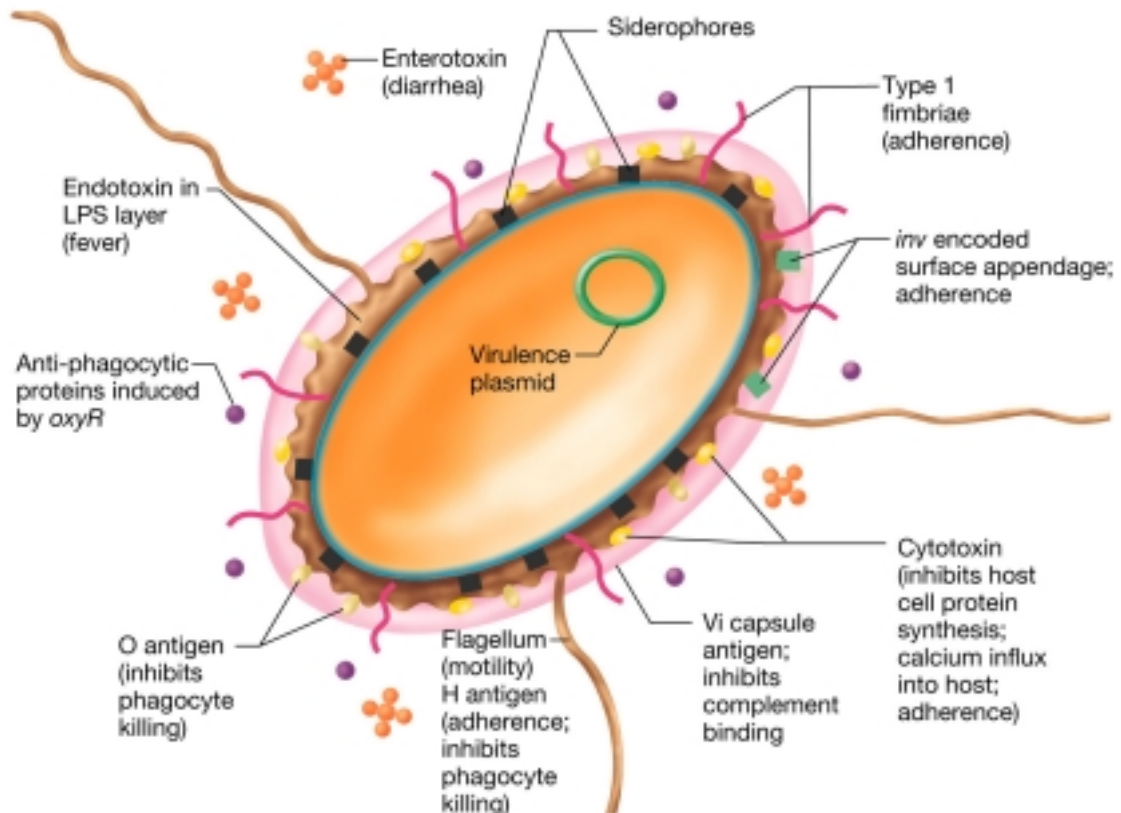


MMG 301 Lec. 32 Bacterial Infections

Questions for Today

1. What are bacterial virulence factors?
2. What are the major types of toxins and how do they work?
3. How are bacterial infections transmitted?
4. What are the key features of some common and emerging bacterial diseases?

Virulence Factor – a pathogen-produced substance that promotes the establishment and maintenance of disease



Types of Virulence Factors

Adherence components (attachment)

Capsules (evasion)

Invasion enzymes (entry into host, colonization)

- *hyaluronidase*: breaks down the polysaccharide that glues the host cells together

- *collagenase*: breaks down collagen network in connective tissues

- fibrinolytic enzymes (e.g., *streptokinase*) that destroys fibrin of blood clots (escape)

- *coagulase*: promotes blood clotting (protection)

- various other proteases, nucleases, lipases

Toxins

- Exotoxins (including enterotoxins)
 - Endotoxins
- } See next page

Additional Features

- Microbial genome sequencing projects show that virulence genes are often clustered in “*pathogenicity islands*”

- Pathogenicity islands may be found in pathogenic strains, while being absent in closely related *avirulent* strains.

