بسم الله الرحمن الرحيم

Introduction to Microbiology

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Lecture 9

Pathogenesis of bacterial infection

Although most bacteria are **harmless** or often **beneficial**, some are **pathogenic**, with the number of species estimated as **fewer than a hundred** that are seen to **cause infectious** diseases in humans.

By contrast, **several thousand species** exist **in the human digestive system without causing disease.**

* less than 100 species can cause disease

* only few bacteria can cause disease for human since :-
1) they should be highly skilled
عشان هم خطرة على إنهم يطوروا
2) because of precense of bacteria that defuse pathogen.

pathogen should overcome this

عندها مهارة عالية جدًا

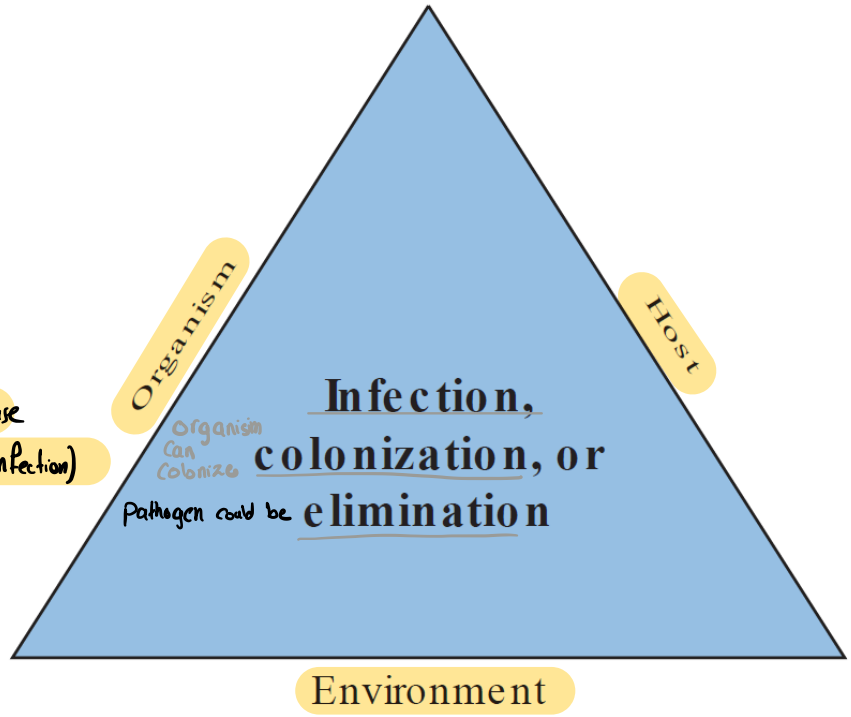
Pathogenicity is, in a sense, a highly skilled trade, and only a tiny minority of all the numberless tons of microbes on the earth has ever involved itself in it; most bacteria are busy with their own business, browsing (التصفح) and recycling the rest of life. Indeed, pathogenicity often seems to me a sort of biological accident in which signals are misdirected by the microbe or misinterpreted by the host.

—Lewis Thomas, *The Medusa and the Snail*

موضوع الجزء اليوم.

وليس كل سبب يصل إلى البدن يفعل فيه بل قد يحتاج مع ذلك إلى أمور ثلاثة: إلى قوة من قوته الفاعلة، وقوة من قوة البدن الإستعدادية، وتمكن من ملاقاة أحدهما الآخر زماناً في مثله يصدر ذلك الفعل عنه.

The Canon of Medicine
القانون في الطب
Avicenna (Ibn Sina) in 1025



when they met → they cause
interaction → حدوث (infection)

Organism can colonize

Pathogen could be

* now, we want to study pathogen that can cause a disease ↓ (organisms)

Pathogenesis of bacterial infection

For bacteria **to cause disease (to be pathogenic)** , it needs to have some attributes to help it reach the host and persist within the host and replicate, while causing harm (disease) to the host. Characteristics of bacteria that are pathogens are sometimes referred to as **virulence factors -**but can be shared with non-pathogenic bacteria- and include:

pathogenic bacteria =

خصائص/عوامل بالبكتيريا بتمكنها تسبب ضرر

- transmissibility,
- adherence to host cells
- motility
- persistence
- invasion of host cells and tissues
- Toxigenicity
- Iron uptake mechanisms
- the ability to evade or survive the host's immune system.
- Resistance to antimicrobials and disinfectants.

Steps How this Pathogenic organisms take place

we will Study them one by one ⇓

Transmission (Cability to be transported).

- Some pathogens come from human, animal, enviroment, soil.
- إذا كانت البكتيريا بتصيب الجهاز التنفسي رح تنتقل عبر الجهاز التنفسي وهكذا...

- Bacteria can adapt to a variety of environments that include external sources such as **soil, water and organic matter** or internal milieu as found **within insect vectors, animals and humans.**

