Brucella, Leptospira, Coxiella and Abdominal TB

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Brucellae

- The **brucellae are obligate parasites of animals and humans** and are characteristically located **intracellularly**.
- ***Brucella melitensis* (MC in middle east)** typically infects **goats**; ***Brucella suis***, **swine**; ***Brucella abortus***, **cattle**; and ***Brucella canis***, **dogs**.
- Although named as species, DNA relatedness studies have shown there is only one species in the genus, ***B. melitensis***, with multiple biovars.
- The disease in humans, **brucellosis**, also called **undulant fever** or **Malta fever**, is characterized by an **acute bacteremic phase** followed by a **chronic stage** that may extend over many years and may involve many tissues.

Morphology and Identification

- The appearance in young cultures varies from **cocci to rods 1.2 µm in length**, with **short coccobacillary forms predominating**.
- They are **Gram-negative.**
- They are **aerobic, nonmotile, and nonspore forming**.
- Small, convex, smooth colonies appear on **enriched media in 2–5 days**.
- Brucellae are adapted to an **intracellular habitat**, and their nutritional requirements are complex.
- Fresh specimens from animal or human sources are usually inoculated on **trypticase-soy agar** or **blood culture media**.
- ***B. abortus* requires 5–10% CO_2** for growth, whereas the other three species grow in air.

Growth Characteristics and Antigenic Structure

- **Catalase and oxidase** are produced by the four species that infect humans.
- **Hydrogen sulfide** is produced by many strains.
- Brucellae are **moderately sensitive to heat and acidity** and are killed in milk by **pasteurization**.
- Because brucellae are **hazardous in the laboratory**, tests to classify them should be performed only in **reference public health laboratories** using appropriate biosafety precautions.

Pathogenesis and Pathology

- Although each species of **Brucella** has a preferred host, all can infect a wide range of animals, including humans.
- Routes of infection in humans are the **intestinal tract** by ingestion of infected milk, **mucous membranes** by droplets, and **skin** by contact with infected tissues of animals.
- Cheese made from **unpasteurized goats' milk** is a particularly common vehicle.
- The organisms progress via **lymphatic channels and regional lymph nodes** to the **thoracic duct and bloodstream t**hen to **parenchymatous organs**.
- 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**.

Pathology by Species and Histologic Reaction

- **Osteomyelitis, meningitis, or cholecystitis** also occasionally occurs.
- ***B. abortus*** usually causes mild disease without suppurative complications; **noncaseating granulomas** of the reticuloendothelial system are found.
- ***B. canis*** also causes mild disease.
- ***B. suis*** infection tends to be chronic with **suppurative lesions**; **caseating granulomas** may be present.
- ***B. melitensis*** infection is more **acute and severe**.
- Placentas and fetal membranes of cattle, swine, sheep, and goats contain **erythritol**, a growth factor for brucellae; there is **no erythritol in human placentas**, and abortion is not part of *Brucella* infection of humans.

Clinical Findings

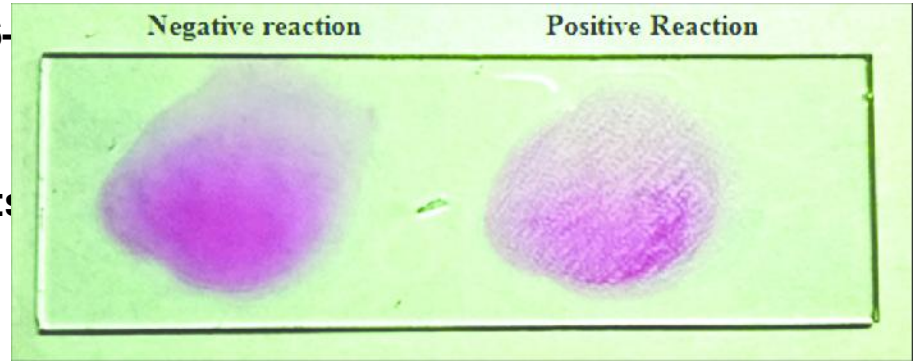
- The incubation period ranges from **1 to 4 weeks**.
- The onset is **insidious**, with **malaise, fever, weakness, aches, and sweats**.
- The fever usually rises in the afternoon; it falls during the night and is accompanied by **drenching sweat**.
- There may be **gastrointestinal and nervous symptoms**.
- **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**.
- A chronic stage may develop, characterized by **weakness, aches and pains, low-grade fever, nervousness (** psychoneurotic symptoms).

