19

Microbiology

Doctor 2018 | Medicine | JU

Sheet Slides

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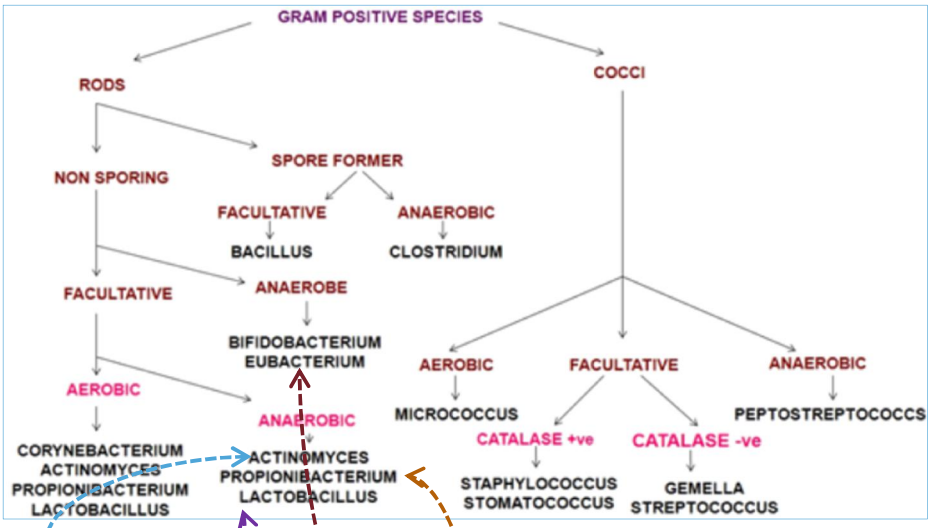
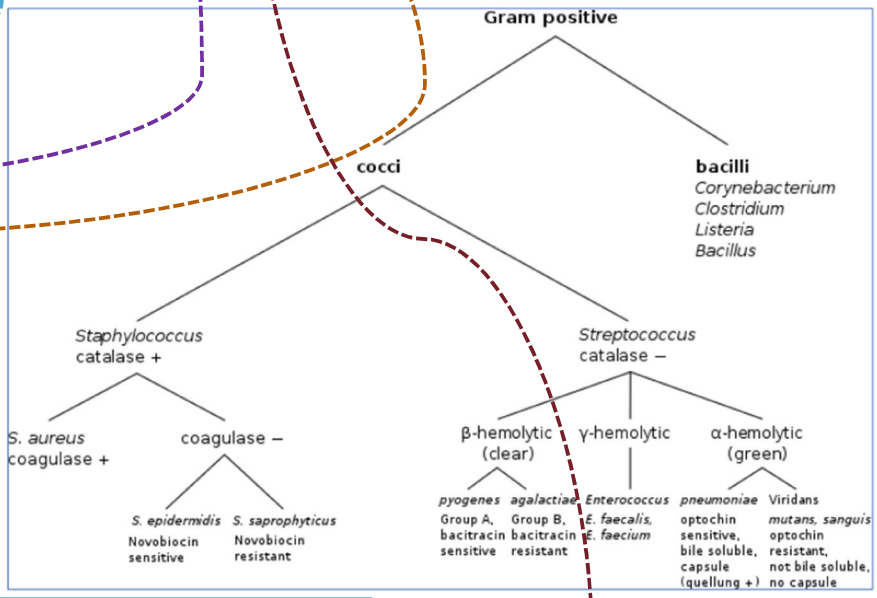
NON-SPORE FORMING BACTERIA

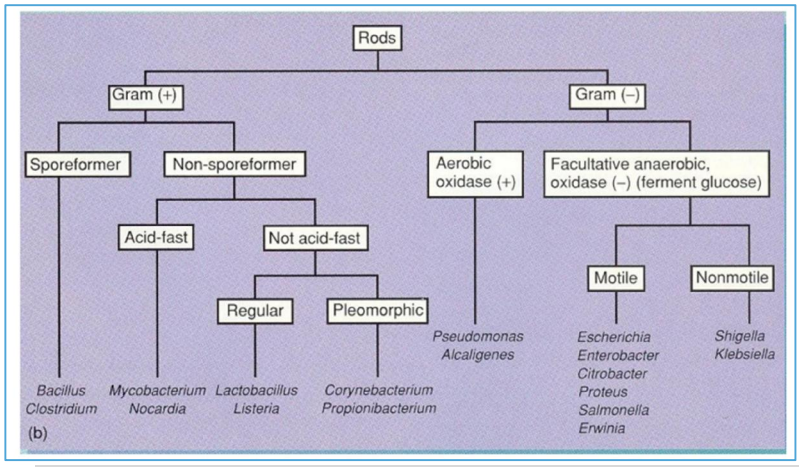
Pathogens that will be discussed this sheet are; non-spore forming gram positive rods (aerobic and anaerobic), anaerobic gram negative rods, and anaerobic gram positive cocci.

The non-spore forming gram positive rods are a diverse collection of facultatively anaerobic or strictly bacteria anaerobic that colonize the skin and mucosal surfaces.



Actinomyces, **Mobiluncus**, **Lactobacillus**, and **Propionibacterium** are well recognized **opportunistic pathogens** (the host must have a weakened immune system).





Other genera such as **Bifidobacterium** and **Eubacterium** (strictly anaerobes) can be isolated in clinical specimens but **rarely** cause human disease (they might be part of the normal flora).