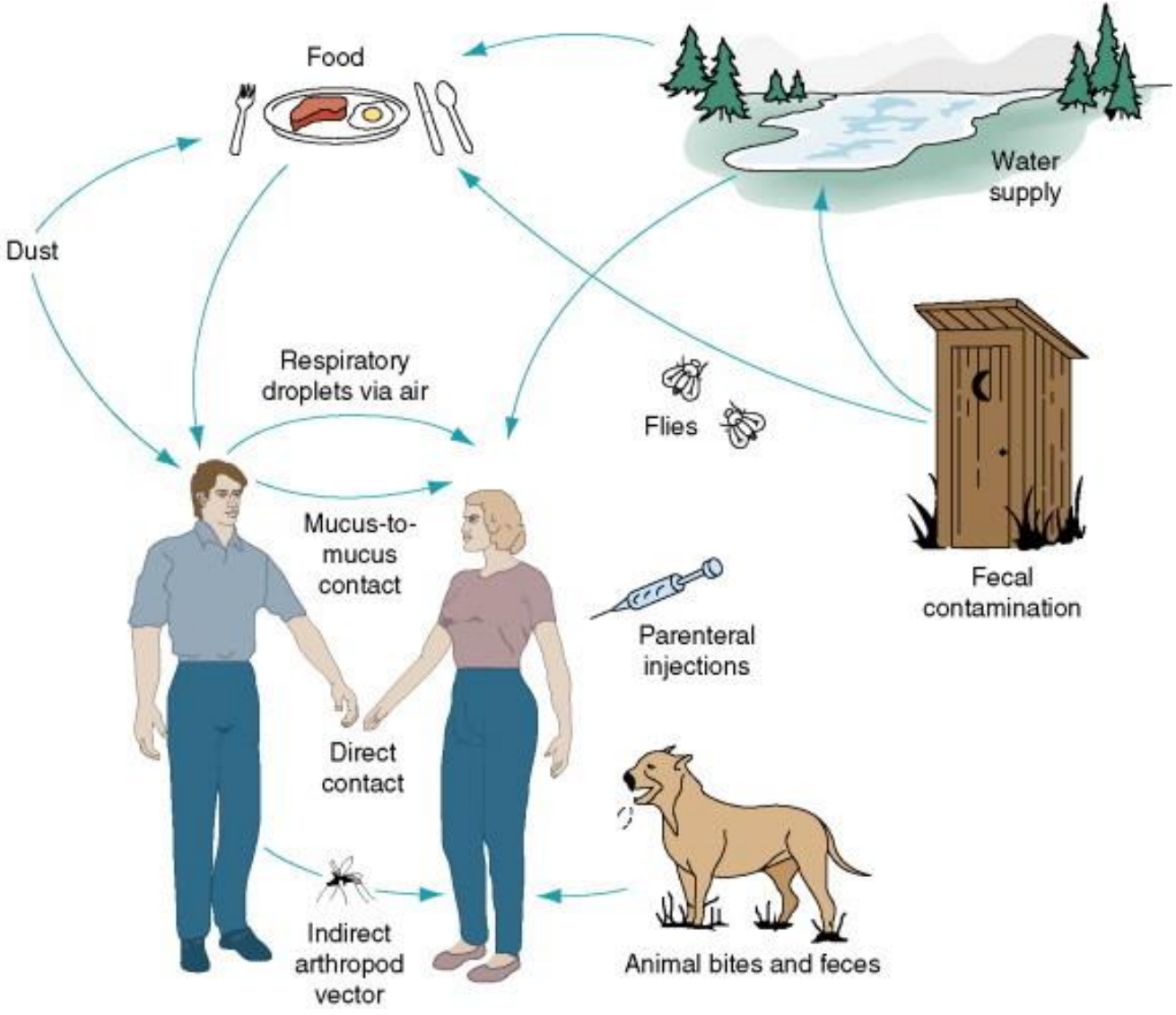
- By producing asymptomatic infection or **mild disease rather than death of the host**, microorganisms that normally live in people **enhance the possibility of transmission from** one person to another.

(مابتظهر أعراض فرح بيتشر بشكل أكبر (يمكن الضحية ما يعرف إنه مصاب ويتدي غيره)

- **The clinical manifestations of diseases** (eg, diarrhea, cough, genital discharge) produced by microorganisms often **promote transmission of the agents**.

(في أعراض ← اه مخاني ، الكحة ---) من خلالهم بتنتشر الأمراض
- وجودهم بعزز لانتشار الجرثوم -

- The respiratory (upper and lower airways), gastrointestinal (primarily mouth), genital,and urinary tracts. Abnormal areas of mucous membranes and skin (eg, cuts, burns, and other injuries) are frequent **sites of entry**.


Food
Water supply
Dust
Respiratory droplets via air
Flies
Fecal contamination
Mucus-to-mucus contact
Parenteral injections
Direct contact
Indirect arthropod vector
Animal bites and feces

Contact

ways to transmit:

Transmission via contact includes direct skin-to-skin or mucous membrane-to-mucous membrane contact or fecal–oral transmission of intestinal bacteria. Transfusion of contaminated blood products also transmits several bacterial infections, such as syphilis.

Airborne

droplet nuclei

Some bacteria are carried on air currents in droplet nuclei. Q fever, tuberculosis, and Legionella travel great distances from their origin. Animals with Q fever have been known to transmit infection to other animals as far as 10 miles away.

Droplet

When an infection is spread via droplets greater than 5 μm in diameter, this type of spread is not considered airborne given that the droplet is unlikely to travel through the air for more than 1 m. They are generally more susceptible than airborne droplet nuclei to filtering in the nose via nasal hairs or to removal by nasal or facial masks.

