Microbiology

Doctor 2017 | Medicine | JU

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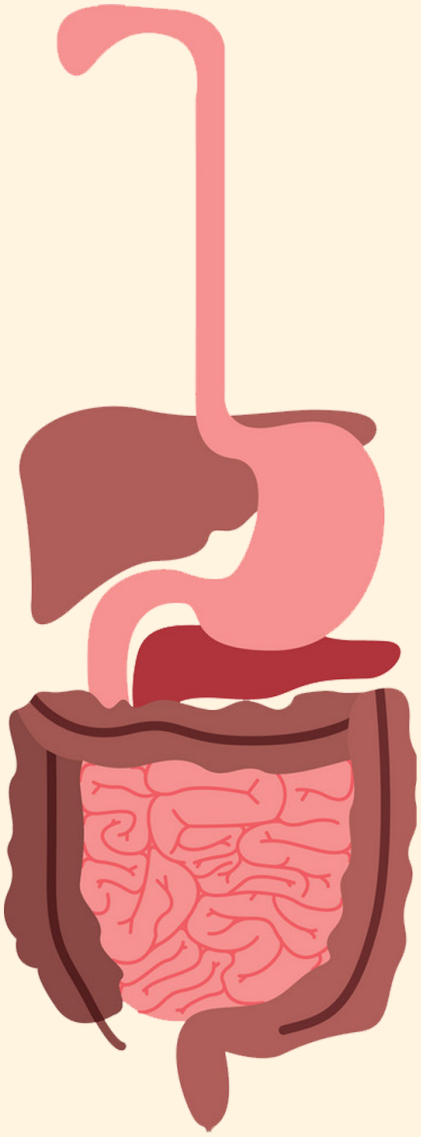
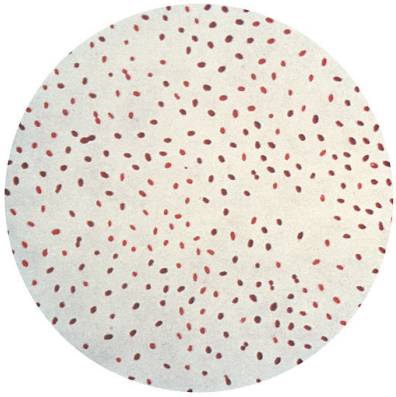


2nd system - GI

Brucellae



- The Brucellae are obligate parasites of animals and humans and are characteristically located intracellularly.

- The appearance of brucellae in young cultures varies from cocci to rods 1.2 µm in length, with ***short coccobacillary*** forms predominating. They are ***gram negative*** but often stain irregularly, and they are ***aerobic, nonmotile, unencapsulated and non-spore forming.***

- Brucellae are adapted to an ***intracellular habitat*** and this is the problem with brucellae as it needs a long duration of treatment.
- Their nutritional requirements are complex.
- Brucellae genus has four species (Although named as species, DNA relatedness studies have shown there is only one member in the genus, ***B. melitensis***, with ***multiple biovars*** (with different reservoirs)):

  - ✓ ***Brucella melitensis*** (the most common cause of ***human Brucellosis***) and the reservoir is ***sheeps and goats.***
  - ✓ ***Brucella canis*** and the reservoir is ***dogs.***
  - ✓ ***Brucella abortus*** (it is named abortus because it causes ***abortion in cattle*** but not in humans) and the reservoir is ***cattle***.
  - ✓ ***Brucella suis*** and the reservoir is ***swine***.

Note: other species of brucellae are only found in animals

- They are ***microaerophilic*** which means they grow under reduced tension of oxygen to 5% as well as 10% of CO2***. (Slides: Whereas B. abortus requires 5–10% CO2 for growth, the other three species grow in air).***
- characteristics used to differentiate them from Enterobacteriaceae and other gram-negative bacteria:
  - ✓ ***Catalase and oxidase*** are produced by the four species that infect humans.
  - ✓ do not ferment any ***carbohydrates***.
  - ✓ They do not produce neither acid nor gas in sufficient amounts for classification.