Actinomyces

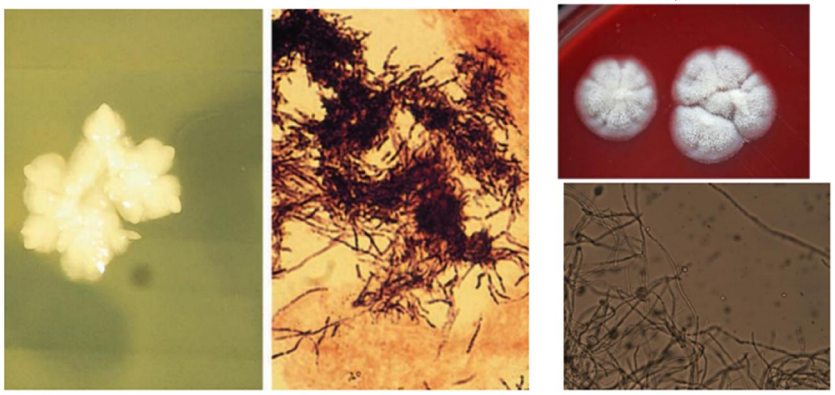
Actinomyces organisms are **facultatively anaerobic** -rarely strictly anaerobic- **gram positive** rods. They grow slowly in culture, and they tend to produce chronic, slowly developing infections.

Actinomyces organisms colonize (as part of the normal flora) the upper respiratory, GIT, and female genital tracts but are **not** normally present on the skin surface.

Infections caused by actinomycetes are **endogenous**, with no evidence of person-to-person spread or disease originating from an **exogenous** source.

Specimens can be contaminated with Actinomyces that are part of the **normal bacterial** population on **mucosal** surfaces.

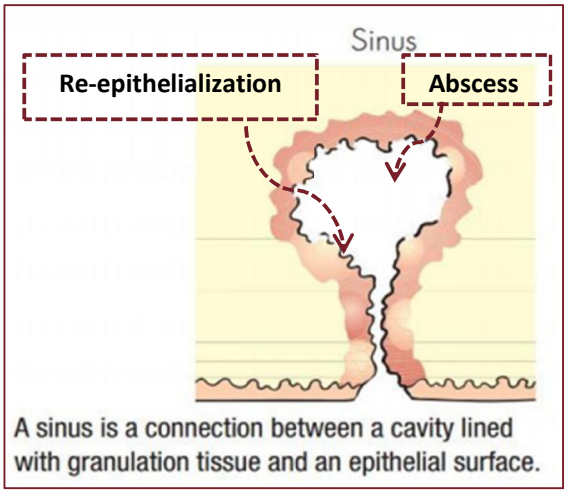
They typically develop delicate filamentous forms or hyphae (**resembling fungi**) in clinical specimens or when isolated in culture.



Actinomyces are **fastidious (special nutritional requirements)** and grow slowly under anaerobic conditions; it can take 2 weeks or more for the organisms to be isolated.

Classic disease caused by Actinomyces is termed actinoMYCOSIS; characterized by the development of **chronic granulomatous lesions** that become **suppurative** and form **abscesses** connected by sinus tracts.

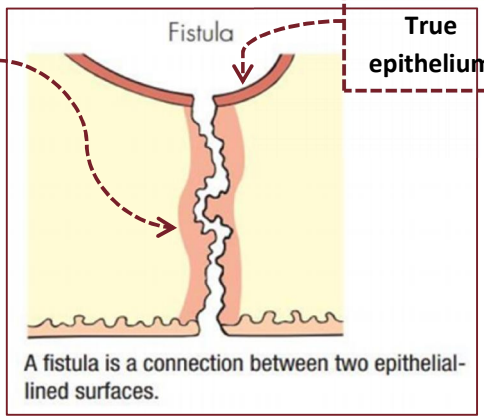
We know that an abscess is a swollen area within body tissue, containing an accumulation of pus. In actinomycetes infections; abscesses extend through the tissue forming narrow openings or passageways underneath the tissue that are called "**sinus tracts**".



A sinus is a connection between a cavity lined with granulation tissue and an epithelial surface.

However, if theses passageways (channels) connect two anatomic spaces or cavities; then they are called "**fistulas**".

Re-epithelialization



A fistula is a connection between two epithelial-lined surfaces.

*To clear up:

A fistula is an abnormal pathway between two anatomic spaces or a pathway that leads from an internal cavity or organ to the surface of the body. A sinus tract is an abnormal channel that originates or ends in one opening.

Therefore, the finding of tissue swelling with fibrosis and scarring, as well as draining sinus tracts along the angle of the jaw and neck, should alert the physician to the possibility of actino**MYCOSIS**.

The major sites of actinomycoses are **cervicofacial**, **abdominopelvic**, and **thoracic**.

Most actinomycetes infections are **cervicofacial** (following invasive dental procedure or oral trauma).

Abdominal and pelvic infections are associated with **abdominal surgery**, tuboovarian abscess, ruptured appendicitis, and **intrauterine contraceptive devices (IUCD).**

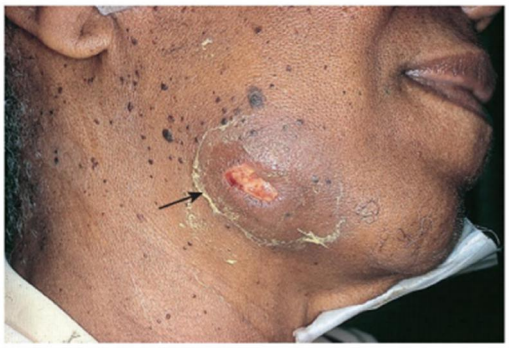


FIGURE 31-4 Patient suffering from cervicofacial actinomycosis. Note the draining sinus tract *(arrow)*.

Treatment for actinomycosis involves the combination of drainage of a localized abscess or **surgical** debridement of the involved tissues (removal of the necrotic tissue), and **prolonged** administration of antibiotics.