Diagnostic Laboratory Tests: Specimens and Culture

- Specimens include **blood for culture**, **biopsy material for culture**, such as lymph nodes or bone, and **serum for serologic tests**.
- 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**.
- All cultures should be incubated in **8–10% CO_2 at 35–37°C** and observed for **3 weeks** before being discarded as negative.
- **Bone marrow and blood** are the specimens from which brucellae are most often isolated.
- Media used in automated blood culture systems readily grow brucellae, usually within **1 week**; holding the cultures for **3 weeks** is recommended.
- Negative culture results for *Brucella* do not exclude the disease, brucellae can be cultivated only during the **acute phase** or during recurrence of activity.
- Tiny **Gram-negative coccobacilli** that are **catalase positive and oxidase positive** suggest Brucella species.
- A positive **urease test** result is characteristic of Brucella species.

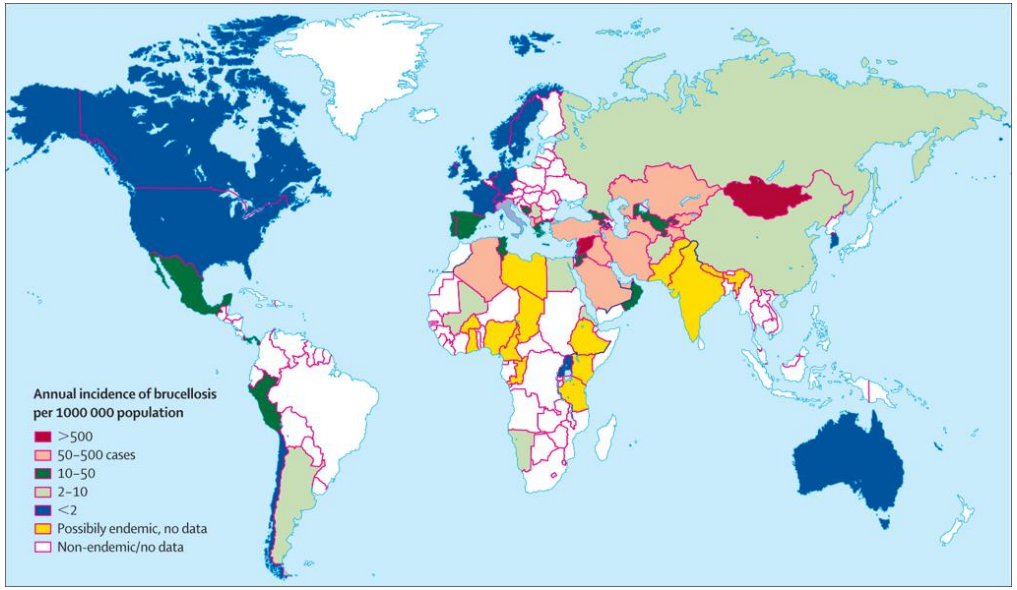
Diagnostic Laboratory Tests: Serology and Immunity

- Laboratory diagnosis of brucellosis is most frequently accomplished by **serologic testing**.
- **IgM antibody levels** rise during the first week of acute illness, peak at **3 months**, and may persist during chronic disease.
- **IgG antibody levels** rise about **3 weeks** after onset, peak at **6-8 weeks**, and remain high during chronic disease.
- **IgA levels parallel the IgG levels**.
- A combination of serological tests, usually **agglutination tests with nonagglutinating assays**, is recommended
- In the agglutination test, **IgG agglutinin titers above 1:80 indicate active infection**.
- **ELISA** assays detect **IgG, IgA, and IgM antibodies** and tend to be more sensitive and specific than the agglutination test, especially in chronic disease.
- An antibody response occurs with infection, and it is probable that some resistance to subsequent attacks is produced.