- Many bacterial pathogens also carry virulence genes on large plasmids

Bacterial Toxins

Exotoxins

- Small proteins that are released into cell surroundings (extracellular toxins)
 - Produced from cells growing in wound or on mucosal surface
 - Alternatively may derive directly from ingestion (e.g., contaminated food)

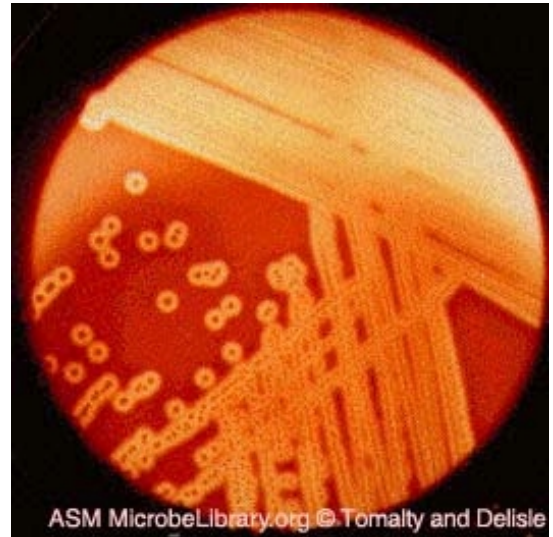
- 3 main types:

1. Cytolytic exotoxins lead to cell lysis

- *Hemolysins*: work on various cells but discovered and easily assayed by ability to lyse RBCs in blood agar.

- *Lecithinases* and *phospholipases*: degrade phospholipids

- *Leukocidins*: kill white blood cells (WBCs)

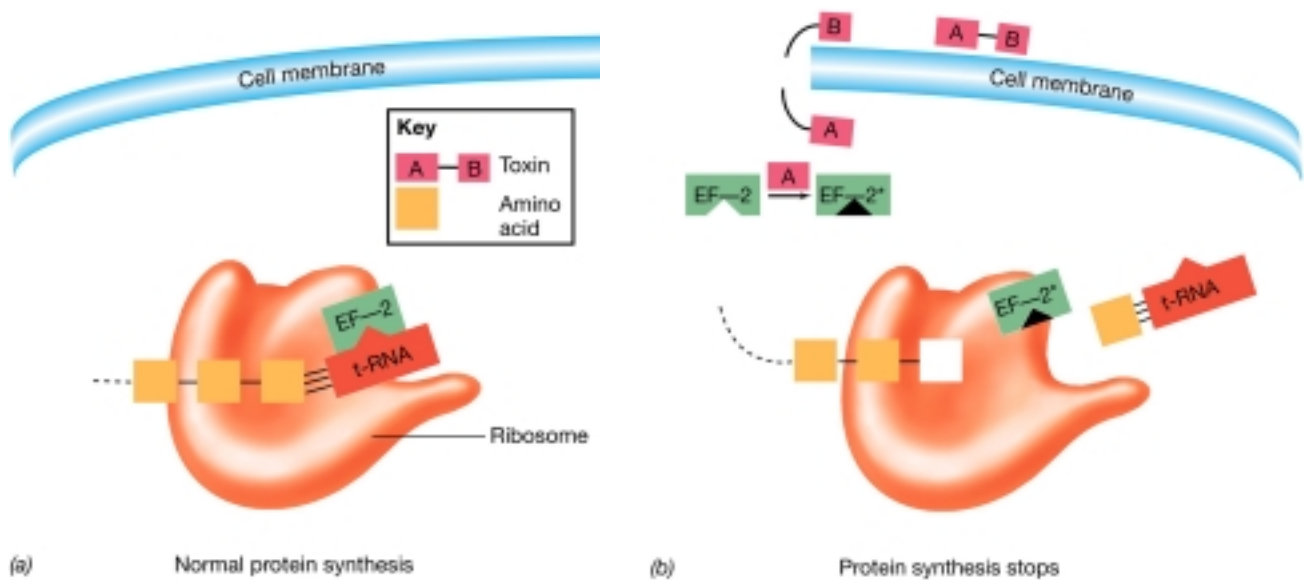


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2. Superantigens stimulate host cells and lead to extensive inflammatory reactions

3. A-B toxins have two components (initially linked together). One binds to host receptor, the other enters and damages the cell

- Diphtheria toxin (*Corynebacterium diphtheriae*)
- Tetanus toxin (*Clostridium tetani*)
- Botulinum toxin (*C. botulinum*)
- Cholera toxin (*Vibrio cholerae*)



Diphtheria toxin B fragment binds tightly to host cell receptors; after binding, a protease cleaves between A and B. The A fragment enters cell and blocks tRNA from entering the ribosome by chemically modifying EF-2 (an elongation factor).