Looks like a molar tooth (طاحونة)

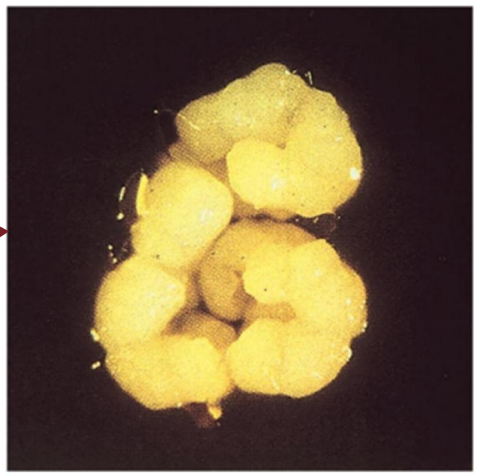


FIGURE 31-6 Molar tooth appearance of *Actinomyces israelii* after incubation for 1 week. This colonial morphology serves as a reminder that the bacteria are normally found in the mouth.

Nocardia (added here for similarity to Actinomyces)

Nocardiae are **strict aerobic** rods that form branched filaments in tissues and culture.

Nocardia is described as "**weakly acid-fast**"; that is, a weak **decolorizing** solution of hydrochloric acid must be used to demonstrate the acid-fast property of nocardia.

This property (being weakly acid-fast) helps in distinguishing Nocardia from the similar Actinomyces. (They both look like fungi).

Growth is slow, requiring 3 to 5 days of incubation before colonies may be observed on the culture plates.

Nocardia infections are **exogenous** (i.e., caused by organisms **not normally** part of the **normal human flora**). ← another difference between Nocardia and Actinomyces.

The ubiquitous presence of the organism in **soil** rich with organic matter and the increasing numbers of **immunocompromised** (**opportunistic**) individuals living in communities have led to dramatic increases in disease caused by this organism.

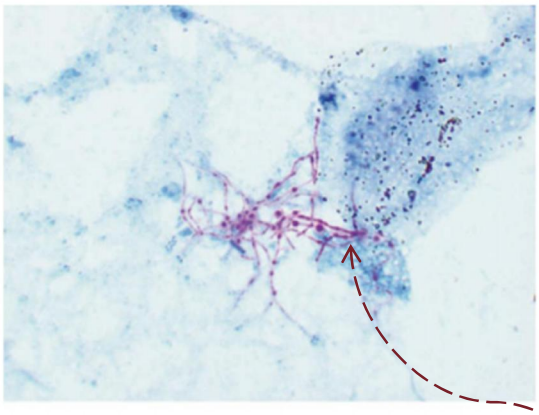


FIGURE 22-10 Acid-fast stain of *Nocardia* species in expectorated sputum. In contrast with the mycobacteria, members of the genus *Nocardia* do not uniformly retain the stain ("partially acid-fast").

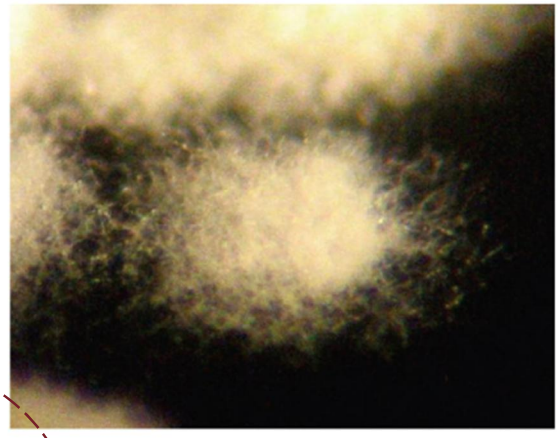


FIGURE 22-12 Aerial hyphae of *Nocardia*.

The combination of both presence of aerial hyphae and acid-fastness is unique to the genus Nocardia and can be used as a rapid test for identification of the genus.

It would appear that the primary factor associated with virulence is the ability of pathogenic strains to avoid phagocytic killing. Through:

Secretion of catalase and superoxide dismutase that counter hydrogen peroxide and superoxide released by phagocytic cells, preventing fusion of the phagosome-lysosome (mediated by cord factor) and preventing acidification of the phagosome.

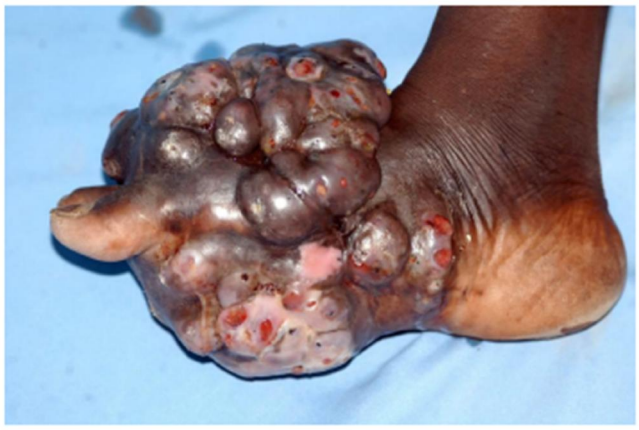
Bronchopulmonary disease develops after the initial colonization of the upper respiratory tract by inhalation and then aspiration of oral secretions into the lower airways, occurs almost always in immunocompromised patients (e.g; HIV patients)

Primary cutaneous nocardiosis develops after traumatic introduction of organisms into subcutaneous tissues, can present in the form of Mycetoma is characterized by a triad of painless subcutaneous mass, multiple sinuses and discharge containing grains.

As many as one third of all patients with Nocardia infections have dissemination to the brain, most commonly involving the formation of single or multiple brain abscesses.

Mycetoma is a chronic suppurative disease of the skin and subcutaneous tissue, characterized by a symptomatic triad: **tumors**, **fistulas** and **grains** (seeds-like). It can be caused by fungi (eumycetoma) and bacteria (actinomycetoma), with similar clinical features.

