever” is a collective term that refers to both typhoid and

paratyphoid fever.

Infections with non-Typhi *Salmonella enterica* can be invasive (i.e. positive blood cultures) and occur overall in about 5% of invasive cases. The invasiveness is age-dependent and varies according to serotype. For serotype Enteritidis and Typhimurium it increases by 10x above the age of 65 years.

Bacterial structure

The bacterium has flagella, structures which should not be confused which those of eukaryotic organisms. Anti-H antibodies bind to the flagella. Many *Salmonella* sp. can form two different H antigens. They sometimes undergo a phase change and possess either one or the other H antigen.

The **bacterial wall structure is typical of Gram-negative bacteria**. Around the cytoplasmic membrane lies a thin layer of peptidoglycans. This so-called murein layer consists of long chains of repetitive disaccharide links. Oligopeptide bridges connect the sugar chains. External to this second layer is a third; outer membrane. It consists of a phospholipid double layer in which complex lipopolysaccharides (LPS) are anchored. These fatty sugars have the following components, seen from the inside out: a fatty part (lipid A) anchored in the membrane, a core and an external sugar part consisting of repeating oligosaccharide chains. The latter form the so-called O antigens. The structure and sugar composition of the O antigens vary between different *Salmonella* species. However they all have the same basic structure, there are many serological cross-reactions. Lipid A is very toxic (endotoxin) and causes a broad spectrum of effects such as fever and shock during Gram-negative septicaemia. Septic shock in infections with Gram-negative bacteria is mainly secondary to the effects of endotoxin. Shock in infections with Gram-positive bacteria is mainly due to the effects of secreted exotoxins. Endotoxin acts on the proteins of the complement pathway and on various cytokine networks.

Specific antibodies are produced by the body: **anti-O and anti-H** (also called TO and TH). The humoral antibodies result in little protection. Protection is based on cellular immunity. The O- and H-antigens are used in serological tests (Widal) [named after the French physician Ferdinand Widal, 1862-1929].

Since all *Salmonella* (not only *Salmonella typhi*) and all bacteria related to *Salmonella* possess similar antigens, there are many cross-reactions (the test is not specific). The test also has low sensitivity. This means that the contribution of serology is limited in many clinical situations.

The **Vi-antigen** (virulence antigen) is a part of the capsule that surrounds the cell wall. It consists of a

polymer of a single sugar. The Vi antigen physically covers the O antigen and thus protects it from anti-O antibodies. If the Vi-antigen is present, phagocytosis is more difficult and the bacterium will be more virulent. The infectious dose (ID50) for strains that possess this antigen is 10^7, which is 10 to 100 times lower than the IG50 of strains without the Vi-antigen. The Vi-antigen also occurs in *Salmonella paratyphi* C and *S. dublin* (a subtype of *S. enteritidis*).

The bacterium produces and excretes a protein known as invasin, which allows non-phagocytic cells to take up the bacterium where it is able to live and replicate intracellularly.

Epidemiology

Historical note on Typhoid fever

It was quite a **long time before typhoid fever was differentiated from other febrile disorders**. Many scientists have contributed to our knowledge about typhoid fever. The French physician Pierre Charles Alexandre Louis first proposed the name “typhoid fever”. Between 1822 and 1827 he studied a total of 138 patients with typhoid fever, 50 of whom died. The post-mortem findings were compared to post-mortem results from 83 people who died from other causes. These ideas of meticulous documentation, the use of controls and numerical analysis of the data were an important milestone in medical history. Early ground-breaking work on the germ theory of disease and on the concept of water-borne transmission of illnesses water was done by Dr. William Budd (1808-1882). He investigated an outbreak of typhoid fever in the small Welsh border town of Cowbridge. In 1853, during the local race week, there were balls on two successive nights; eight of those who celebrated subsequently died of “typhoid fever.” The diagnosis of typhoid fever was confirmed at autopsy. Dr. Budd noticed that the local well was close to the septic pit of the inn, suggesting water contamination. He also noticed that a patient who was recovering from typhoid fever had left the inn two days before the parties took place. All the people who became ill had been given lemonade, prepared with water from the contaminated well. The water from the well was the only possible source of infection common to all those who died. He reinforced his theories in 1866 when he and a colleague, Dr. Grace, traced a similar outbreak in several farm cottages. The fever was brought there by the father of one of the families. No one else was ill at the time he arrived and it was obvious that he had contracted the disease elsewhere, probably in nearby Bristol. Dr. Budd and his colleague noted that 4 weeks later several other cases of typhoid fever occurred in persons who lived in cottages which lay a quarter of a mile below the original outbreak. Those who lived in cottages at a higher level escaped entirely. They found that the drains from all the cottages were linked to the same stream and that the second outbreak had occurred