Tetanus toxin (from infection in deep wounds) binds to motor neurons, blocks glycine-stimulated relaxation, leads to “spastic paralysis”.

Botulinum toxin (most toxic substance known, found in improperly canned food) binds to presynaptic motor neurons, prevents release of acetylcholine, leads to “flaccid paralysis” .

Cholera toxin is an example of an *enterotoxin*: a toxin that exerts its effects in the small intestine. The B fragment activates adenylate cyclase, this increases the concentration of cyclic AMP and stimulates excretion of Na^+ and HCO_3^- , the result is massive water loss (diarrhea) that may be fatal.

Endotoxins

- formed from cell-bound lipopolysaccharides that are usually released upon lysis of the bacterial cell; the lipid component is the main toxin.
- leads to fever in the host by stimulating endogenous pyrogens (temp controllers).
- also see inflammation, diarrhea.
- less toxic than exotoxins; LD₅₀ 200-440 µg vs. 25 pg for botulinum toxin.
- in contrast to exotoxins, the endotoxins are not destroyed by heating.

Transmission of pathogens:

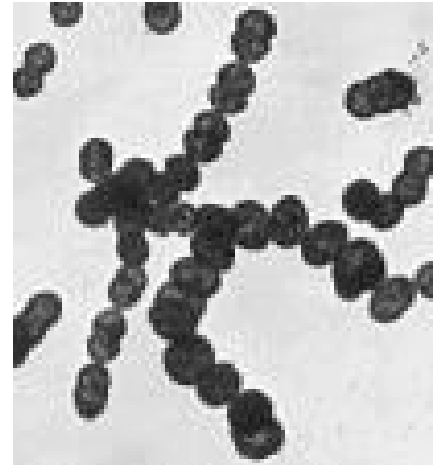
- Airborne: enter through lungs
- Animals: pathogen may typically infect an animal, but mutation or a compromised host may allow it cross the species boundary.
- Insects and ticks: pathogen life cycle includes some component in an arthropod “vector”
- Sexually transmitted: requires direct contact
- Water or food: contaminated materials are ingested.

As we discuss specific examples of bacterial pathogens, note the types of virulence factors utilized (including toxins) and the mechanism of transmission used.

Streptococcal diseases

Streptococcus pyogenes and *S. pneumoniae*

- Gram-positive cocci; usually grow in long chains
- Mainly found in upper respiratory tract
- cause of streptococcal pharyngitis (strep throat),
- Most isolates produce
 β -hemolysis

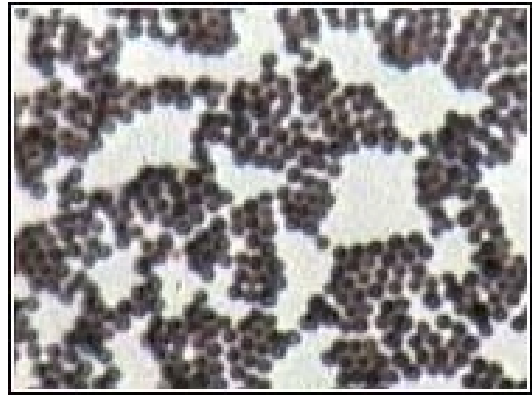


- *S. pyogenes* is responsible for about $\frac{1}{2}$ of all severe sore throat cases
- Also associated with:
 - Scarlet fever – certain strains of *S. pyogenes* have a prophage that produces an erythrogenic exotoxin (causes pink-red rash)
 - Rheumatic fever – a delayed sequelae, or a follow-up disease;
 - bacterial surface antigen resembles a human protein
 - patient's immune system attempts to defend against foreign cells, but attacks heart, kidney, joint tissues (autoimmune disease)
 - “flesh-eating bacteria” (necrotizing fasciitis) – exotoxins and “M-protein” of bacterial surface act as a superantigen (elicits a hyper immune response leading to tissue destruction; 30% fatality rate)