So, they are relatively inactive metabolically

- They are killed by ***boiling and pasteurization*** but are resistant to ***freezing and drying***.

- Brucellae causes the human disease ***brucellosis*** which is commonly known as ***undulant fever, Malta fever and Mediterranean Sea fever.*** The disease characterized by an acute bacteremic phase followed by a chronic stage that may extend over many years and may involve many tissues.

- Brucellae targets the ***Reticuloendothelial system*** starting from macrophages and lymph nodes reaching the liver, spleen and bone marrow.

Epidemiology:

- Brucellae are animal (wild or domestic) pathogens (***zoonotic disease)*** transmitted to humans by accidental contact with infected ***animal feces, urine, milk, or tissues***. The common sources of infection for humans are ***unpasteurized milk, milk products, and cheese*** as well as ***occupational contact*** (eg, farmers, veterinarians, laboratory workers and slaughterhouse workers) with infected animals. Cheese made from unpasteurized goat's milk is a particularly common vehicle for transmission of brucellosis.

- Brucellosis may be acquired by ***ingestion, inhalation, mucosal or percutaneous exposure.*** **Percutaneous** exposure is the **most common** root and it includes needle sticks, abrasions or skin cuts which allow the entry of brucellae.

- Brucellosis used to be very endemic in our region that is why it is commonly known as Mediterranean Sea fever or the Malta fever because people were at close contact with animals. It was very common to the point that any one presented with undulant fever (means temperature goes up and down) with an abnormal gait (walking) was diagnosed with brucellosis until proven otherwise.

- Accidental injection of the live vaccine strains of B. abortus (S19 and RB51) and B. melitensis (Rev 1) can cause disease. B. melitensis and B. suis have historically been developed as biological weapons by several countries and could be exploited for bioterrorism.
- Because brucellosis is a zoonotic disease, the prevention of the disease depends mainly on controlling the animals.

- In general, microorganisms are classified into 4 biosafety levels (1 is the simplest and 4 is the most severe). Brucellae is considered as ***biosafety level 3*** which means you **can't work with it in a standard laboratory**, you need a biosafety **level 3 cabine**.

Pathogenesis:

- Although each species of Brucella has a preferred host, all can infect a wide range of animals, including humans.

- Despite being Gram-negative bacteria, brucellae endotoxin activity is less sever. They do not produce any exotoxin either.

- The common routes of infection in humans are the intestinal tract (ingestion of infected milk), mucous membranes (droplets), and skin (contact with infected tissues of animals). Cheese made from ***unpasteurized goats' milk*** is a particularly a common vehicle.

- Brucellae route of infection:

    1. From the portal of entry, they pass the epithelial barrier and innate immune cells reaching the ***macrophages*** (antigen-presenting cells). They multiply ***inside*** the macrophages and they get carried with them. to reticuloendothelial system.

    2. Via lymphatic channels and regional lymph nodes to the thoracic duct and the bloodstream, which distributes them to the parenchymatous organs.

    3. ***Granulomatous nodules*** that may develop into abscesses form in lymphatic tissue, liver, spleen, bone marrow, and other parts of the reticuloendothelial system. In such lesions, the brucellae are principally ***intracellular***.

- The Hallmark of brucellae pathology is the formation of ***granulomas*** which consist of epithelioid and giant cells, with central necrosis and at advantage stage peripheral fibrosis.