downstream. They reasoned that the agent which provoked typhoid fever was carried there, contaminating the drinking water of the second group of cottages. Dr Budd claimed that **typhoid fever was disseminated via the faecal-oral route, a new concept.** Nevertheless, the community and the medical world were not yet ready for this theory. The earlier hypothesis that typhoid fever could be caused by “rotting material” (pythogenic fever). This was disproved in 1858-1859, when the great “Thames Stink” occurred in London. Due to certain hydrological and meteorological circumstances there was a huge wave of stench in London. The enormous amounts of rotting material in the river should have produced ideal conditions for typhoid fever, yet there were noticeably few cases during those years. The famous Canadian physician Sir William Osler (1849-1919) campaigned for a long time against the term “typhomalaria” which had been introduced by Dr Woodward to describe difficult febrile cases. In 1911, Elie Metchnikoff (1845-1916) fulfilled one of Koch’s postulates reproducing disease in chimpanzees after throat inoculation with *Salmonella typhi*.

Military impact

Throughout history epidemics of infectious illnesses have often played an important part in military conflicts. Famous examples are the American Civil War (1861-1865) with 75,361 cases of typhoid fever, of which 27,056 died. Note that these data are from the time before the bacterium had been isolated. In the Boer War in South Africa (1899-1902) 56,686 cases of typhoid fever were recorded, with 8,225 dead, compared to 7,582 who died from battle wounds. In the brief Spanish American War (1898) there were 20,738 cases out of a total of 107,973 soldiers, with 1,500 deaths. In those days, there was total disregard of the most elementary hygiene. This is in sharp contrast to the Russian-Japanese War of 1904-5, in which the Japanese boiled their water, tested their drinking water wells, covered latrines, disinfected excreta and sterilised cooking utensils, plates and mess tins. The low number of infected soldiers was probably due to these innovations. As well as typhoid fever, the role of epidemic typhus, epidemic borreliosis and bacillary dysentery in these conflicts should not be overlooked.

Transmission

Transmission is mainly via **contaminated water and food**. The bacteria survive for a varying number of weeks in water, ice, dust and can multiply in food. In many regions the infection is endemic. Sometimes there may be local epidemics. One classic mechanism is the contamination of a drinking water reservoir with the contents of a septic tank. In the past this was checked with a fluoresceine test. The bacteria only infect humans. **There is no animal reservoir** unlike the majority of the other Salmonella species.

Recent convalescent patients form the most important reservoir. People can be **healthy carriers and excrete Salmonella typhi for prolonged periods** (concept published in 1903 by Robert Koch : the healthy chronic “Typhusbazillenträger”).