Given its slow progression, painless nature, massive lack of health education and scarcity of medical and health facilities in endemic areas, many patients present late with advanced infection where amputation may be the only available treatment.

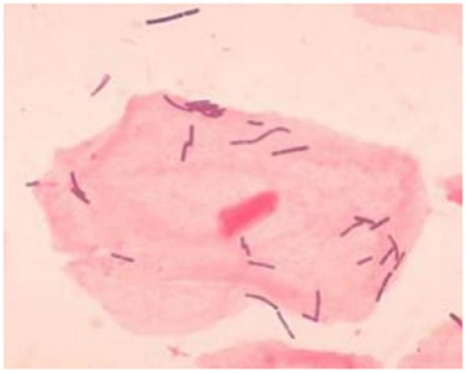


Lactobacillus

Lactobacillus species are **facultatively anaerobic** or strictly anaerobic rods that **ferment to yield lactic acid.**

They are found as part of the **normal flora** of the mouth, stomach, intestines, and genitourinary tract. In around 70% of women, a Lactobacillus species is **dominant** in the **female genital tract**.

Commonly found in **probiotics**; some brands of yogurt contain Lactobacillus as beneficial probiotics.



They VERY rarely cause infections.

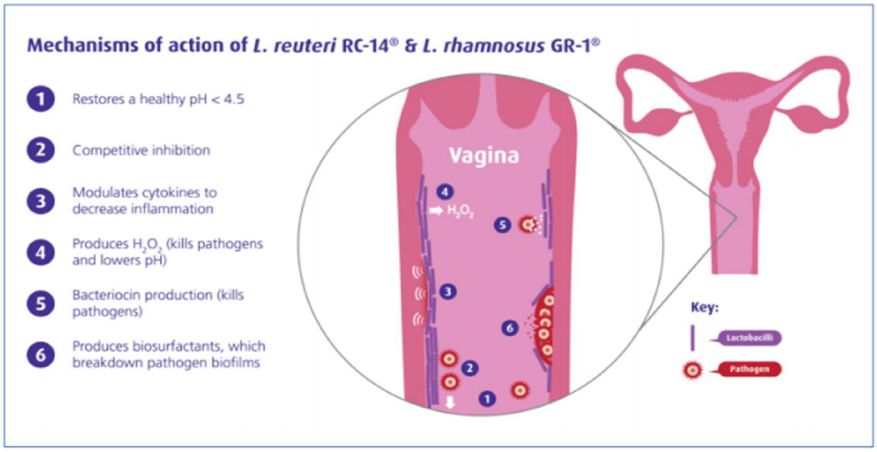
Some Lactobacillus species are used as starter cultures in **industry** for controlled fermentation in the production of yogurt, cheese, sauerkraut, pickles, beer, and cider (to yield lactic acid).

Invasion into **blood** (sepsis) occurs -**rarely**- in one of the following three settings:

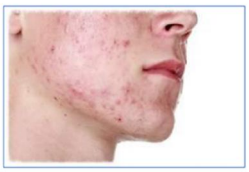
1. Transient bacteremia from a genitourinary source (e.g., **after childbirth** or a gynecologic procedure).

2. Endocarditis.

3. Opportunistic septicemia in an **immunocompromised patient**.



Propionibacterium



Propionibacteria are small gram-positive rods often arranged in short chains or clumps, commonly found on the **skin** (in contrast with the **Actinomyces**), conjunctiva, external ear, oropharynx and female genital tract.

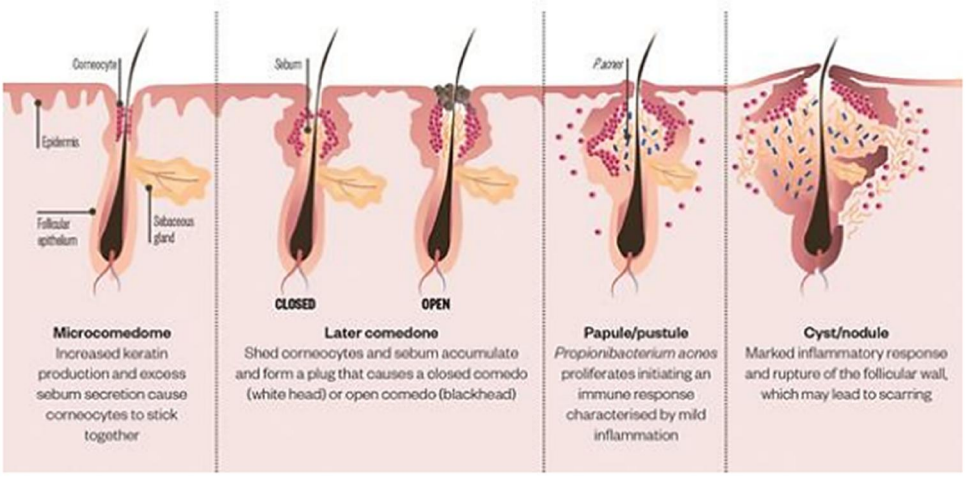
The **most commonly** isolated species is “Propionibacterium acnes”.

P. acnes species is responsible for two types of infections:

1. Acne vulgaris in teenagers and young adults.

2. **Opportunistic** infections in patients with **prosthetic devices or intravascular lines**.

P. acnes species does not cause/originate acne vulgaris; it **only triggers** the disease when it meets **favorable** dermato-physiological terrain; P. acnes colonization of the **skin** is therefore **necessary** but **not sufficient** for the establishment of the pathology.