Treatment, Epidemiology, Prevention, and Control

- Brucellae may be susceptible to **tetracyclines, rifampin, trimethoprim–sulfamethoxazole, aminoglycosides, and some quinolones**.
- 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**, such as **doxycycline**, and either **streptomycin or gentamicin for 2–3 weeks** or **rifampin for 6–8 weeks** is recommended.
- In patients with **endocarditis** or evidence of **neurological disease**, triple therapy with **doxycycline, rifampin, and an aminoglycoside** is suggested.
- Brucellae are animal pathogens transmitted to humans by accidental contact with infected animal **feces, urine, milk, or tissues**.
- Common sources include **unpasteurized milk, milk products, cheese**, and occupational contact among **farmers, veterinarians, and slaughterhouse workers**.
- **Pasteurization of milk and milk products**, and reduction of occupational hazards wherever possible.



https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(06)70382-6

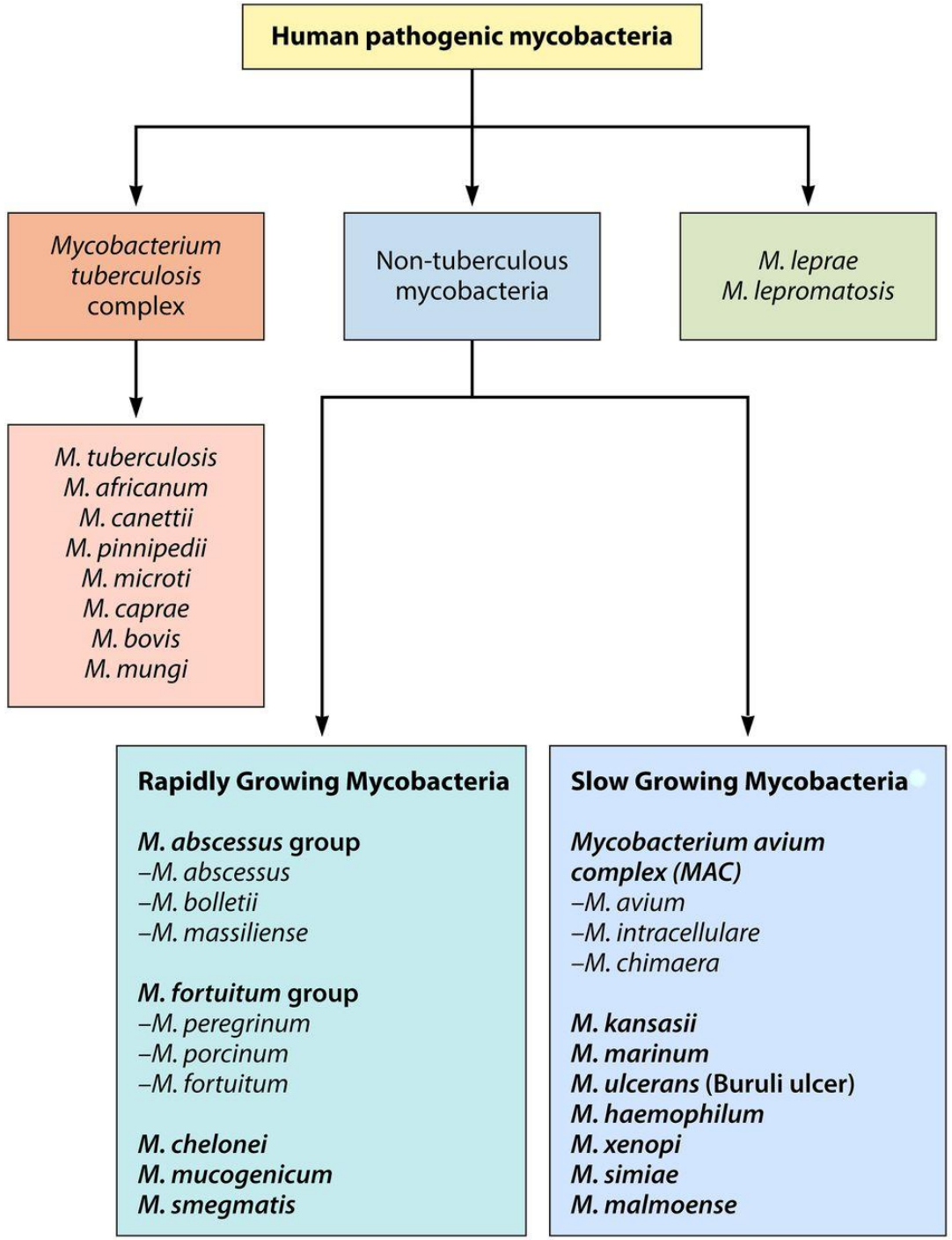
Mycobacteria

- Mycobacteria are **rod-shaped, obligate aerobic bacteria** that **do not form spores**.
- Their cell wall contains **peptidoglycolipids, mycolic acids, fatty acids, and waxes**. These cell wall compounds explain **slow growth, acid fastness, resistance to detergents, and resistance to common antibiotics**.
- Because of the high lipid content, mycobacteria do **not stain well with Gram stain** and require special stains such as **carbolfuchsin**.

- more than **200 Mycobacterium species**, including many **saprophytes**. The most common human pathogens *are* ***M. tuberculosis*** **Complex MTBC,** ***M. leprae*****, and** ***M. ulcerans***.
- **MTBC** causes tuberculosis; ***M. leprae*** causes Hansen's disease; ***M. ulcerans*** causes necrotizing skin and soft tissue infections.
- ***Mycobacterium avium*** **Complex**, or **MAC**, and other **nontuberculous mycobacteria** are opportunistic pathogens in patients with **AIDS** and other immunocompromised persons.