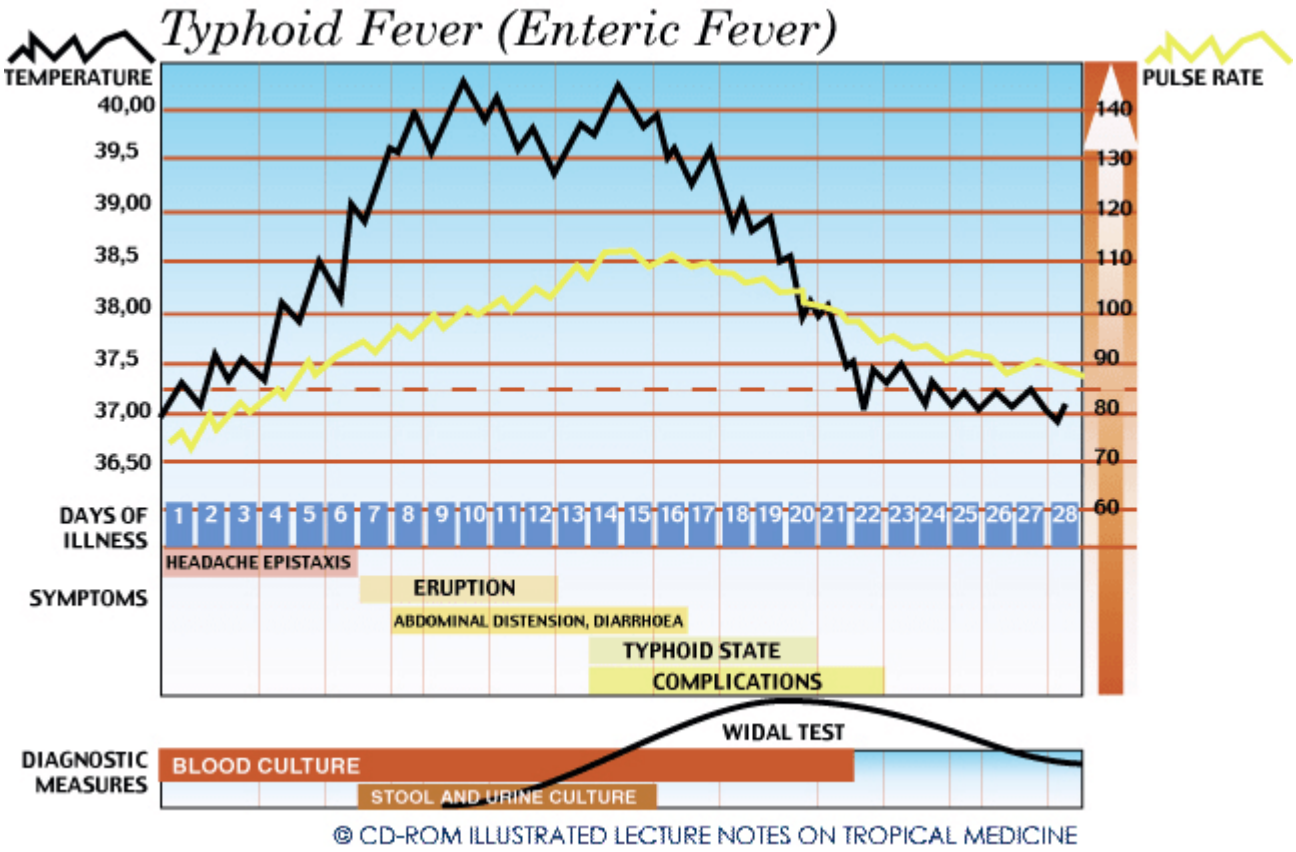
Typhoid Mary

A classic example of a healthy carrier is the case of “Typhoid Mary” the nickname of an Irish woman who became very famous at the beginning of the 20th century. In 1904 there was an epidemic of typhoid fever in a district of Long Island, New York. It was discovered that patients belonged to households where Mary Mallon had been cook. When she was tracked down by George Soper in 1907, she initially refused to cooperate. She was taken by the police, tested positive for S. typhi and was subsequently forced to stay at Riverside Hospital on North Brother Island. After three years she was released after pressure from the media. She then caused further cases including some at the Sloane Maternity Hospital where she worked in the kitchen under a false name. Overall it is certain that there were 53 cases, with 3 deaths, but possibly there were many more (possible role in the outbreak in Ithaca of 1903, with >300 cases).