Clinical Findings:

- The incubation period ranges from 1–4 weeks. The onset is insidious, with malaise, fever, weakness, aches, sweats and musculoskeletal symptoms.
- The fever is the main symptom, and it is characterized as an ***undulant*** fever which means it gets very high then it goes down (similar to typhoid fever but less sever). Fever usually rises in the afternoon and its fall during the night is accompanied by drenching (profound) sweat.
- There may be gastrointestinal and nervous symptoms. Lymph nodes enlarge, and the spleen becomes palpable. Hepatitis may be accompanied by jaundice.
- Deep pain and disturbances of motion, particularly in vertebral bodies, suggest osteomyelitis. These symptoms of generalized Brucella infection generally subside in weeks or months, although localized lesions and symptoms may continue.
- After the initial infection, a chronic stage may develop, characterized by weakness, aches and pains, low-grade fever, nervousness, and other nonspecific manifestations compatible with psychoneurotic symptoms.

There are 3 possible presentations of brucellosis:

1. High grade **undulant** fever.(similar to typhoid fever but its less severe)
2. For younger people, fever is associated with ***monoarthritis*** (inflammation of one of the joints) usually of the ***hip or knee joint.*** This is what affects the gait.
3. For older people, fever is associated with ***low back pain*** because of the involvement of the vertebral body. (hence causing the gait previously mentioned)

Diagnostic Laboratory Tests:

- Definitive diagnosis of brucellae infections requires **isolation** by taken specimens and culture them:
  1. Specimens:
     - ✓ ***Blood or biopsy material*** (lymph nodes, bone and bone marrow, spleen and so on) should be taken for culture, and serum for serologic tests.
  2. Culture:
     - ✓ ***Brucella agar*** a selective agar plate specifically designed to culture Brucella species. The medium is highly enriched and —in reduced form— is used primarily in cultures for anaerobic bacteria. We incubate the in microaerophilic conditions to optimize their growth.
     - ✓ Brucella species bacteria grow on commonly used media, including trypticase-soy medium with or without 5% sheep blood, brain–heart infusion medium, and chocolate agar.

Note: The typical virulent organism forms a smooth and transparent colony upon culture

- The problem with brucellae culture is that it is very hard to isolate and it takes a long time to grow as you need to incubate it for at least 8 weeks. This is why we may need ***serology***:
  - ✓ Immunoglobulin M (IgM) antibody levels start rising in 3 weeks of acute illness (***slides: during the first week***) and peak at 3 months.
  - ✓ IgG and IgA antibody levels rise about 3 weeks after onset of acute disease and peak at 6–8 weeks, and remain high during chronic disease. (***start earlier and peak earlier***)

The serology criteria **should include agglutination and non-agglutination tests**:

1. serum agglutination test: IgG agglutinin titers above 1:80 (some books say 1:160) or four folds increase in the titers is presumptive diagnosis (indication for active infection). ***Note***: usually when we test for acute infection, we look for IgM antibodies, but **with brucellae infection we look for IgG** antibodies as they rise and peak earlier.

Problems with agglutination test:

- ✓ **Cross reaction** with other bacteria or antigens such as Individuals infected with cholera or injected with cholera vaccine may develop agglutination titers to brucellae.
- ✓ ***Prozone phenomena***: serum agglutination test of brucellae infected individuals may give a false negative (no agglutination) at lower dilutions (higher concentrations) but agglutination may appear at higher dilutions. The reason for that is because of IgA antibodies which act as blocking antibodies interfering with IgG agglutination. To over come this problem, we do ***Coombs test*** by adding ***Anti-Human Globulins*** to isolate the effect of IgA from interfering with IgG.

2. Non-agglutination tests such as ***ELISA***. IgG, IgA, and IgM antibodies concentrations may be detected using enzyme-linked immunosorbent assay (ELISA), which use cytoplasmic proteins as antigens. These assays tend to be more sensitive and specific than the agglutination test especially the setting of chronic disease.

Treatment & Immunity:

- Brucellae may be susceptible to tetracyclines, rifampin, trimethoprim–sulfamethoxazole, aminoglycosides, and some quinolones. Symptomatic relief may occur within a few days after treatment with these drugs. However, because of their intracellular location, the organisms are not readily eradicated completely from the host.