Staphylococcal diseases

Staphylococcus aureus

- Gram-positive cocci that form irregular clumps
- Produce several exotoxins
 - hemolysins – lyse red blood cells
 - coagulase – causes blood clotting around the cells; protects from host immune system
 - leukocidins – destroys leukocytes
- Mostly found in upper respiratory tract – many people are carriers and do not get disease unless resistance is compromised
- antibiotic resistant strains are a problem
- some strains are responsible for *toxic shock syndrome* (fever, diarrhea, vomiting, sometimes fatal; first identified in menstrating women where tampons supported bacterial growth)
 - toxic shock toxin – an exotoxin that is a superantigen; causes massive T cell reaction and inflammatory response
- some strains produce enterotoxin A – the most common form of food poisoning in the US



(C/NW)

Diphtheria

Corynebacterium diphtheriae – Gram-positive rod

- infects upper respiratory tract (tonsils and throat)
- can be immunized with vaccines
- inflammatory response to infections result in lesions called pseudomembrane - can block the airway
- some strains also produce diphtheria toxin – inhibits protein synthesis (ADP ribosylation)

Pertussis (whooping cough)

Bordetella pertussis

- attaches to upper respiratory tract cells
- produces pertussis exotoxin
 - induces cyclic AMP synthesis in host cells that eventually leads to tissue damage
- produces an endotoxin that promotes some symptoms
- protection is part of “DPT” vaccine

Meningitis

Neisseria meningitidis, several bacteria & viruses

- inflammation of the meninges (membrane surrounding nervous system)
- airborne, to nasopharynx then bacteremia
- caused several MSU deaths

Tuberculosis

Mycobacterium tuberculosis

- at the time of discovery by Koch (1882), accounted for 1/7 of all deaths in Europe and 1/3 of deaths of young adults
- 26,000 new cases, 12,000 deaths annually in US
- inhaled bacterium settles in lungs and grows
 - bacteria are phagocytosed by macrophages
 - hypersensitivity immune response forms around infection sites creating nodules (tubercles)
 - disease may stop, but in some cases bacteria can remain alive
 - in time, tubercule can calcify – visible on X-ray
 - the immunity that develops can be tested for with a TB skin test

- Drug-resistant strains are a major concern.
- Even with effective drugs, the patients may not follow the long-term regimen needed for treatment



Bacterial sexually transmitted diseases

Gonorrhea

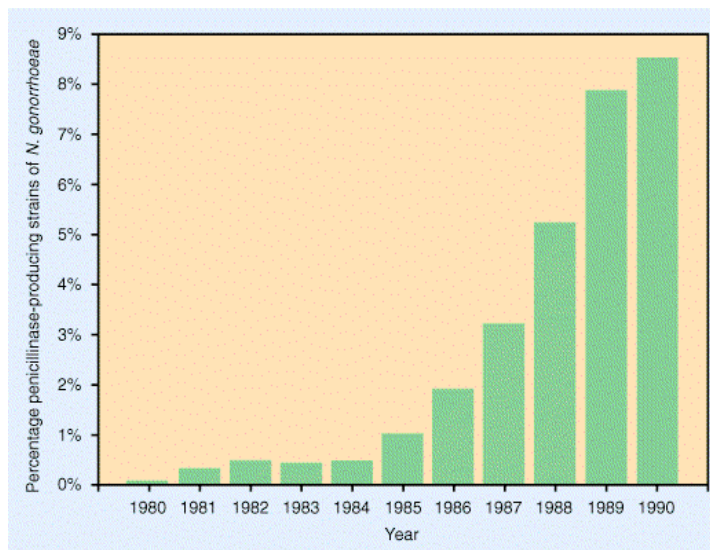
Neisseria gonorrhoeae



- Gram-negative, non-motile, aerobic, diplococcus
- infect mucous membranes of genitourinary tract, eye (newborns), rectum, throat
- Very sensitive to conditions like drying, UV light
- Spread by direct person-to-person contact
- Treated with penicillin antibiotic in the past – now have new penicillin resistant forms
- Resistance due to plasmid encoded penicillinase

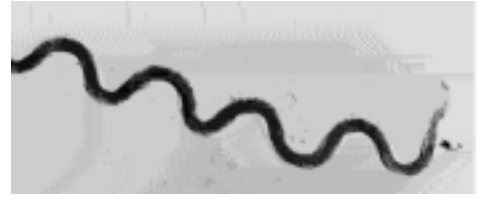
Females develop mild vaginitis

Males develop painful infection of the urethral canal



Syphilis *Treponema pallidum* a spirochete

Entry through breaks in the epithelium. Multiplies in three stages



1. Forms a chancre at initial infection site which later disappears,
2. cells can spread to other tissues causing characteristic skin rash
3. A latent stage, not infectious, that can last years; lesions form on skin, bone, nervous system (blindness, insanity)