Pathophysiology

After infection the bacterium penetrates the intestinal mucosa via **M cells that overlie the ileal Peyer’s patches**. M cells are phagocytic cells in the mucous membrane whose function is to sample microbes from the intestinal lumen and pass them on to the lymphoid tissue of the Peyer’s patch in order to activate the immune defences against intestinal microbes. Once inside the M cell the ***Salmonella* replicate within the phagosome**, subsequently killing the cell and spreading to adjacent cells. The bacteria are then taken up by mononuclear cells in the intestinal lymphoid tissue. There is **intracellular multiplication in the mesenteric lymph nodes**. From the lymphatic tract the bacteria pass into the blood (**bacteraemia**) and are disseminated through the whole body (spleen, liver, gall bladder, etc.). The intestine will be re-infected through the bile. The seeding of extra-intestinal organs can result in **extra-intestinal complications** virtually anywhere.

Clinical aspects



Overview of the symptoms during “classic” typhoid fever. Copyright ITM

Early clinical

Symptoms are quite variable. The **incubation period is usually 10 to 14 days**. This is considerably longer than the incubation time of 1-5 days for most other intestinal bacterial pathogens. One of the factors that determines the incubation period is the number of bacteria in the inoculum. There is always fever, which rises progressively. Initially there may be a brief episode of diarrhoea. Inflammation of the lungs leads to a dry cough. The combination of cough with fever sometimes leads to an assumption that the illness is a respiratory tract disorder. General malaise and headache are prominent. The illness may initially be confused with malaria. The patient is severely ill and sometimes apathetic or confused (typhoid = stuporous).

Half of the patients will subsequently develop abdominal pain. Diarrhoea -often described as pea soup- or constipation occur in roughly equal proportions (40 %). One third of patients vomit. The intestinal mucosa of the small intestine at the antimesenteric border becomes inflamed. The lymph

follicles (Peyer's patches) that are present in this location become infected and necrotic. Intestinal ulcers result which may subsequently perforate. If this does occur, the perforation is found in the final 60 cm of the ileum. Invasion of the liver and spleen leads to mild or moderate hyperplasia of the reticulo-endothelial system resulting in hepatosplenomegaly. Small red spots (2 to 5 mm) which recede when pressed can be observed on the trunk on white skin in a small number of patients. These "roseola typhosa" are quite difficult to see on a white skin and almost impossible to make out on a darker skin. The skin rash disappears after a few days. The heart rate is sometimes relatively slow for the fever (Faget's sign, French physician Jean Faget 1818-1884). Tachycardia would be expected when the temperature is 39.5°C or 40°C. Relative bradycardia is not a constant finding however and is also non-specific. For example, it also occurs in yellow fever. If a liver biopsy is taken, very typical lobular aggregates of Kupffer's cells are seen in the parenchyma (typhoid nodules). They simulate granulomas and illustrate the hyperplasia of the reticulo-endothelial system.

Complications

If untreated the fever remains high for two weeks, after which there is progressive improvement during the third week. If ileum perforation occurs, it is usually during this period. Generalised peritonitis results. There is then a sudden deterioration of the general condition: tachycardia, hypotension and pain in the right iliac fossa. A similar deterioration occurs in the case of gastrointestinal bleeding.

Without antibiotics the mortality in typhoid fever is 10%, chiefly due to intestinal perforation, internal bleeding, septicaemia with toxaemia and the formation of abscesses in other organs. If there are no complications (deep-seated abscesses, cholecystitis, osteomyelitis, etc.), the fever disappears in the third week. Spontaneous abortion may be triggered by this severe illness. Hair loss may be extensive.

Often the bacteria can still be detected using coproculture or urine culture, after the symptoms have disappeared. This is still possible one year after the illness in patients who become chronic carriers (1-6%, on average 3 % of patients). Carriers are more frequent in patients with gallstones or schistosomiasis. Prolonged salmonellosis in schistosome-infected patients is due to an association of *Salmonella* sp. with the schistosome worms themselves through pili which specifically recognize and bind glycolipids on the surface of the worms. The worms thus provide a multiplication focus for these bacteria in the portal mesenteric system, with a persisting blood stream infection following. Most carriers are asymptomatic.