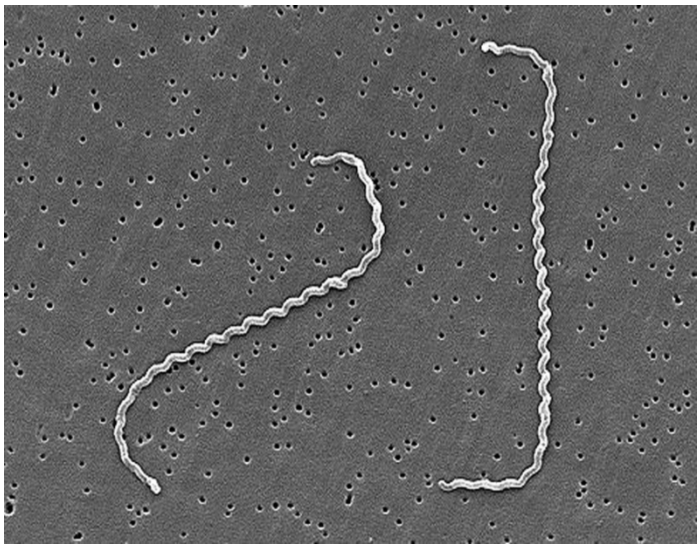
- For best results, **treatment must be prolonged**. Combined treatment with a tetracycline (eg, doxycycline given 200 mg/day instead of the regular 100mg) and either streptomycin for 2–3 weeks or rifampin (1g/day) for 6 weeks (**45 days**) is recommended.
- The treatment has a lot of side effects.

Prevention, and Control:

- Eradication of brucellosis in cattle can be attempted by test and slaughter, active immunization of heifers with avirulent live strain 19, or combined testing, segregation, and immunization. Cattle are examined by means of agglutination tests.
- Although there is Active immunization of animals against Brucella infection, human vaccination is still experimental.
- Control rests on limitation of spread and possible eradication of animal infection, pasteurization of milk and milk products, and reduction of occupational hazards wherever possible.

Leptospira

- ***Spirochete*** (spiral shaped) bacteria.
- the genus Leptospira comprised two species:
  - ✓ the **pathogenic to humans*: L. interrogans***
  - ✓ The free living saprophytic ***L. biflexa.***
- ***Rodents (rats and mice)*** are the main reservoir for Leptospira.
- Leptospirosis is ***zoonotic disease*** caused by pathogenic Leptospira species and is characterized by a broad spectrum of clinical manifestations, varying from mild self-limiting asymptomatic infection, flu like illness to the fulminant and fatal disease (**Weil's Syndrome**).



- Weil's syndrome is characterized by a biphasic disease: ***a leptospiremia phase*** followed by ***a window period*** when the patient is feeling comfort and resolution then followed by ***the second phase (the immune phase***) when the bacteria leave the blood circulation and establish themselves in solid organs with lungs, liver and kidneys usually being their targets. It may cause pulmonary hemorrhage, jaundice and acute renal failure (nitrogen retention).

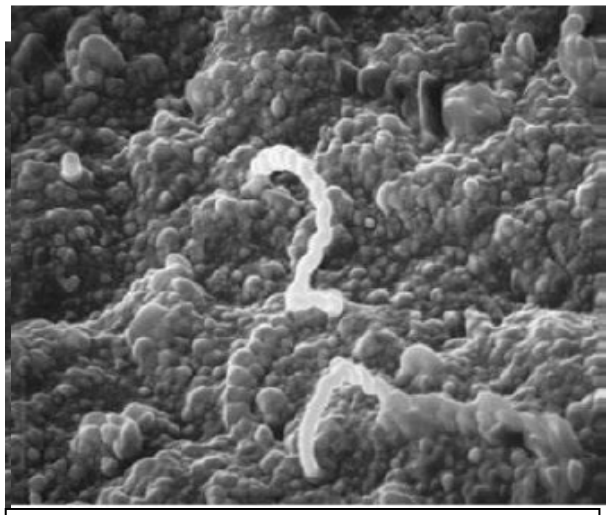
- Kidney involvement in many animal species is chronic and results in the shedding of large numbers of Leptospira in the ***urine***; this is probably the main source of environmental contamination resulting in infection of humans. So, leptospirosis is a zoonotic disease and humans are accidentally infected. The main route of transmission is by ***urine*** either by directly affecting susceptible patients (***most commonly through skin abrasions followed by mucous membranes like the conjunctiva)*** or indirectly by contamination of food and water (***less commonly***).