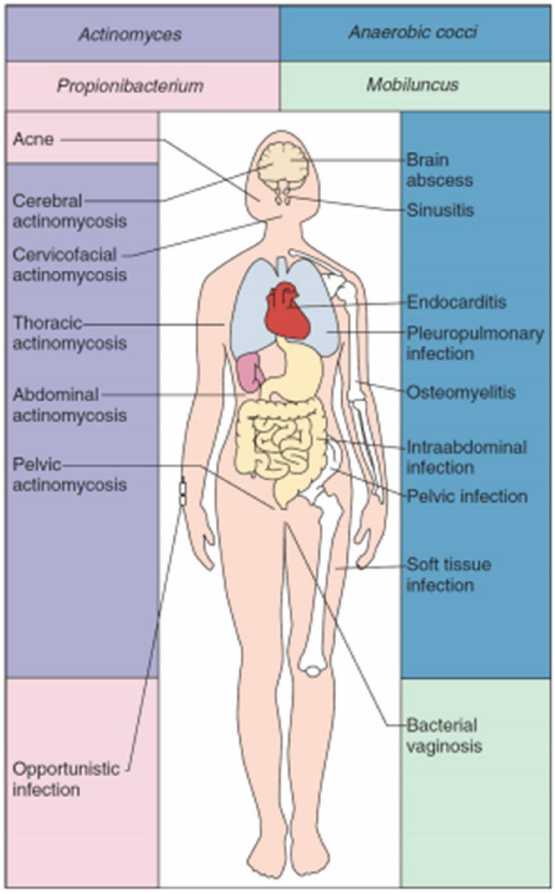


← Too much sebum become trapped inside sebaceous glands, causing them to swell and form black heads under the skin which clog the pores, creating a desirable environment for P.acnes to thrive, which can lead to inflammation by releasing peptides and inflammatory mediators forming pimples or acnes.

Other Non-Spore Forming Anaerobic Gram Positive Rods

Mobiluncus

Members of the genus Mobiluncus are **obligate anaerobic, gram variable (when staining is not conclusive)** or gram negative, curved **rods** with tapered ends.



Despite their appearance in Gram stained specimens (some appear gram negative and others are not clear "gram-variable"); they are classified as gram positive rods because they have a **gram positive cell wall**, lack endotoxin (which are found in gram negative bacteria) , and are **susceptible** to vancomycin, clindamycin, erythromycin, and ampicillin but **resistant** to colistin (like some other gram positive bacteria).

M. curtisii is rarely found in the vaginas of healthy women but is abundant in women with **bacterial vaginosis** (shift in the vaginal microbiota).

Bifidobacterium and Eubacterium

They are commonly found in the oropharynx, large intestine, and vagina. They usually represent clinically insignificant contaminants (as they are parts of the normal flora).

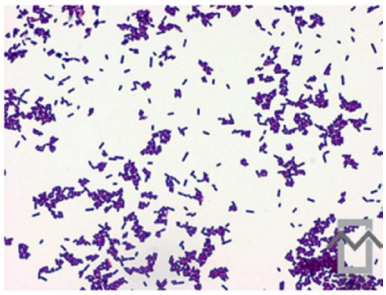
Non-Spore Forming Aerobic Gram Positive Rods

They are a heterogeneous group of bacteria; some are well-recognized **human** pathogens (Listeria monocytogenes, Corynebacterium diphtheria), others are primarily **animal** pathogens that can cause human disease (Erysipelothrix rhusiopathiae), and some are **opportunistic** pathogens that typically infect **hospitalized** or immunocompromised patients (Corynebacterium jeikeium).

↑The doctor said that Listeria and Corynebacterium diphtheria are considered opportunistic pathogens.

Listeria monocytogenes

L. monocytogenes is a short (0.4 to 0.5 × 0.5 to 2 μm), non-branching, gram positive, **facultatively anaerobic** rod -**although it's mostly aerobic**- . The short rods appear singly, in pairs, or in short chains and can be mistaken for Streptococcus pneumonia →.



The organisms are **motile** at room temperature but less so at 37°C, and they exhibit a characteristic end-over-end tumbling motion when a drop of broth is examined microscopically.

L.monocytogenes exhibits **weak β-hemolysis** when grown on sheep blood agar plates.

These differential characteristics (Gram stain morphology, **motility**, and β-hemolysis) are useful for the preliminary **identification** of Listeria.

Although the bacteria are **widely distributed in nature**, human disease is **uncommon** and is restricted primarily to several well-defined populations: **neonates, the elderly, pregnant women, and patients with defective cellular immunity (Listeria is an opportunistic facultative intracellular pathogen)**.

Clinical Case 21-1 *Listeria* Meningitis in Immunocompromised Man

The following patient described by Bowie and associates (*Ann Pharmacother* 38:58–61, 2004) illustrates the clinical presentation of *Listeria* meningitis. A 73-year-old man with refractory rheumatoid arthritis was brought by his family to the local hospital because he had a decreased level of consciousness and a 3-day history of headache, nausea, and vomiting. His current medications were infliximab, methotrexate, and prednisone for his rheumatoid arthritis. On physical examination, the patient had a stiff neck and was febrile, had a pulse of 92 beats/min, and had a blood pressure of 179/72 mm Hg. Because meningitis was suspected, blood and cerebrospinal fluid (CSF) were collected for culture. The Gram stain of the CSF was negative, but *Listeria* grew from both blood and CSF cultures. The patient was treated with vancomycin, the infliximab was discontinued, and he made an uneventful recovery despite using less-than-optimal antimicrobial therapy. Infliximab has been associated with a dose-dependent monocytopenia. Because monocytes are key effectors for clearance of *Listeria*, this immunocompromised patient was specifically at risk for infection with this organism. Failure to detect *Listeria* in CSF by Gram stain is typical of this disease because the bacteria fail to multiply to detectable levels.