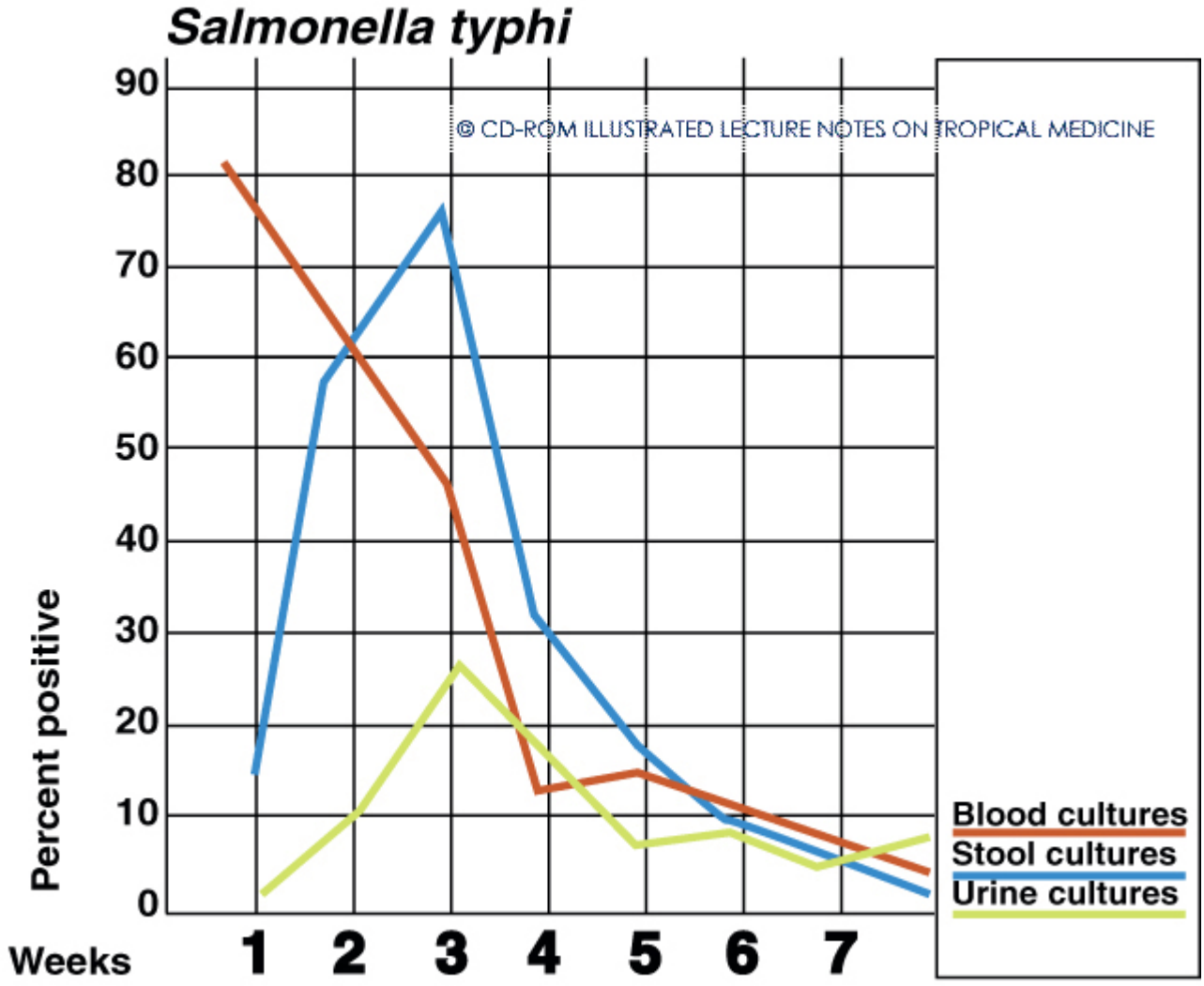
Relapse

Relapse occurs in 2 to 10% of patients 5 days to 2 weeks after the fever has subsided. This usually has a milder course than the first episode. The relapse is caused by multiplication of reactivated persistent intracellular bacteria which were previously “dormant”. It is not due to antibiotic resistance; so that treatment of a relapse is the same as that for the first attack. If there is a lack of clinical improvement in the first disease episode notwithstanding antibiotic treatment, the bacteria are likely resistant and the antibiotic must be changed.

Differential diagnosis:

Differentiation from other febrile disorders is initially difficult. The differential diagnosis should include: respiratory tract infection (clinical, chest X-ray), brucellosis (undulating fever pattern, vertebral involvement, blood cultures for which specific media need to be used), malaria (thick smear, thrombocytopenia), subacute bacterial endocarditis (heart auscultation, splinter haemorrhages, embolic problems, painful Osler’s nodes at the finger tips, Roth’s spots on the retina, blood cultures), kala azar (chronic splenomegaly, bone marrow amastigotes), deep pyogenic abscesses (elevated neutrophil count, ultrasound, aspiration of pus), liver amoebiasis (leukocytosis, clinical examination, ultrasound, serology, aspiration), typhus (often pronounced rash, sometimes chancre, meningeal signs, DIC [disseminated intravascular coagulation]). Differentiation from viral infections may be very difficult. Differentiating typhoidal ileal ulcers from those caused by tuberculosis or Crohn’s disease is usually easy.

Diagnosis



Blood cultures in typhoid fever have higher sensitivity than coprocultures in the early stages of the disease.
Later, the inverse applies. Copyright ITM

Clinical

The diagnosis of typhoid fever is usually based on clinical criteria and in the majority of cases it will be made without formal proof. Perforation of the terminal ileum is quasi pathognomonic for typhoid fever, but the diagnosis should be made before this complication arises. In clinical practice there are actually few disorders that cause perforations in the terminal ileum: typhoid fever, tuberculosis, trauma (e.g. ingested tooth pick) and Crohn's disease. In many developing countries, two diseases