MYCOBACTERIUM TUBERCULOSIS

- Active tuberculosis (TB) affects 10.8 million people worldwide (0.13-0.14% of population as of 2023); 25% of the world has latent TB infection; only 5–10% of those develop active disease.
- Gastrointestinal TB can be observed both in the context of **active pulmonary disease** and as a **primary infection with no pulmonary involvement**.
- Involvement of the gastrointestinal tract by TB remains prevalent in certain areas of the world and in certain **at-risk patient populations**.
- Only **16 to 30%** of patients with intestinal TB have evidence of concurrent **active pulmonary disease**, but intestinal TB may be underrecognized because it can be asymptomatic.
- Abdominal TB accounts for **1% to 3% of all TB cases worldwide** and represents **6% to 13% of extrapulmonary TB cases**, with rates varying by geography.


Human pathogenic mycobacteria
Mycobacterium tuberculosis complex
Non-tuberculous mycobacteria
M. leprae
M. lepromatosis
M. tuberculosis
M. africanum
M. canettii
M. pinnipedii
M. microti
M. caprae
M. bovis
M. mungi
Rapidly Growing Mycobacteria
M. abscessus group
–M. abscessus
–M. bolletii
–M. massiliense
M. fortuitum group
–M. peregrinum
–M. porcinum
–M. fortuitum
M. chelonei
M. mucogenicum
M. smegmatis
Slow Growing Mycobacteria
Mycobacterium avium complex (MAC)
–M. avium
–M. intracellulare
–M. chimaera
M. kansasii
M. marinum
M. ulcerans (Buruli ulcer)
M. haemophilum
M. xenopi
M. simiae
M. malmoense

Risk factors

- Risk factors include **HIV/AIDS**, treatment with **anti-tumor necrosis factor agents**, and **solid-organ transplantation**.
- Reactivation of **latent TB infection** is a concern with increased use of immunosuppressant medications and diseases of immunodeficiency.
- Immigration from a region of high prevalence is an additional risk factor in industrialized nations.
- Gastrointestinal TB remains more significant in parts of the **Middle East, Africa, and Asia**.