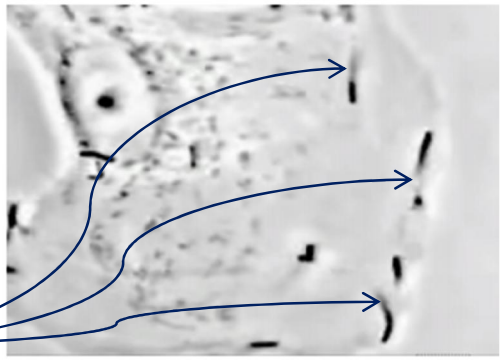
This drug blocks the effect of TNF-α and thus inhibits immune responses.

Monocytes have an important role in fighting Listeria monocytogenes.

***monocytopenia: ↓ deficiency of monocytes.**

Following **ingestion** of contaminated food, L. monocytogene **adhere** to host cells via the interaction of proteins on the surface of the bacteria (internalin A) with glycoprotein receptors on the host cell surface (e.g. epithelial cadherin).

After penetration into the cells, the acid pH of the **phagolysosome** that surrounds the bacteria activates a bacterial **pore-forming cytolysin** (listeriolysin O) and two different **phospholipase C enzymes**, leading to release of the bacteria into the **cell cytosol (it destroys they phagolysosome and enters the cytosol)**.



This movement is mediated by a bacterial protein, (ActA) that coordinates assembly of **actin**.

These bacteria can replicate in **macrophages** and move **within** cells, thus avoiding antibody-mediated clearance (intracellular). Patients with defects in cellular immunity, but **not in humoral immunity**, are particularly susceptible to severe infections.

The primary source of infection with this organism is consumption of contaminated food; causing Foodborne Listeriosis.

*People who are at higher risk for Listeria infection (elderly and immunocompromised people) should avoid eating cold cuts (e.g. salami, turkey) to prevent FBL.

Human-to-human transmission can occur primarily from mother to child in utero or at birth (neonatal → weak immunity).

Neonatal Disease can be an early-onset disease; acquired transplacentally (through the placenta) in utero, or late-onset disease; acquired at or soon after birth.

Early-onset disease can result in **abortion, stillbirth, or premature birth**. Late-onset disease occurs 2 to 3 weeks after birth in the form of **meningitis** or **meningoencephalitis** with **septicemia**.

Most infections in pregnant women occur during the third trimester when cellular immunity is most impaired.

Disease in healthy adults is **self-limited** and **asymptomatic** or in the form of a **mild** influenza-like illness.

Corynebacterium diphtheria

Corynebacteria are **aerobic** or facultatively anaerobic, non-motile, and catalase positive. They are **ubiquitous** in plants and animals, and they **normally colonize** the **skin, upper respiratory tract, gastrointestinal tract, and urogenital tract in humans.**

The most famous of these is **C. diphtheria** -the etiologic agent of diphtheria-.

C. diphtheriae is an **irregularly** staining, **pleomorphic rod** -sometimes it looks like rods and other times like cocci- (0.3 to 0.8 × 1.0 to 8.0 µm).

Humans are the **only** known reservoir for this organism.

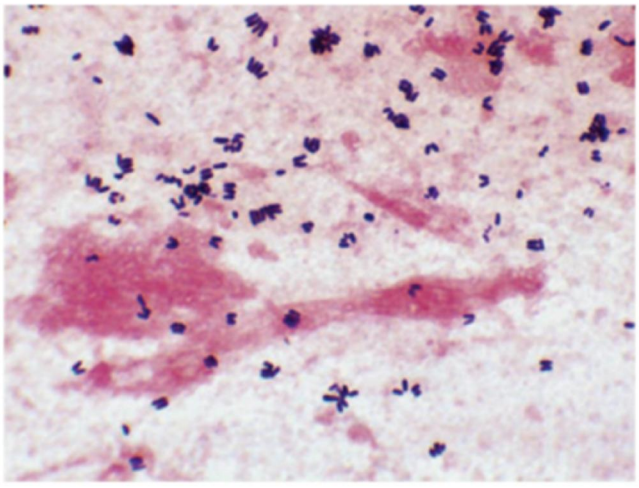


FIGURE 21-4 Gram stain of *Corynebacterium* species in sputum specimen.

Respiratory droplets or skin contact transmits it from **person to person**.

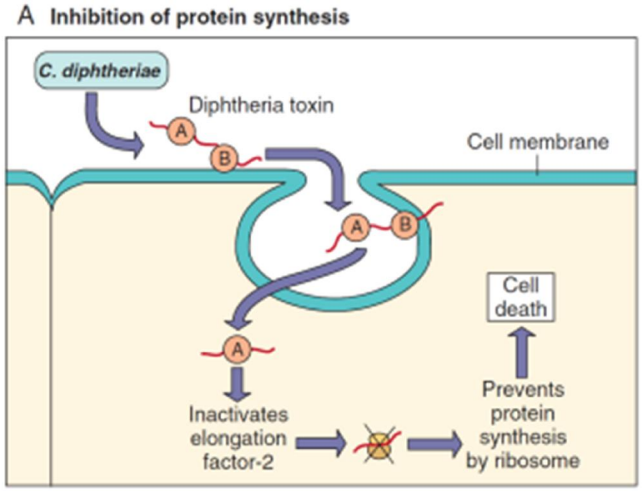
Diphtheria toxin is the major virulence factor of C. diphtheria (it is an example of the classic A-B exotoxin).

Three functional regions exist on the toxin molecule:

1. A catalytic region on the A subunit.

2. A receptor-binding region.

3. A translocation region on the B subunit.



The receptor for the toxin is heparin-binding epidermal growth factor precursor (HB-EGF) present on many **epithelial membranes** and is endocytosed by the cell.

After the toxin get into the cell, B subunit (translocation region) become inserted into the endosomal membrane, facilitating the movement of the A subunit (catalytic region) into the cytosol. The A subunit then ADP-ribosylates (inactivates) elongation factor-2 (EF-2).