- Human urine also may contain spirochetes in the second and third weeks of disease.

Leptospira interrogans:

- Leptospira are tightly coiled, thin, flexible ***spirochetes*** 5–15 µm long, with very fine spirals 0.1–0.2 µm wide; one end is often bent, forming a hook. They are ***motile***.

- They are actively motile, which is best seen using a ***dark-field microscope.*** (not under the light microscopes as many other microorganisms)
- For staining of Leptospira we use ***Giemsa stain or silver impregnation of the tissue.***
- Leptospira derive energy from oxidation of long-chain fatty acids and cannot use amino acids or carbohydrates as major energy sources. Ammonium salts are a main source of nitrogen.



Transmission electron microscope photo of L. interrogans showing the spirally question mark shaped bacteria with two periplasmic flagella.

- Leptospira can survive for weeks in water, particularly at alkaline pH.

Epidemiology:

- Leptospirosis has a worldwide distribution but occurs most commonly in the tropics and subtropics because the climate and occasionally poor hygienic conditions favor the pathogen's survival and distribution.
- Current information on global human leptospirosis varies but indicates that approximately 1 million severe cases occur per year, with a mean case–fatality rate of nearly 10%.
- The vast majority of infections with Leptospira cause no or only mild disease in humans. A small percentage of infections (~1%) lead to severe, potentially fatal complications.

Pathogenesis:

- Transmission occurs through cuts, abraded skin, or mucous membranes, especially the conjunctival and oral mucosa. After entry, and an incubation period of 1–2 weeks.
- The organisms proliferate, cross tissue barriers, and disseminate hematogenously to all organs (***leptospiremic phase***). This is followed by a ***window period.***
- They then leave the blood and establish themselves in the parenchymatous organs (most commonly kidneys followed by the liver). The severest disease is called ***Weil's syndrome*** producing hemorrhage and necrosis of tissue and resulting in dysfunction of those organs (jaundice, pulmonary hemorrhage, nitrogen retention). This is called ***the immune phase*** because antibodies start to appear in this phase.

Clinical Findings:

- The presentation depends on the leptospiremia phase. When bacteria are circulating in the blood there is chills, fever, night sweat, nausea, vomiting, abdominal pain, musculoskeletal symptoms and redness of the eye (if the infection was through the conjunctiva). When bacteria reach the organs then the hallmark is the pathology of the organs.
- The illness is often biphasic. After initial improvement, the second phase develops when the IgM antibody titer rises. It manifests itself often as "aseptic meningitis" with an intense headache, stiff neck, and pleocytosis of the CSF.
- Nephritis and hepatitis may also recur, and there may be skin, muscle, and eye lesions. The degree and distribution of organ involvement vary in the different diseases produced by different Leptospira in various parts of the world.
- Many infections are mild or subclinical. Hepatitis is frequent in patients with leptospirosis.

Diagnostic Laboratory Tests:

- Specimens: consist of ***blood, CSF, urine and tissues*** for microscopic examination and culture.
- Microscopic Examination: ***Dark-field examination*** or thick smears stained by the Giemsa technique or silver impregnation.
- Culture:
  - ✓ Leptospira grow best under aerobic conditions at 28–30 C in semisolid medium (eg, ***Ellinghausen-McCullough-Johnson-Harris EMJH*** which **is selective for Leptospira**) in 10 mL test tubes with 0.1% agar and 5-fluorouracil.
  - ✓ Growth is slow, and cultures should be kept for at least 8 weeks.