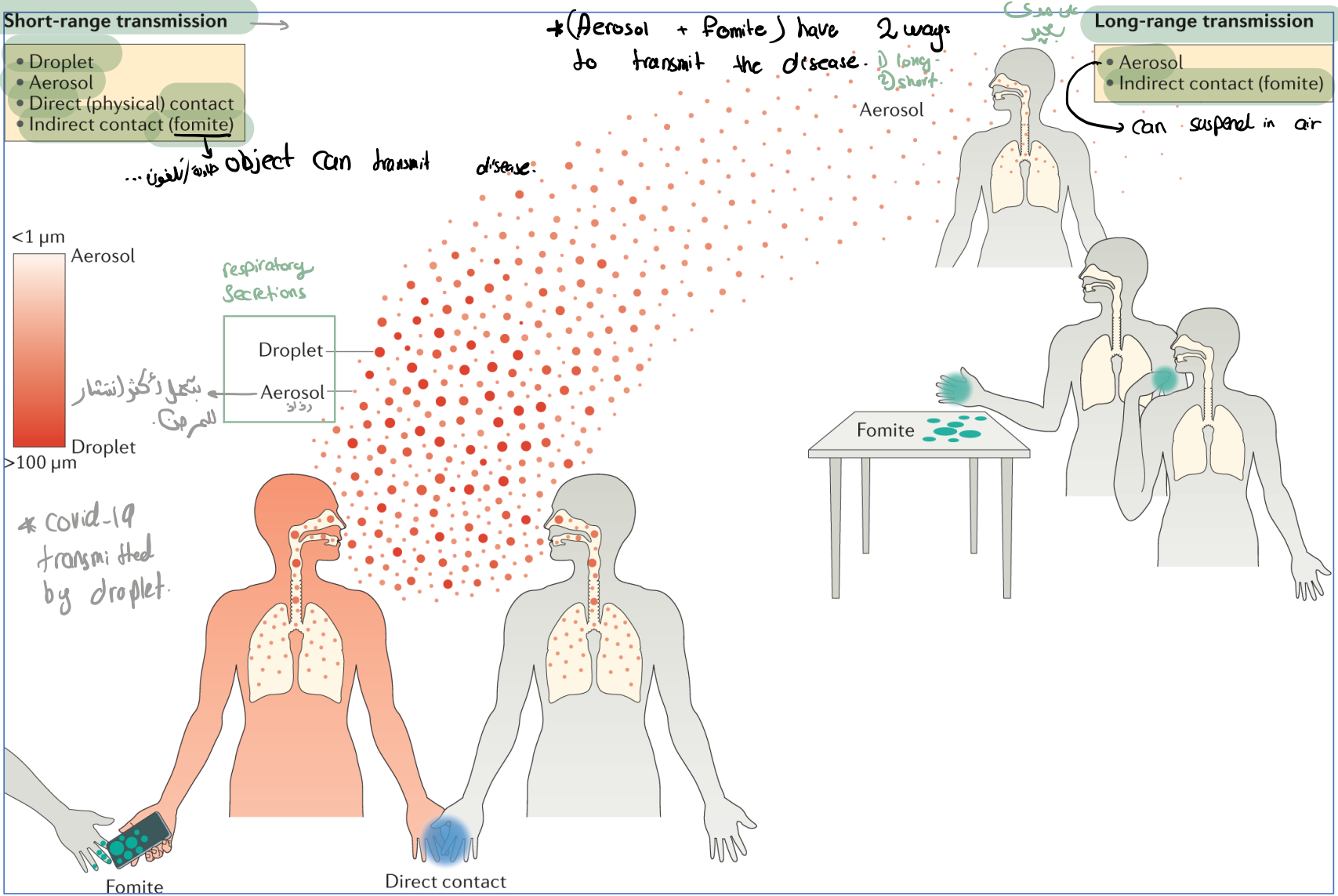
Vectors

Typically, the arthropod (mosquito, tick, louse) takes a blood meal from an infected host (which can be human or animal) and transfers pathogens to an uninfected individual. Bacteria such as *Shigella* can adhere to the foot pad of house flies and be transmitted in this manner.

Vehicular (including food, water, and fomite transmission)

Bacterial infection due to food and water generally develops when bacteria enter the intestine via the mouth. Those organisms that survive the low pH of the stomach and are not swept away by the mucus of the small intestine adhere to the cell surfaces. There they may invade the host cells or release toxins, causing diarrhea.

Infection acquired from fomites is usually the result of the organism attaching to the host's skin (generally on their hand) when they come in contact with a contaminated object, and then being deposited onto a mucus membrane when the host touches his or her face, or in some cases his or her genitals, with the contaminated body part (Table 2).


Short-range transmission
• Droplet
• Aerosol
• Direct (physical) contact
• Indirect contact (fomite)
*(Aerosol + Fomite) have 2 ways to transmit the disease. 1) long- 2) short-
... object can transmit disease.
Long-range transmission
• Aerosol
• Indirect contact (fomite)
can suspend in air
Aerosol
<1 µm
Aerosol
Droplet
>100 µm
respiratory secretions
Droplet
Aerosol
Fomite
* covid-19 transmitted by droplet.
Fomite
Direct contact