often act as default diagnoses: malaria and typhoid fever. This illustrates the difficulties and uncertainties with which clinicians are confronted, together with the fact that both diseases are relatively frequent and are treatable (low threshold for diagnosis). Further too much importance is attached to a Widal test and the interpretation of a thick smear is often not reliable in a local laboratory (the problem is not the thick smear itself but the reading of it).

Bacterial culture

Positive cultures still form the gold standard for diagnosis. Cultures (bone marrow, blood, faeces, urine, duodenal aspirate or string test) will often be positive, but are often not feasible in practice. The chance of obtaining a positive culture is higher if repeated cultures are taken while culturing a sufficient volume of blood per culture. Blood cultures are positive in 40 to 80% of patients. In untreated patients there are ten times more bacteria per ml bone marrow than per ml blood.

Serology

Serological tests for antibodies to O and H antigens can be carried out (Widal or newer anti body-based rapid tests). A Widal test is only positive in 50 % at the beginning of hospitalisation, and may be positive due to salmonellosis suffered previously (e.g. due to *Salmonella* enteritidis) or due to an earlier vaccination. Routinely requesting this test under third world conditions makes no sense. The test can be used to detect a rising titer (seroconversion). Antibodies to the O antigen rise swiftly, and return to negative or to low titers in a couple of months (in particular type IgM antibodies). Anti-H antibodies rise more slowly but will stay positive for longer (in particular type IgG antibodies). If the presence of advanced typhoid fever is suspected on clinical grounds and if malaria is ruled out and a single Widal test is carried out (preferably using O antigen), then a high titer of these antibodies is a relatively strong argument that the patient does indeed have typhoid fever. Nothing can be decided from a negative result.