- Serology: The diagnosis of leptospirosis in most cases is **confirmed serologically** with microscopic agglutination test (***MAT***) and ***ELISA***.

Treatment & Immunity:

- Self-limited disease may just need symptomatic treatment.
- Treatment of mild leptospirosis should be with oral doxycycline, ampicillin, or amoxicillin.
- Severe leptospirosis patients should be administered to the hospital and treated with ***IV penicillin*** as soon as the diagnosis is considered to prevent Weil's syndrome and organs failure.
- Serovar-specific immunity follows infection, but reinfection with different serovars may occur.

Prevention, and Control:

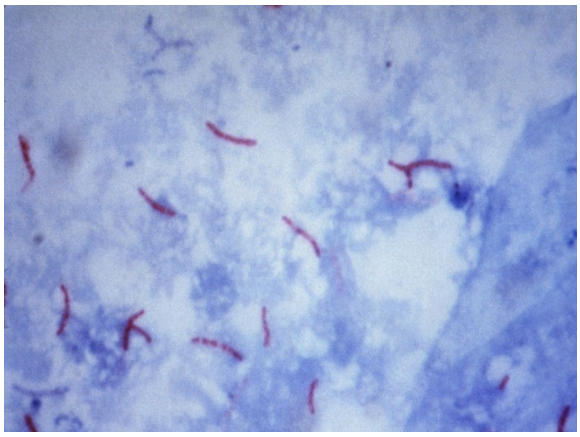
- Leptospirosis is a zoonotic disease and the bacteria are excreted in the urine in both the active disease and the asymptomatic carrier state. So, the prevention depends Avoidance of exposure to urine and tissues from infected animals through proper eyewear, footwear, and other protective equipment.
- Targeted rodent control strategies could be considered.
- Leptospira remain viable in stagnant water for several weeks; drinking, swimming, bathing, or food contamination may lead to human infection. Persons most likely to come in contact with water contaminated by rats (eg, miners, sewer workers, farmers, and fishermen) run the greatest risk of infection
- Vaccines for agricultural and companion animals are generally available, and their use should be encouraged. However, there is no human vaccine.

Mycobacterium Tuberculosis (Mtb)

- It was not until the 19th century, when Robert Koch utilized s new staining method (ZN stain) and applied it to sputum from patients discovering the causal agent of the disease Tuberculosis (TB); Mtbor Koch bacillus.
- The genus mycobacterium has 3 members:
  - ✓ ***Mycobacterium tuberculosis*** the causative agent of tuberculosis
  - ✓ ***Mycobacterium leprae*** the causative agent of leprosy
  - ✓ ***Non-tuberculous mycobacterium (NTM)*** also known as ***environmental mycobacteria*** and they mainly affect immune-compromised patients. One example of them is ***Mycobacterium avium complex.***
- Tuberculosis consume patients and cause weight loss and white plaque (extreme pallor seen among patients).
- The leading cause of death for HIV or immune-compromised patients is the mycobacteria either the tuberculous (more severe) or the environmental.
- Mycobacterium tuberculosis is a member of mycobacterium tuberculosis complex (MTC) and it is the prototype and the most common. The complex includes 11 members: M. tuberculosis (Mtb), Mycobacterium africanum, ***Mycobacterium bovis (was a common cause of tuberculosis before the introduction of BCG vaccine and milk pasteurization)***, Mycobacterium microti, Mycobacterium caprae, Mycobacterium pinnipedii, Mycobacterium suricatte, Mycobacterium mungi, Mycobacterium dassie, Mycobacterium oryxand Mycobacterium canetti ➔ all of them can cause human tuberculosis.