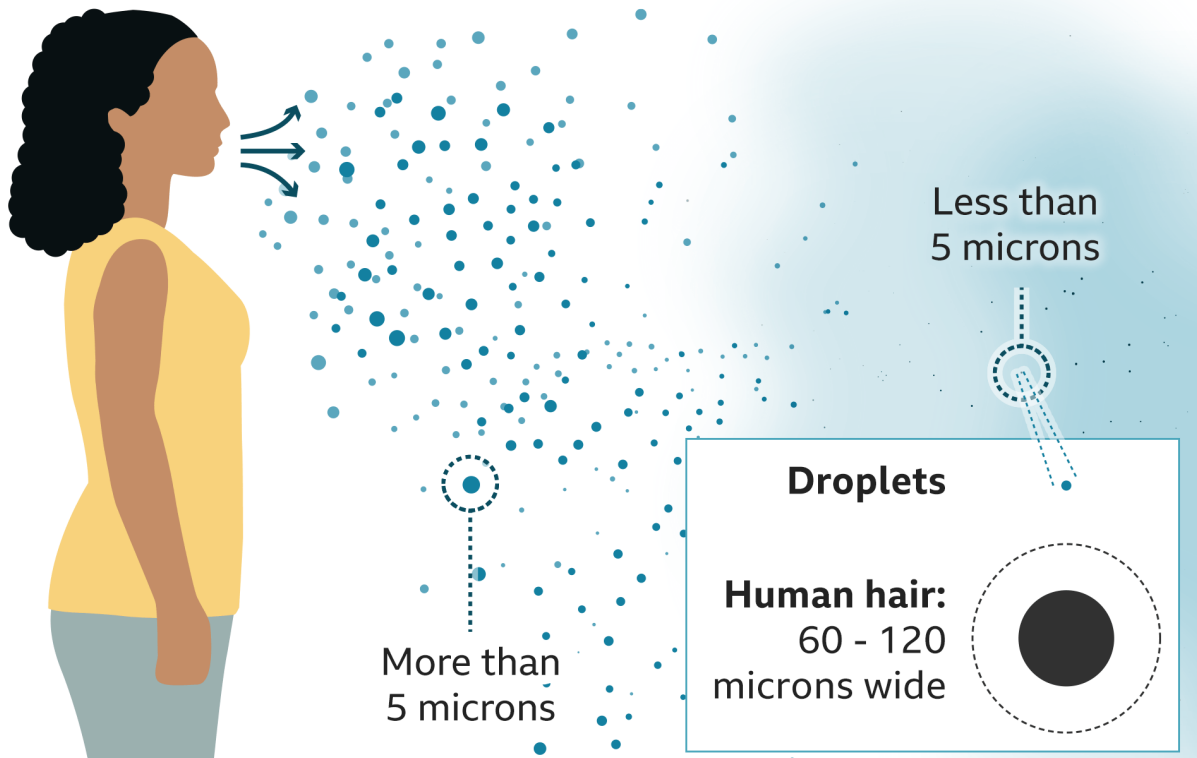
The difference between droplet and airborne transmission

Droplet transmission

Coughs and sneezes can spread droplets of saliva and mucus

Airborne transmission

Tiny particles, possibly produced by talking, are suspended in the air for longer and travel further



Source: WHO

BBC

Face Covering and Mask
to Minimise Droplet Dispersion
& Aerosolisation

Transmission

Portal of entry

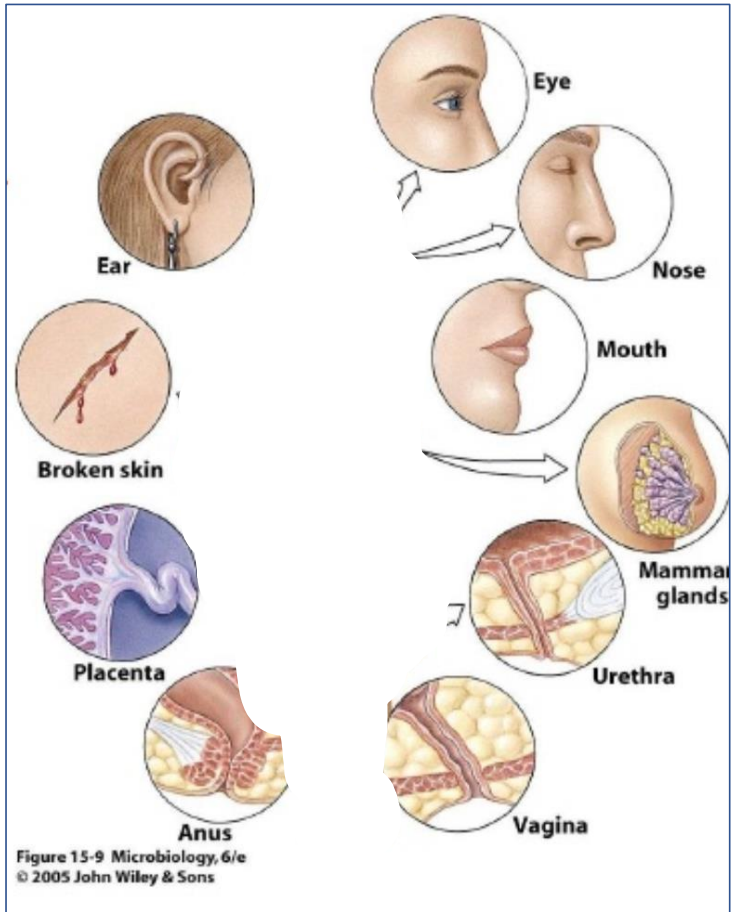


Figure 15-9 Microbiology, 6/e
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Portal of exit