Pathogenesis of Gastrointestinal TB: Routes and Sites

- Mycobacterial infections of the gastrointestinal tract occur by: **swallowing infected sputum** in active pulmonary disease, **hematogenous or lymphatic spread** from a distant focus, **direct extension** from a contiguous site, or ingestion of milk products infected with ***Mycobacterium bovis***.
- Milk products remain a viable means of mycobacterial infection in some countries, particularly where **raw milk** is consumed.
- The entire gastrointestinal tract, from the **esophagus to the anus**, can be involved.
- The **ileocecal region** is the most common location, involved in **44 to 93%** of cases, followed by the peritoneum.
- Visceral organ TB may involve the **liver, gall bladder, spleen, pancreas, kidneys, and adnexa**.

Pathogenesis of Intestinal Lesions and Complications

- **Granulomas with caseous necrosis** form and release organisms into the lymphatics.
- Ulcerated mucosa develops and after healing can lead to **stricture formation**.
- Complications include **bleeding, diarrhea, weight loss, luminal obstruction, intussusception, perforation, stricturing disease, and fistulae**.

Clinical Manifestations of Gastrointestinal TB

- There are **no pathognomonic signs** for enteric TB, and it may mimic **Crohn's disease, colorectal cancer, appendicitis, and other inflammatory conditions**.
- Presentation is chronic; symptoms present for **several weeks to months**.
- Abdominal pain is the most common symptom, seen in **70 to 100%** of patients, and is usually **colicky and intermittent,** in the **right lower quadrant** or **periumbilical regions**.
- **Weight loss, anorexia in addition to fever are commonly seen.**
- A change in bowel habits occurs in **42 to 76%** of affected patients, with **diarrhea more common than constipation**

Culture and Morphology

- On artificial media, **coccoid and filamentous forms** may be seen.
- TB bacilli appear as **“Gram-invisible”** or as clear zones called **“ghosts.”**
- The **Ziehl-Neelsen technique** is used for acid-fast staining from culture; fluorochrome stains such as **auramine and rhodamine** are the **preferred stains for clinical specimens**.