EF-2 is required for protein synthesis; when it is inactivated by the toxin, the host cannot make protein and thus dies.

The clinical presentation of diphtheria is determined by:

1. Site of infection.

2. Immune status of the individual (opportunistic).

3. Virulence of the organism.

* Exposure to C. diphtheria may result in **asymptomatic** colonization in **fully** immune people.

***Diphtheria toxin** is produced at the site of the infection and then disseminates through the **blood** to produce the systemic signs of diphtheria.

Cutaneous Diphtheria

A papule develops first and then evolves into a chronic, non-healing ulcer.

Respiratory Diphtheria

The symptoms of diphtheria involving the respiratory tract develop after a 2- to 4-day **incubation period**.

The onset is sudden, with malaise, sore throat**, exudative pharyngitis**, and a low-grade fever.

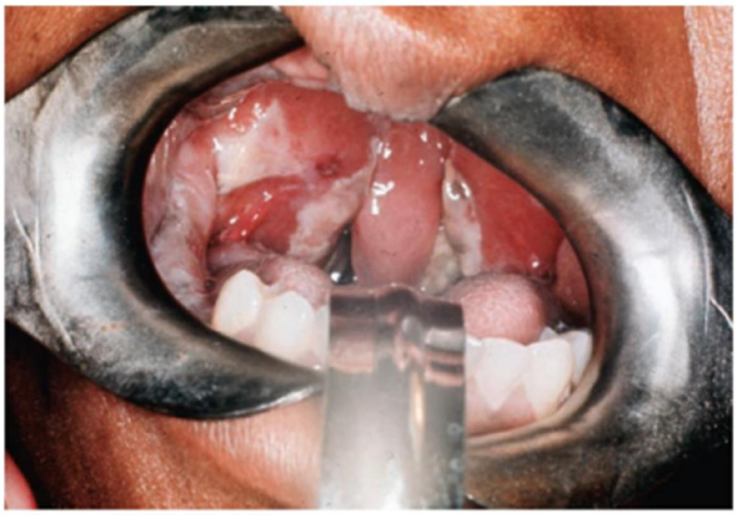


FIGURE 21-5 Pharynx of a 39-year-old woman with bacteriologically confirmed diphtheria. The photograph was taken 4 days after the onset of fever, malaise, and sore throat. Hemorrhage caused by removal of the membrane by swabbing appears as a dark area on the left. (From Mandell G, Bennett J, Dolin R: *Principles and practice of infectious diseases,* ed 8, Philadelphia, 2015, Elsevier.)

The exudate evolves into a thick pseudomembrane composed of bacteria, lymphocytes, plasma cells, fibrin, and dead cells that can **cover** the tonsils, uvula, and palate and can extend up into the nasopharynx or down into the larynx (difficult to breathe).

Evidence of **myocarditis** can be detected in the majority of patients (systemic complications involving the heart).

Diphtheria has become uncommon in the United States because of an active immunization program, as shown by the fact that more than 200,000 cases were reported in 1921 but no cases have been reported since 2003.

Read this clinical case and notice the symptoms, age of the patient, and being unvaccinated.→

Clinical Case 21-3 Respiratory Diphtheria

Lurie and associates (*JAMA* 291:937–938, 2004) reported the last patient with respiratory diphtheria seen in the United States. An unvaccinated 63-year-old man developed a sore throat while on a week-long trip in rural Haiti. Two days after he returned home to Pennsylvania, he visited a local hospital with complaints of a sore throat and difficulties in swallowing. He was treated with oral antibiotics but returned 2 days later with chills, sweating, difficulty swallowing and breathing, nausea, and vomiting. He had diminished breath sounds in the left lung, and radiographs confirmed pulmonary infiltrates as well as enlargement of the epiglottis. Laryngoscopy revealed yellow exudates on the tonsils, posterior pharynx, and soft palate. He was admitted to the intensive care unit and treated with azithromycin, ceftriaxone, nafcillin, and steroids, but over the next 4 days he became hypotensive with a low-grade fever. Cultures were negative for *Corynebacterium diphtheriae.* By the eighth day of illness, a chest radiograph showed infiltrates in the right and left lung bases, and a white exudate consistent with *C. diphtheriae* pseudomembrane was observed over the supraglottic structures. Cultures at this time remained negative for *C. diphtheriae,* but polymerase chain reaction testing for the exotoxin gene was positive. Despite aggressive therapy the patient continued to deteriorate, and on the seventeenth day of hospitalization he developed cardiac complications and died. This patient illustrates (1) the risk factor of an unimmunized patient traveling to an endemic area, (2) the classic presentation of severe respiratory diphtheria, (3) delays associated with diagnosis of an uncommon disease, and (4) the difficulties most laboratories would now have isolating the organism in culture.

Anaerobic Gram-Negative Rods

These anaerobes are **the predominant bacteria on most mucosal surfaces,** outnumbering aerobic bacteria 10 to 1000 fold.

Despite the abundance and diversity of these bacteria, most **infections** are caused by relatively few species.

Bacteroides, **Fusobacterium**, **Parabacteroides**, **Porphyromonas**, **and Prevotella**.

Characteristically, **Bacteroides** growth is stimulated by **bile**.

Although Bacteroides species grow rapidly in culture, the other anaerobic gram negative rods are **fastidious**; and cultures may have to be incubated for 3 days or longer before the bacteria can be detected.

Bacteroides species are **pleomorphic** in size and shape and resemble a mixed population of organisms in a casually examined Gram stain.

Bacteroides have a typical gram negative cell wall structure, which can be surrounded by a polysaccharide capsule.