get out
بتطلع من المكان اي في
اصلاً بتكون موجودة فيه

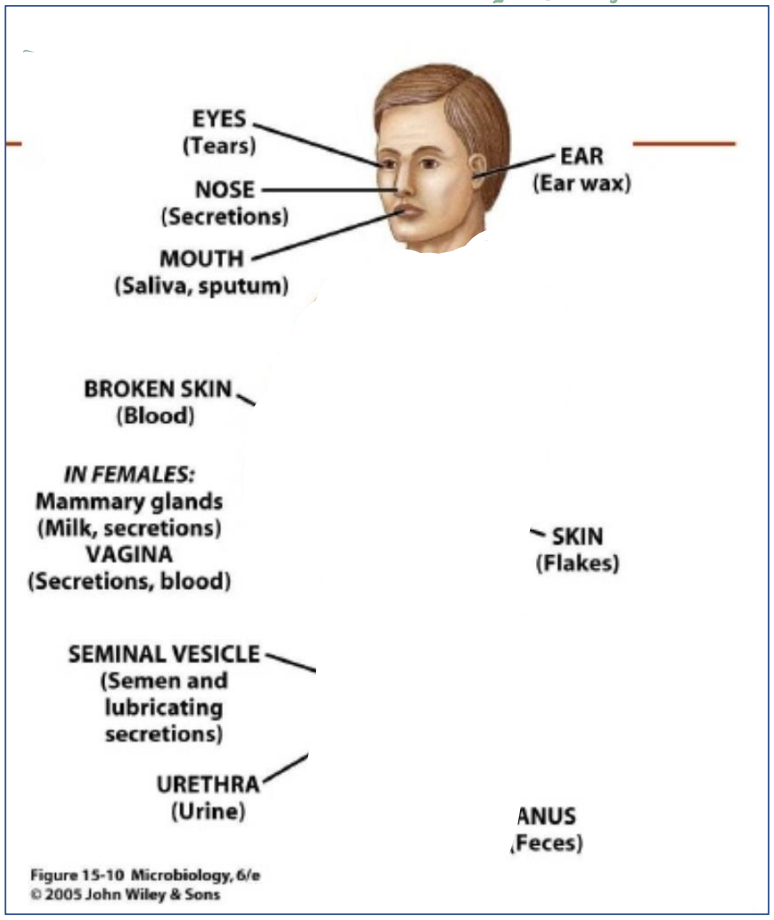


Figure 15-10 Microbiology, 6/e
© 2005 John Wiley & Sons

Adhesion

* after microorganism is transmitted succesfully the next step is adhesion

كلام مثلاً تلزق بجلدك عشان بعدها تدخل ع الخلايا ما صار adhesion خليها لما تكتسل للي أو هواء أو أي أشي راح يستقبلها.

- Bacteria also have specific surface molecules that interact with host cells. Many bacteria have **pili**, thick rodlike appendages or **fimbriae**, shorter "hairlike" structures that extend from the bacterial cell surface and help mediate adherence of the bacteria to host cell surfaces

- When bacteria enter the body of the host, they must adhere to cells of a tissue surface. **if they did not adhere, they would be swept away** by mucus and other fluids that bathe the tissue surface.

* pili is maded from smaller protein called pilin.
  pilin will polymerize and become extending pilus.
  then this extended pilus will attach to the surface.

* when Pilus depolymerize it's start to become shorter
  this shortange will lead to surface movement of bacteria.

* pili inhibit phagocytic cells

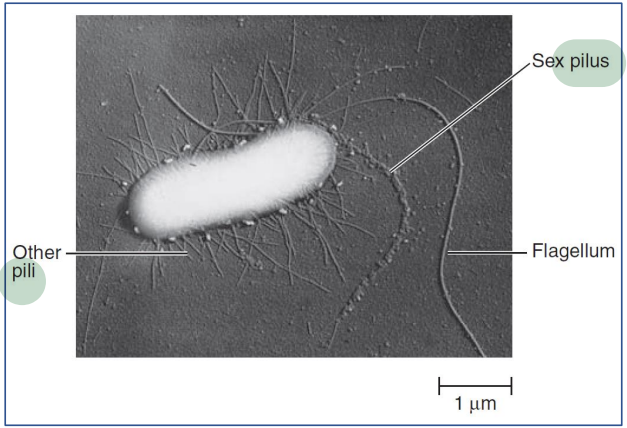
So, any succesful pathogen Can have group of wags/proteins to do "adhesion"

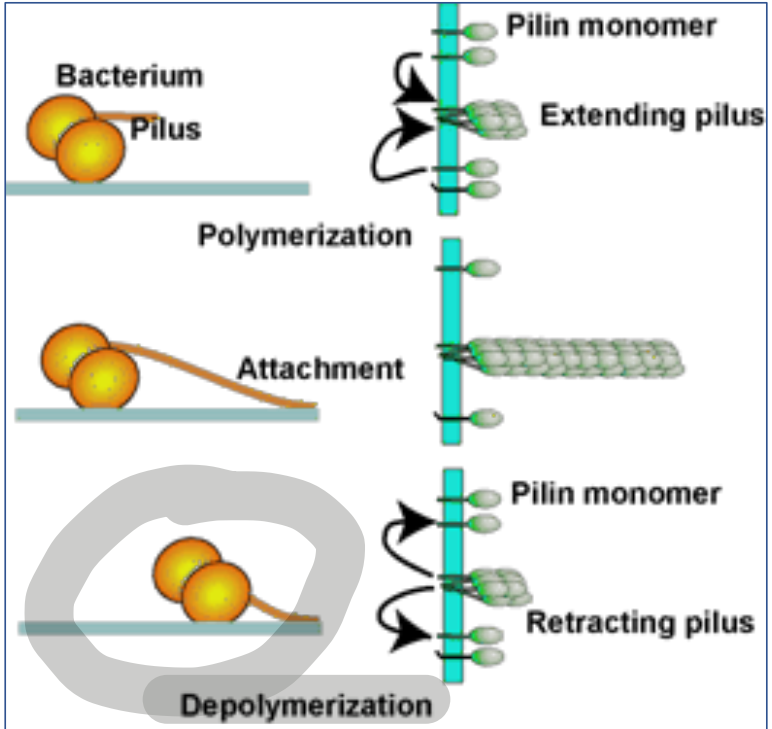
Pili (fimbria)

Composed of structural protein subunits termed **pilins**. Minor proteins termed **adhesins** are located at the tips of pili and are responsible for the attachment properties.

Two classes can be distinguished: **ordinary pili**, which play a role in the **adherence** of symbiotic and pathogenic bacteria to host cells, and **sex pili**, which are responsible for the attachment of donor and recipient cells in bacterial **conjugation.**
Pili inhibit the phagocytic ability of leukocytes.

Their tips strongly adhere to surfaces at a distance from the cells. Pili then depolymerize from the inner end, thus retracting inside the cell. The result is that the bacterium moves in the direction of the adhering tip. This kind of surface motility is called **twitching** and is widespread among piliated bacteria. **pili grow from the inside of the cell outward**.