https://casereports.bmj.com/content/2013/bcr-2012-008477

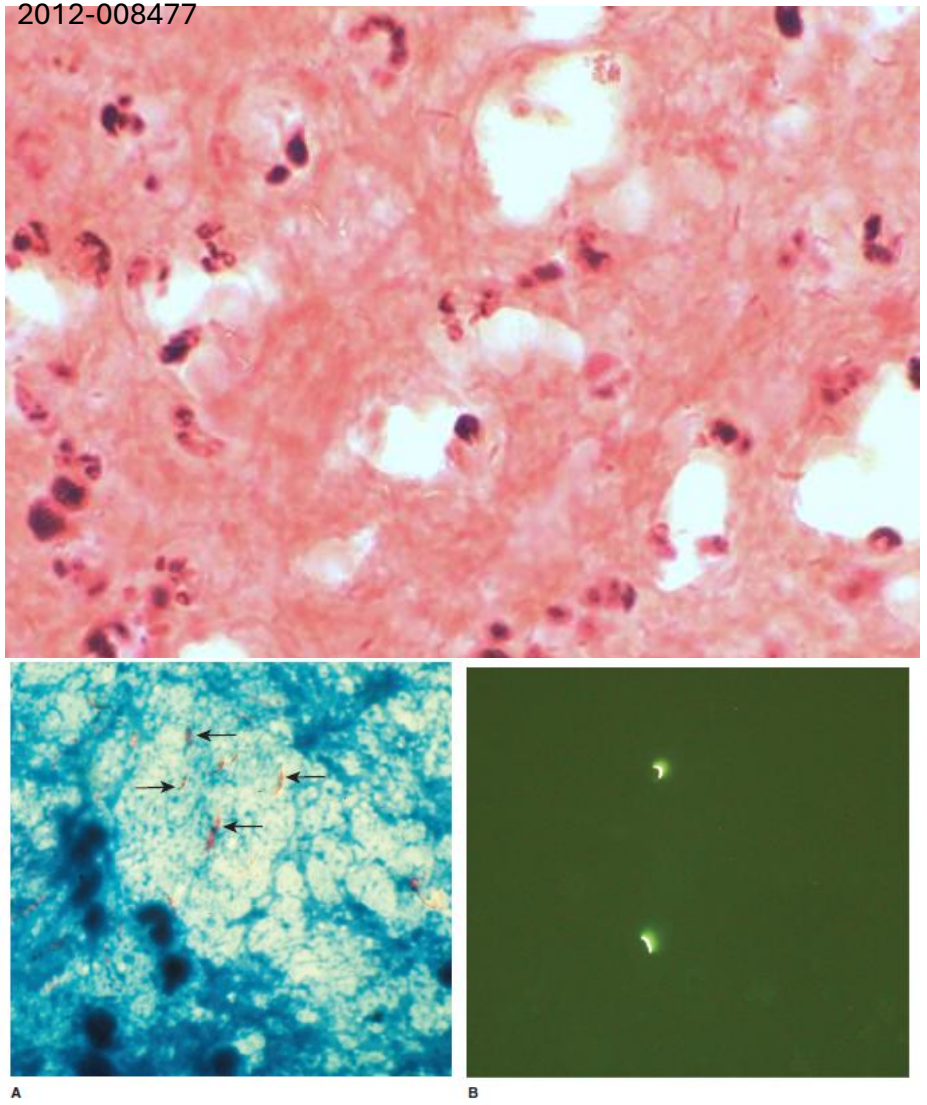
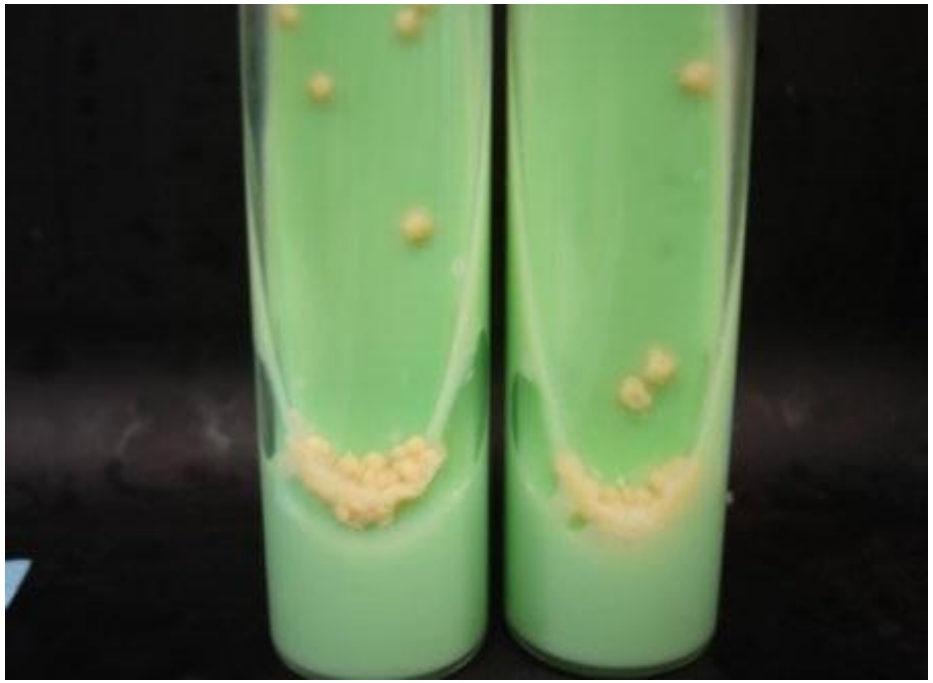