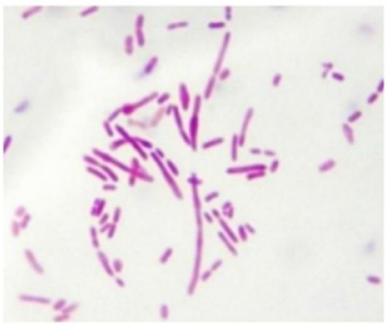
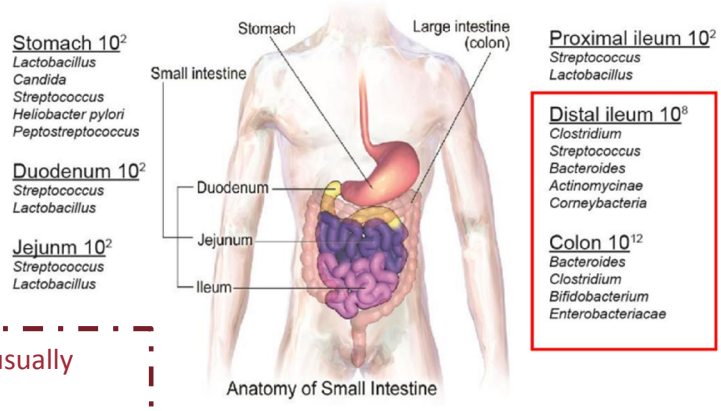


FIGURE 31-13 Growth of *Bacteroides fragilis* on *Bacteroides* bile-esculin agar. Most aerobic and anaerobic bacteria are inhibited by bile and gentamicin in this medium, whereas the *B. fragilis* group of organisms is stimulated by bile, resistant to gentamicin, and able to hydrolyze esculin, producing a black precipitate.

In contrast to the **LPS** molecules in the aerobic gram negative rods, the **Bacteroides** LPS has little or no endotoxin activity; this is because the lipid [A] in **Bacteroides** lacks certain structural components that are present in the LPS molecules in the anaerobic gram negative rods “structural differences”.

To cause disease, Bacteroides fragilis in the resident **flora** are able to spread by trauma or disease from the **normally** colonized **mucosal surfaces** to sterile tissues or fluids.



Anatomy of Small Intestine

Infections are usually **polymicrobial**.

Respiratory Tract Infections

Nearly half of the chronic infections of the **sinuses (a cavity within the bones of the skull) and ears**, and virtually all periodontal (affecting the structures surrounding and supporting the teeth) infections, involve **mixtures** of gram negative anaerobes, with **Prevotella, Porphyromonas, Fusobacterium**, and **non-fragilis Bacteroides** the most commonly isolated.

Bacteremia

Anaerobes were at one time responsible for more than 20% of all clinically significant cases of bacteremia; however, these organisms now cause 3% to 10% of such infections.

Intra-abdominal Infections

Anaerobes are recovered in virtually all of these infections, with B. fragilis the most common organism.

Skin and Soft-Tissue Infections

B. fragilis is the organism most commonly associated with significant disease.

Gastroenteritis

Strains of enterotoxigenic B. fragilis that cause **self-limited watery** diarrhea by produce a **heat-labile zinc metalloproteas** toxin **(B. fragilis toxin).**

This toxin causes morphologic changes of the intestinal epithelium via **F-actin** rearrangement, with the resultant stimulation of **chloride secretion** and **fluid loss**.

Anaerobic Gram Positive Cocci

The anaerobic gram positive cocci normally colonize the **oral cavity, gastrointestinal** (GI) tract, **genitourinary** tract, and **skin**. They produce infections when they spread from these sites to normally sterile sites.

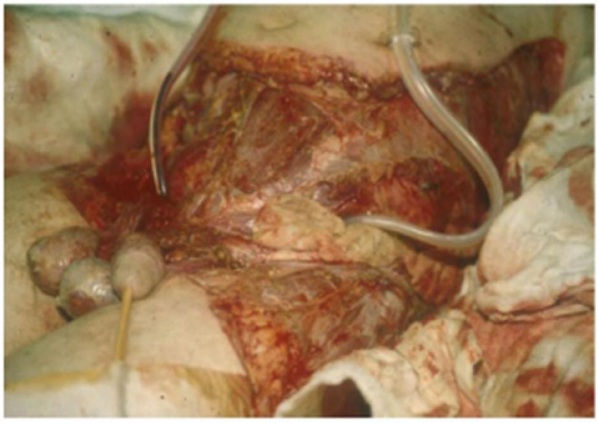


FIGURE 31-12 Synergistic polymicrobial infection involving *Bacteroides fragilis* and other anaerobes. The infection started at the scrotum and rapidly spread up the trunk and down the thighs, with extensive myonecrosis.

Although anaerobic cocci can be isolated from infections at **all body sites**, a predisposition for certain sites has been observed.

Peptostreptococcus species have been recovered more often from **subcutaneous** and **soft tissue abscesses** and **diabetes-related foot ulcers** than from **intra-abdominal** infections.

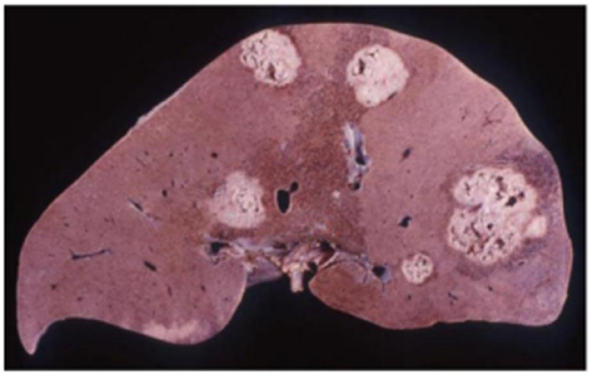


FIGURE 31-11 Liver abscesses caused by *Bacteroides fragilis*.

***Peptostreptococcus** infections occur **more often in chronic** infections.

*Many infections caused by peptostreptococcus bacteria are **synergistic**.

The End.