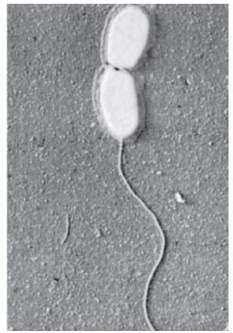
Motility

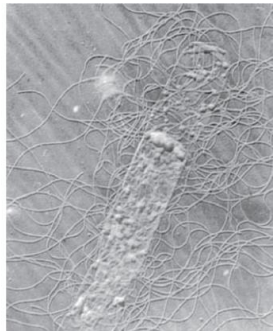
- A huge advantage for bacteria to reach the host, and manoeuvre in the host and evade the immune system is for a bacterium to be **motile** – to have the ability to direct its own movement.

- The bacterial **flagellum** is an amazingly complex molecular machine with a diversity of roles in pathogenesis including reaching the optimal host site, **colonization** or **invasion**, **maintenance** at the infection site, and post-infection **dispersal**

* usually GI pathogen need motality.
However, skin pathogen need to replicat.

Flagella





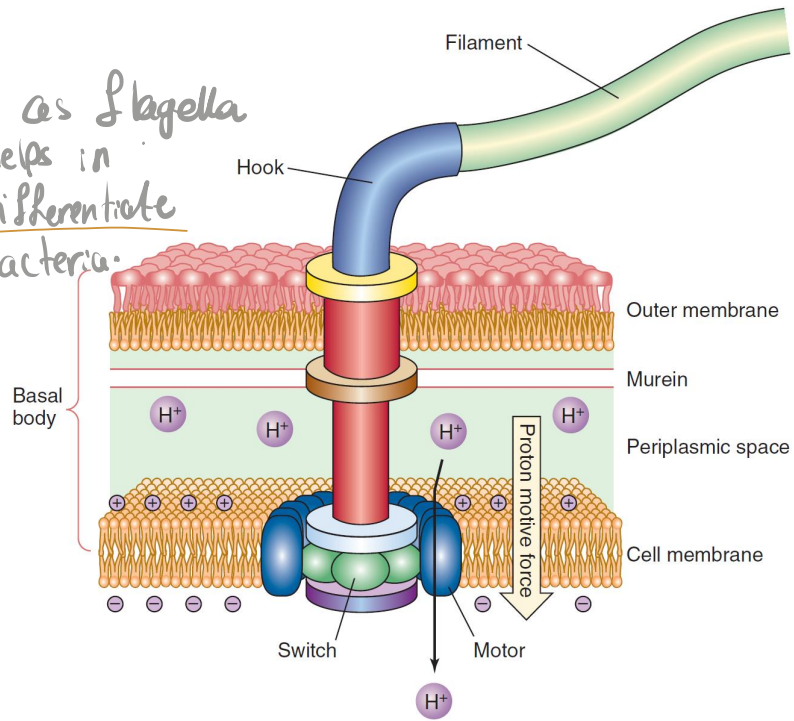
- Bacterial flagella are thread-like appendages composed of a protein subunit called **flagellin**.

- Rotation is driven by the flow of protons into the cell down the gradient produced by the primary proton pump

- highly antigenic **(H antigens) (**immune responses to infection can be directed against these proteins).

- **chemotaxis**: the net movement of the cell toward the source (a sugar or an amino acid). cell behavior brought about in response to a change in the environment is called **sensory transduction.**

يسمى سلوك الخلايا الذي يحدث استجابة للتغير في البيئة بالتحويل الحسي.



* Some pathogenes will not stay on surface, they need to go deeper: (from epithelium to blood for example make it more pathogenic!)

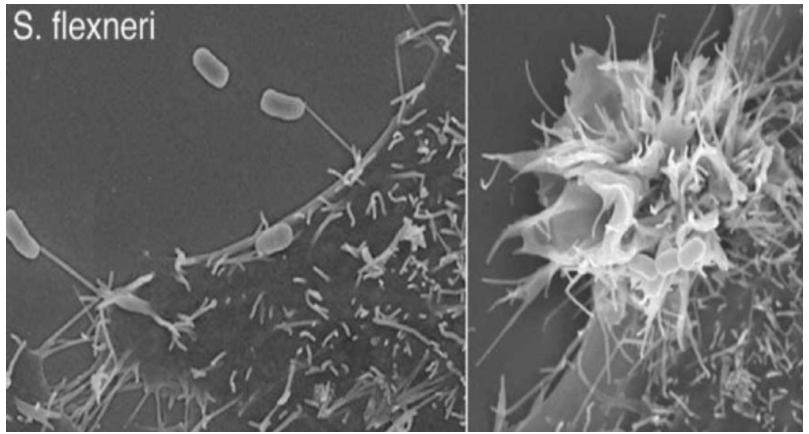
Invasion

↳ not all pathogens have this ability.

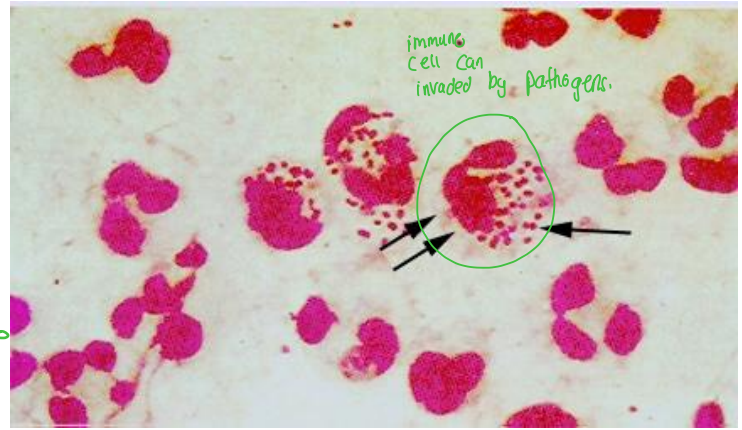
Invasion can happen **through tight junctions of epithelial surfaces**, or **through internalization** into epithelial cells.