FIGURE 23-1 **A:** *M. tuberculosis* (*arrows*) in a processed sputum specimen stained by Ziehl-Neelsen stain. The *M. tuberculosis* is red against a blue background. **B:** The fluorescent dye Auramine O was used to stain a sputum sample. It shows two fluorescent *M. tuberculosis*. Original magnification ×1000. (Courtesy of G Cunningham.)

- Nonselective and selective media (antibiotics added) used for culture:
- 1. **Semisynthetic agar media**, such as **Middlebrook 7H10 and 7H11**
- **2. Inspissated egg media**, such as **Löwenstein-Jensen (growth in 3-6 weeks)**
- **3. Broth media**, such as **Middlebrook 7H9 and 7H12,** (e.g., MGIT BACTEC commercial system) **(give more rapid growth)**
- Growth rate is slower than other bacteria, CO2 enhances growth; saprophytes grow more rapidly and are less acid fast



https://hardydiagnostics.com/media/assets/product/documents/Middlebrook7H10.pdf
https://www.bd.com/en-sea/products-and-solutions/products/product-families/bd-bactec-mgit-mycobacterial-growth-indicator-tubes#overview

Diagnosis of Gastrointestinal TB

- Diagnosis requires a **high index of suspicion**, especially in patients with abdominal symptoms from an area where TB is endemic.
- Endoscopic evaluation is best facilitated by **multiple biopsies**, with specimens sent for **histology, acid-fast bacillus stain/culture, and PCR**.
- Under ideal circumstances, mucosal biopsy specimens demonstrate **acid-fast bacilli** or **caseous necrosis**, but the prevalence of these findings is low.
- Acid-fast bacillus staining and culture has low sensitivity but high specificity and remains an important component of testing (Abdominal TB is a **paucibacillary disease**).

- **PCR** analysis of mucosal biopsy specimens has high specificity and is more sensitive than acid-fast stains and culture.
- **Tuberculin Skin Test (TST**) and **Interferon gamma release assays (IGRAs**) can't differentiate between active and latent TB; TST often yield false negative results.
- IGRAs (such as QuantiFERON-TB Gold Plus or T-SPOT.TB) may help differentiate intestinal TB from **Crohn's disease**.
- CT, magnetic resonance imaging, barium studies, PET scans, and endoscopic ultrasound provide supportive information but rarely establish the diagnosis alone.

Treatment of Abdominal TB

- A standard **4-drug regimen** consisting of **isoniazid, rifampicin, pyrazinamide, and ethambutol** is recommended.
- These 4 drugs are used **for the first 2 months**, followed by **isoniazid and rifampin for an additional 4 months**.
- Most treatment guidelines recommend a **6-month course of anti-TB therapy** for luminal TB.
- Prolonged therapy may be needed when concern for **disseminated disease** is present.
- **Surgery** is an adjunct for complications such as **significant bleeding, obstruction, abscess formation, and large or drug-refractory fistulae**.
- Prevention and control include reducing transmission from **active pulmonary TB**, identifying and treating **latent TB infection** in at-risk immunosuppressed patients, and avoiding ingestion of **unpasteurized milk products**.