Emerging bacterial infections

Incidence in humans has increased within the past ~20 years

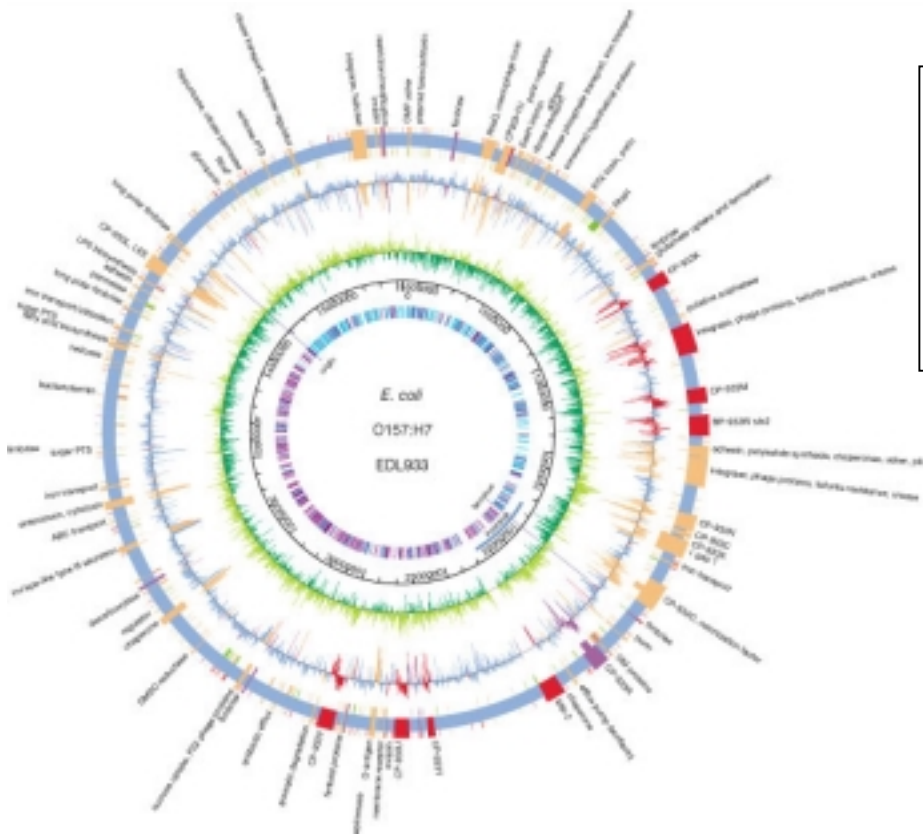
Lyme disease – first described in 1975 (in Old Lyme, CT) (Range is increasing and now entering MI)

- tick-borne zoonosis (spread from animals to humans); usually deer and field mice
- *Borrelia burgdorferi* – a spirochete
- About 24 hours of attachment of tick is necessary for disease transmission
- Use repellents, dress accordingly
- Lyme disease has three stages:

1. 1 week – 10 days: Expanding red ring around tick bite lesion; flu-like symptoms
2. Dissemination of organism: several weeks to months; neurological problems, heart inflammation, arthritis
3. Years later – demyelination of neurons with symptoms resembling Alzheimer's disease

Escherichia coli O157:H7

- An enterohemorrhagic strain:
- Food sources: undercooked hamburger in most cases, also raw milk, unpasteurized fruit juice
- Has two toxins that cause severe damage to intestinal lining
- Genes for toxins [verotoxin (VT), shiga-like toxin] are closely related to toxins from *Shigella dysenteriae*
- The illness is characterized by severe cramping (abdominal pain) and diarrhea which is initially watery but becomes grossly bloody
- 1996 outbreak in Japan resulted in 6,000 cases (2 deaths)



Note the pathogenicity islands in yellow and red

Legionella pneumophila - Legionnaires' disease

- First outbreak at an American Legion convention in Philadelphia, 1976
- aerobic, Gram-negative rod
- Water-borne transmission route
- part of a microbial community in water storage tanks, air conditioning systems, soil and aquatic habitats
- inhaled and settles in the lungs
- live inside macrophages
- *Legionella pneumophila* also causes Pontiac fever (outbreak in Pontiac Michigan); causes flu-like symptoms