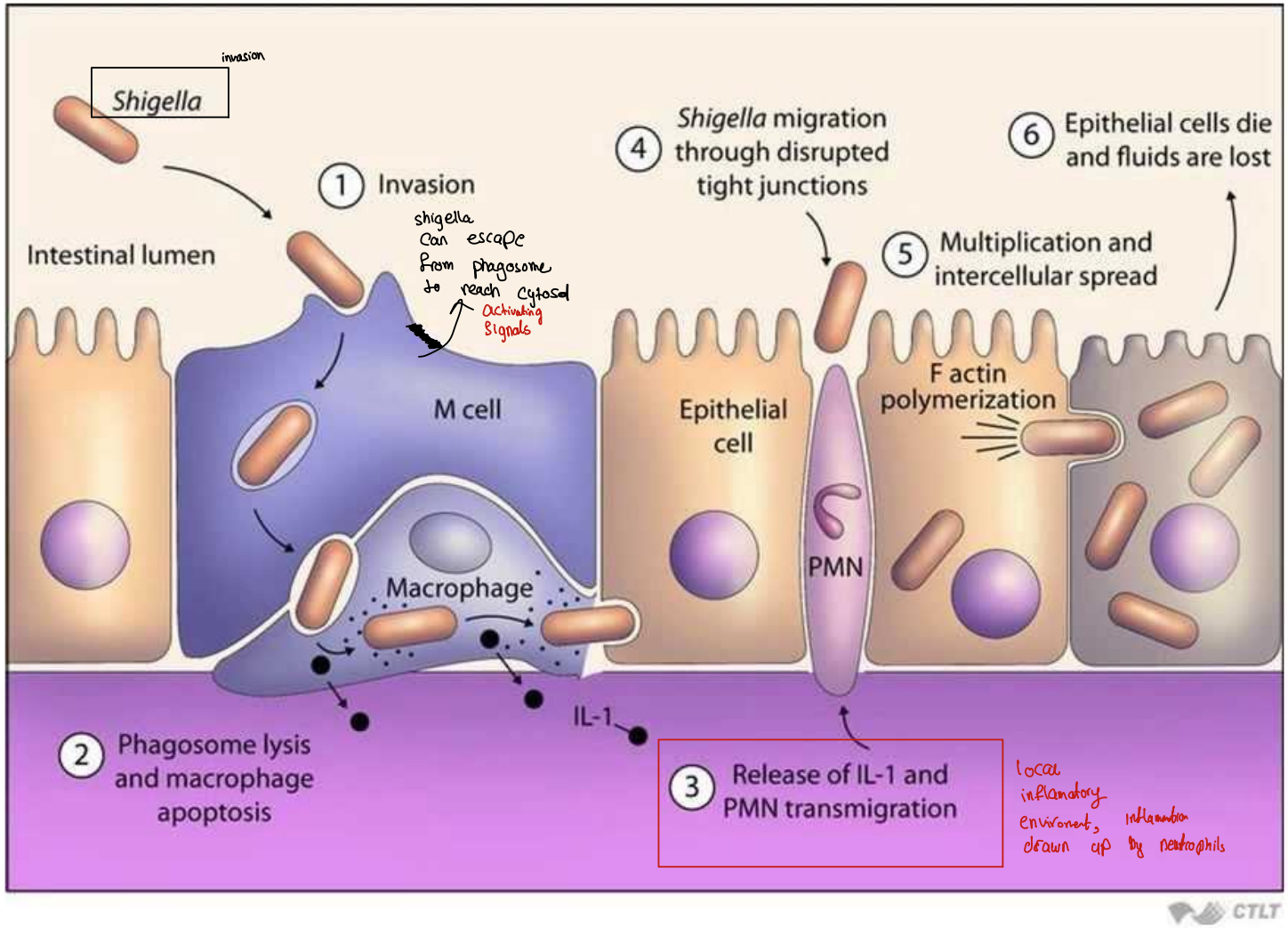
Active process between cells and pathogen. Usually requires **actin polymerization**

Once inside the cells, the bacteria can be transported by **vesicles to the lysosome, or can remain or escape the vesicles to multiply in the cytoplasm, or be released to the extracellular space to invade other cells**. Bacteria can also induce **apoptosis** in cells they invade.



there are many ways for bacteria to escape!




invasion
Shigella
1 Invasion
shigella can escape from phagosome to reach cytosol
activating signals
Intestinal lumen
M cell
Macrophage
2 Phagosome lysis and macrophage apoptosis
IL-1
4 Shigella migration through disrupted tight junctions
Epithelial cell
PMN
3 Release of IL-1 and PMN transmigration
local inflammatory environment, drawn up by neutrophils
5 Multiplication and intercellular spread
F actin polymerization
6 Epithelial cells die and fluids are lost
CTLT

Toxins/ Exotoxins (production of toxin).

Secrete toxic out side the cell.

Exotoxins (secreted actively, by contact only, or by cell death) or **endotoxins** (part of bacterial cell wall) .