- ***it is an intracellular pathogen*** that can live inside macrophages despite being professional phagocytes and antigen presenting cells, ***by inhibiting the phagosome-lysosome fusion***. It can live within the macrophages for years as a ***latent tuberculosis*** with no symptoms or signs and without being infectious to others. this is the problem with tuberculosis as humans have been fighting it for ages and still haven't reached a full solution.
- Mtb is a slow growing, obligate aerobe, facultative intra-cellular bacterium, non-spore forming, non-motile acid-fast bacilli. It divides every 24 hours (compared to 20 mins of E. coli) that is why you need to culture them at least for 4-5 weeks before starting to see colonies and you need up to 8 weeks before deciding that the culture is negative.

Mycobacterium Tuberculosis (Mtb) staining:



- If you stain them with gram stain, it may appear as a weak positive. But in general gram stain is not applicable for Mtb.
- We need ***Ziehl-Neelsen (ZN)*** technique ***(acid-fast staining).***
- So Mtb is an acid-fast bacillus because of its complex wall.
- Mtb cell wall is mainly composed of lipids especially: ***WAX-D, Mycolic acid and the cord factor*** which are the main virulence factors of Mtb.

Epidemiology:

- Two TB-related conditions exist; latent TB infection (LTBI) and TB disease. If not treated properly, TB disease can be fatal. People who have latent TB infection do not feel sick, do not have any symptoms, and cannot spread TB to others
- Not every one infected with the bacteria well become ill. There is the ***10-3-1 formula*** which states that every 10 people exposed to the mycobacterium tuberculosis, 3 of them well develop latent TB and 1 only well develop active TB while the remaining 6 somehow clear the infection by either their innate or the adaptive immune system.
- About one third of the world's population is infected with TB bacteria (TB latency). However, only small proportion of those become sick with TB if thier immune status become compromised ***(this is called secondary TB or TB reactivation).***
- TB is considered an airborne infectious disease although M. tuberculosis complex organisms can be spread through un-pasteurized milk, direct inoculation and other means. Over crowding and poor social and economic status are risk factors for TB.
- TB remains a leading cause of infectious diseases morbidity and mortality. In 2015, an estimate of 10.4 million new TB cases were seen worldwide.
- Fortunately, here in Jordan TB incidence has dropped to 25/100000.

Tuberculosis TB:

- Patients who have been exposed to Mtb may develop active tuberculosis and acute infection from the beginning. 80-90% of the cases it is pulmonary tuberculosis, the other 10-20% might develop extra-pulmonary tuberculosis (it can attack any part of the body such as meninges of the brain especially in children causing tuberculous meningitis which is the severest form of tuberculosis,

affecting the bone (mainly spine) causing Pott's disease, affecting the lymph nodes causing Scrofula, pericardium or abdominal tuberculosis.

- The primary site of TB is usually lung, from which it can get disseminated into other parts of the body. The other routes of spread can be contiguous involvement from adjacent tuberculous lymphadenopathy or primary involvement of extrapulmonary organ.
- The Hallmark of tuberculosis is the formation of granulomas.

Gastrointestinal (GI) tuberculosis pathogenesis:

- The abdominal TB), which is not so commonly seen as pulmonary TB (represents only 5% of the total extra-pulmonary TB), can be a source of significant morbidity and mortality and is usually diagnosed late due to its nonspecific clinical presentation.
- The abdominal TB usually occurs in four forms: tuberculous lymphadenopathy, peritoneal tuberculosis, gastrointestinal (GI) tuberculosis and visceral tuberculosis involving the solid organs

- 3 pathways may lead to abdominal tuberculosis:
  - ✓ Ingestion of tuberculous mycobacteria through ingestion of contaminated milk with mycobacterium bovis which lives in Cattel, sputum or undercooked meat (was the most common before the introduction of mild pasteurization).
  - ✓ In the setting of active or miliary TB, hematogenous or lymphatic spread of mycobacterium form other focus of infection may occur.
  - ✓ Direct spread (contagious spread) from peritoneum tuberculosis or tuberculosis of the ovaries and fallopian tubes (called retrograde spread from fallopian tubes).