Other arguments

A complete blood count and differential often shows normal or reduced white blood cells. The eosinophils will be low or zero. In intestinal perforation there is leukocytosis, and in intestinal bleeding there is significant anaemia. A chest X-ray is often normal, in spite of the frequent presence of respiratory symptoms.

Treatment

Salmonella Typhi in many parts of the world have become **resistant** against chloramphenicol and other first line antibiotics (e.g. ampicillin, co-trimoxazole).

In addition, chloramphenicol has no effect on the relapse rate and is of no benefit to carriers. Ceftriaxone and quinolones (ofloxacin, ciprofloxacin) have subsequently become first line choice but are more expensive and there is quickly growing resistance for fluoroquinolones. The resistance of *S. typhi* to antibiotics varies from region to region but is increasing everywhere. Azithromycin or ceftriaxone are the drug of choice in areas with high levels of fluoroquinolone resistance such as Southeast-Asia. In many patients the time to defervescence may take from several days up to more than a week.

Adjunctive treatments include laparotomy in case of intestinal perforation and drainage of abscesses is recommended.

Prevention

Hygiene

General sanitary provisions such as clean drinking water, toilets and availability of soap to wash hands play a central role. If an epidemic occurs, in the first instance the source of infection should be sought.

When treating patients with typhoid fever attention should be given to the disinfection of linen, disposal of faeces and hand washing. Treatment of chronic carriers, in particular those involved in the preparation of food is important (cf. Typhoid Mary), but opinions vary on this. Patients who are ill or convalescing are the chief source of bacteria in the community. A second problem is that in the tropics carriers cannot usually be traced due to the lack of infrastructure. Most patients stop excreting bacteria in the weeks following typhoid fever, and no new antibiotic treatment should be started in the first months after the acute illness, unless the patient is working in food preparation. Chronic carriers with gallstones often harbour bacteria in the biofilm on the surface of the stones. If treatment is needed, a cholecystectomy is suggested together with a quinolone for a longer period (not chloramphenicol). If there is urinary schistosomiasis, this should also be treated with praziquantel. The worms may harbour bacteria in their intestinal systems or in their tegument.

Vaccination

The old TABC vaccine had quite a number of side effects and no longer used nowadays. At present there is an oral live vaccine (Vivotif®), which uses an attenuated strain of S. typhi. This vaccine contains no Vi-antigen. Vivotif® is administered as follows: 1 capsule taken on an empty stomach on days 1, 3 and 5. This provides protection in 70 % of individuals for 3 years. The vaccine containing Vi-antigen (Typhim Vi®) is injectable (1 injection) and provides the same degree of protection. The production of a Salmonella typhi Vi-conjugated vaccine (Vi-rEPA) is a new development. In this; the immunogenic polysaccharide of the bacteria is conjugated with non-toxic recombinant Pseudomonas aeruginosa exotoxin A. Trials have shown efficacy of 91% in children between 2 and 5 years and may confer longer immunity.

Non-typhoid *Salmonella* blood stream infection

Non-typhoid *Salmonella* bacteraemia is most likely to occur in immunocompromised hosts such as those who are at either extreme of the age spectrum or those who have diabetes, cancer, HIV positive, or who use immunosuppressive medications. When bacteraemia occurs, extra intestinal signs and symptoms may include osteomyelitis, abscess formation, and meningitis. Salmonellae may adhere to endothelial surfaces, resulting in cardiovascular infections, such as infectious endocarditis and endarteritis. Although atherosclerotic blood vessels are more susceptible to bacterial adhesion, infection of normal endothelial surfaces can also occur. The organisms may infect pre-existing aneurysms or atherosclerotic plaques, leading to arterial-wall necrosis and rapid aneurysm formation. The most frequently involved site is the infrarenal abdominal aorta.

Antibiotic resistance levels are even higher and mostly combined. Third generation cephalosporins and azithromycin have become drugs of choice.

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