Leptospira: Morphology, Culture, and Growth

- **Leptospirosis is a zoonosis of worldwide distribution** caused by spirochetes of the genus ***Leptospira***.
- There is one pathogenic species, ***Leptospira interrogans***, but more than **200 serovars**.
- Leptospirae are **tightly coiled, thin, flexible spirochetes** with one end forming a **hook**.
- They are **actively motile**, best seen using a **dark-field microscope.**
- Leptospires grow best under **aerobic conditions at 28–30°C** in semisolid medium, such as **Ellinghausen-McCullough-Johnson-Harris medium**.
- Leptospirae can survive for **weeks in water**, particularly at **alkaline pH**.

Pathogenesis, Clinical Findings, and Immunity

- Human infection usually results from leptospires entering through **breaks in the skin** and **mucous membranes**; ingestion is considered less important.
- Incubation period is **1–2 weeks**, after which spirochete establish themselves in **parenchymatous organs (particularly liver and kidneys).**
- Organ dysfunction due to hemorrhage and necrosis rmay result in **jaundice, hemorrhage, and nitrogen retention**.
- The illness is often **biphasic**; the second phase develops when the **IgM antibody titer rises**.
- The second phase often manifests as **aseptic meningitis**, with **intense headache, stiff neck, and pleocytosis of the CSF**.
- Many infections are **mild or subclinical**.
- **Serovar-specific immunity** follows infection, but reinfection with different serovars may occur.

Diagnosis, Treatment, Epidemiology, and Prevention

- Specimens include **blood in a heparin tube, CSF, tissues**, and carefully collected **urine**; serum is collected for **agglutination tests**.
- Dark-field examination or **Giemsa-stained thick smears** may show leptospirae in fresh blood from early infections; dark-field examination of centrifuged urine may also be positive.
- Culture can be done in semisolid medium, but growth is slow and cultures should be kept for at least 8 weeks.
- Diagnosis is most often confirmed **serologically.**
- Agglutinating antibodies first appear **5–7 days after infection** and peak at **5–8 weeks**.
- Treatment of mild leptospirosis: oral **doxycycline, ampicillin, or amoxicillin**.
- Treatment of moderate or severe disease: intravenous **penicillin, ampicillin, or ceftriaxone**.
- Human infection is accidental after contact with water or materials contaminated with animal excreta (**rats, mice, wild rodents, cattles etc)**.
- Prevention includes avoiding contaminated water, **rodent control**, and **doxycycline 200 mg orally once weekly during heavy exposure** as prophylaxis.

Coxiella burnetii

- ***C. burnetii* causes Q fever** and is a **small obligate organism** that grows only in **cytoplasmic vacuoles**.
- It has a membrane similar to **Gram-negative bacteria**, but **does not stain with Gram stain.**
- It is **resistant to drying**, survives for **months in dried feces or milk**, and may survive **60°C for 30 minutes**.
- **Phase I** is the **virulent infectious form**; **Phase II** is **not infectious** and occurs after serial passage in cell culture.
- *C. burnetii* is found in ticks, which transmit the agent to sheep, goats, and cattle, but transmission by ticks to humans is uncommon.
- Main reservoirs are **sheep, goats, cattle**, and parturient cats; infection occurs mainly by **inhalation of contaminated dust or aerosols** from placenta, dried feces, urine, or milk.
- Ingestion of unpasteurized dairy less common

Disease, Diagnosis, Treatment, and Prevention

- **Acute Q fever** resembles **influenza, atypical pneumonia, and hepatitis**, with antibodies to **phase II** antigen.
- **Chronic Q fever** lasts more than **6 months**; **infective endocarditis** is the most common form, with high antibodies to **phase I** antigen.
- Diagnosis is mainly by **serology.**
- **PCR** is useful in **culture-negative endocarditis** caused by *C. burnetii*.
- Treatment of acute Q fever: **doxycycline**; newer **macrolides** may treat acute pneumonia.
- Chronic Q fever: **doxycycline + hydroxychloroquine** for **18 months or longer**; valve replacement may occasionally be required.
- Prevention: **pasteurization at 71.5°C for 15 seconds** destroys viable *Coxiella* species.

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