- The mucosal layer of the GI tract can be infected with the bacilli with formation of epithelioid tubercles in the lymphoid tissue of the submucosa. After 2-4 weeks, caseous necrosis of the tubercles leads to ulceration of the overlying mucosa which can later spread into the deeper layers and into the adjacent lymph nodes and into peritoneum. Rarely, these bacilli can enter into the portal circulation or into hepatic artery to involve solid organs like liver, pancreas and spleen.

Gastrointestinal TB clinical finding:

- general complaints of tuberculosis like chills, fever, anorexia, profuse night sweat, loss of appetite and weight loss.
- Specific symptoms depend on the involved organ. In this case abdominal TB may cause abdominal pain, abdominal cramps and vomiting.
- Although any portion of the gastrointestinal tract may be affected, the terminal ileum and the cecum are the sites most commonly involved. Abdominal pain (at times similar to that associated with appendicitis) and swelling, obstruction, hematochezia, and a palpable mass in the abdomen are common findings at presentation.

Laboratory diagnostic methods:

- Smear microscopy: Three specimens from each patient with suspected TB should be examined microscopically for Acid Fast Bacilli AFB (classically Ziehl-Neelsen) or mycobacteria can be demonstrated by yellow fluorescence after staining with auramin.
- Culture (Culture for acid fast bacilli is the most specific test for TB and allows direct identification and determination of susceptibility of the causative organism): Both liquid and solid mycobacterial

cultures should be performed for every specimen, and recovered isolates should be according to standard criteria. Lowenstein-Jensen agar plate is used here, while Radiometric broth culture (BACTEC radiometric system) or Middlebrook 7H10 are used in the developed world. mycobacterial growth indicator tube (MGIT) can be used also.

- Available screening tests: (not diagnostic test because there are a lot of variables)
  - ✓ Tuberculin skin tests (TSTs) ➔ purified protein derivate from the bacteria is injected intradermally. The patient must come back after 48 hours to measure the induration (it is erythema and raise of the skin not erythema alone) diameter. More than 10 mm diameter is positive while less than 5 mm is negative with a border line in between. Problems of this test may include false positives to vaccinated people, previous infection or exposure to non-tuberculous mycobacteria.
  - ✓ Interferon-gamma release assays (IGRAs) ➔ the blood of suspected patients is incubated with antigens of tuberculosis. If the immune cells have been sensitized to tuberculosis, they will produce enough amount of IFN-ϒ to produce a positive test.
  - ✓ A nucleic acid amplification test (NAAT).

Treatment:

- The course of TB treatment depends on whether the individual is in the latent or active stage, and on his or her probability of risk.
- Treatment of TB usually involves a drug cocktail, or a mixture of multiple drugs, with an intensive initial 2-month phase (isoniazid (INH), rifampin (RIF), pyrazinamide (PZA), and either ethambutol (EMB) or streptomycin (SM)). followed by a slower 4-to 6-month continuation phase with isoniazid and rifampin alone.
- A lot of side effects which include nephrotoxicity, hepatotoxicity, ototoxicity and body fluids (mainly urine) color change due to rifampin.
- Isoniazid preventive therapy IPT is the recommended treatment for latent TB for 9 months.

Prevention:

- Mycobacterium bovis Bacillus Calmette–Guérin (BCG), an attenuated vaccine derived from M. bovis is the only licensed vaccine against tuberculosis (TB). In Jordan it is given in the first month of life. The problem is that the protection ranges from 0-80% for pulmonary TB but it is the best to prevent tuberculous meningitis as well as miliary TB (when the TB starts to spread in the circulation).

- The best way to prevent TB is to diagnose and isolate infectious cases rapidly and to administer appropriate treatment until patients are rendered noninfectious (usually 2–4 weeks after the start of proper treatment) and the disease is cured.
- Additional strategies include BCG vaccination and treatment of persons with LTBI who are at high risk of developing active disease.

The end