Exotoxins are bases for some vaccines (toxoids) بالأسفل

toxins Made of poly peptid with 2 subunits — catalytic Subunit (that cause the damage) — bind to receptor

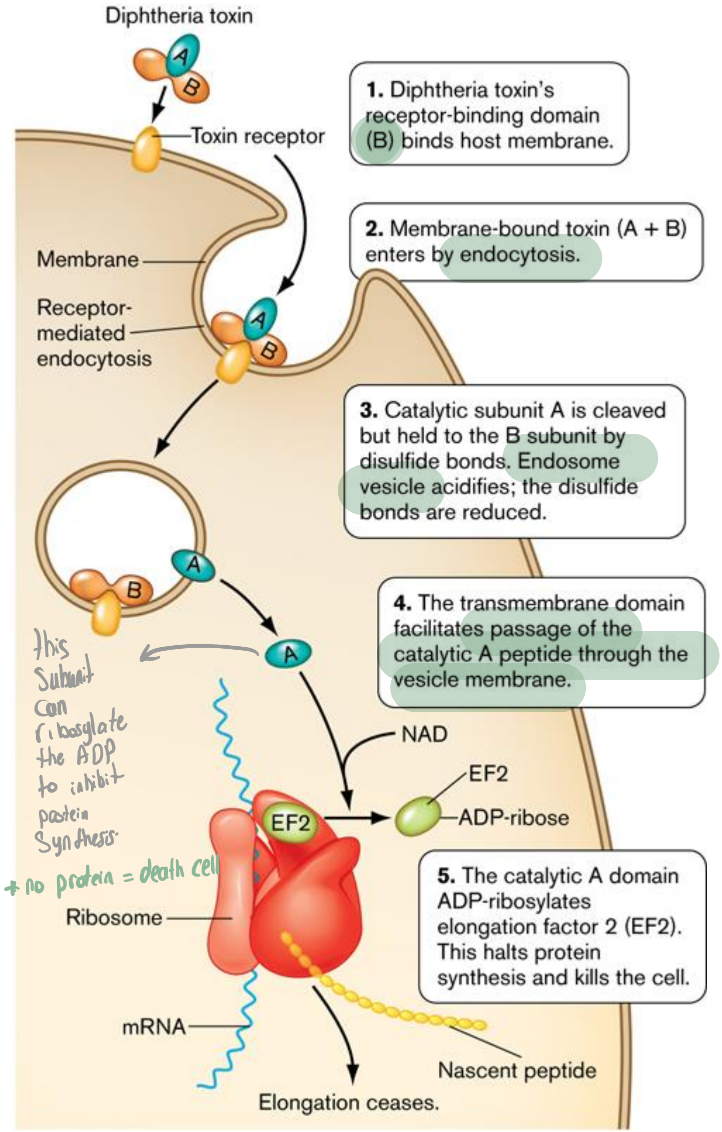
Made of A (toxic activity) and B (helps attachment and internalization into cells) subunits.

Exotoxins associated with diarrheal diseases are frequently called **enterotoxins.** (toxins that are secreted in GI tract)

* antibody can neutralize toxic by binding to it before the toxin bind to the receptor. so they (bacteria) become inactive we call them toxoids

مع ال toxin ← inactive
بس لازم الجسم يكون يصنع منه Antibody
لذلك منعطي نتعامله بال vaccine.

* these toxins are secreted by secretion system



no need to memorize them now

Toxin	Organism	Gene Location	Subunit Structure	Target Cell Receptor	Biological Effects
Anthrax toxins	*Bacillus anthracis*	Plasmid	Three separate proteins (EF, LF, PA)	Tumor endothelial marker-8 (TEM-8); capillary morphogenesis protein 2 (CMG2)	EF + PA: increase in target cell cAMP level, localized edema; LF + PA: death of target cells and experimental animals
Bordetella	*Bordetella* spp.	Chromosomal	A-B	Unknown, probably glycolipid	Adenylate cyclase toxin. Increase in target cell cAMP level, modified cell function, or cell death
Botulinum toxin	*Clostridium botulinum*	Phage	A-B	Polysialogangliosides plus synaptotagmin (co-receptors)	Decrease in peripheral presynaptic acetylcholine release, flaccid paralysis
Cholera toxin	*Vibrio cholerae*	Chromosomal	$A\text{-}B_5$	Ganglioside (GM_1)	Activation of adenylate cyclase, increase in cAMP level, secretory diarrhea
Diphtheria toxin	*Corynebacterium diphtheriae*	Phage	A-B	Growth factor receptor precursor	Inhibition of protein synthesis, cell death
Heat-labile enterotoxins	*Escherichia coli*	Plasmid	Similar or identical to cholera toxin		
Pertussis toxin	*Bordetella pertussis*	Chromosomal	$A\text{-}B_5$	Surface glycoproteins with terminal sialic acid residues	Block of signal transduction mediated by target G proteins
Pseudomonas exotoxin A	*Pseudomonas aeruginosa*	Chromosomal	A-B	α_2-Macroglobulin receptor (α_2-MR)	Similar or identical to diphtheria toxin
Shiga toxin	*Shigella dysenteriae*	Chromosomal	$A\text{-}B_5$	Globotriaosylceramide (Gb3)	Inhibition of protein synthesis, cell death
Shiga-like toxins	*Shigella* spp., *E. coli*	Phage	Similar or identical to Shiga toxin		
Tetanus toxin	*Clostridium tetani*	Plasmid	A-B	Polysialogangliosides plus 15-kDa glycoprotein (co-receptors)	Decrease in neurotransmitter release from inhibitory neurons, spastic paralysis

Secretion systems (facilate the secretion of toxins from inside bacteria cell to outside)

Bacterial secretion systems are **protein complexes present on the cell membranes** of bacteria **for secretion of substances**. Specifically, they are the cellular devices used by **pathogenic bacteria** to **secrete their virulence** (as toxins) **factors** (mainly of proteins) to invade the host cells. They can be classified into different types based on their specific structure, composition and activity.

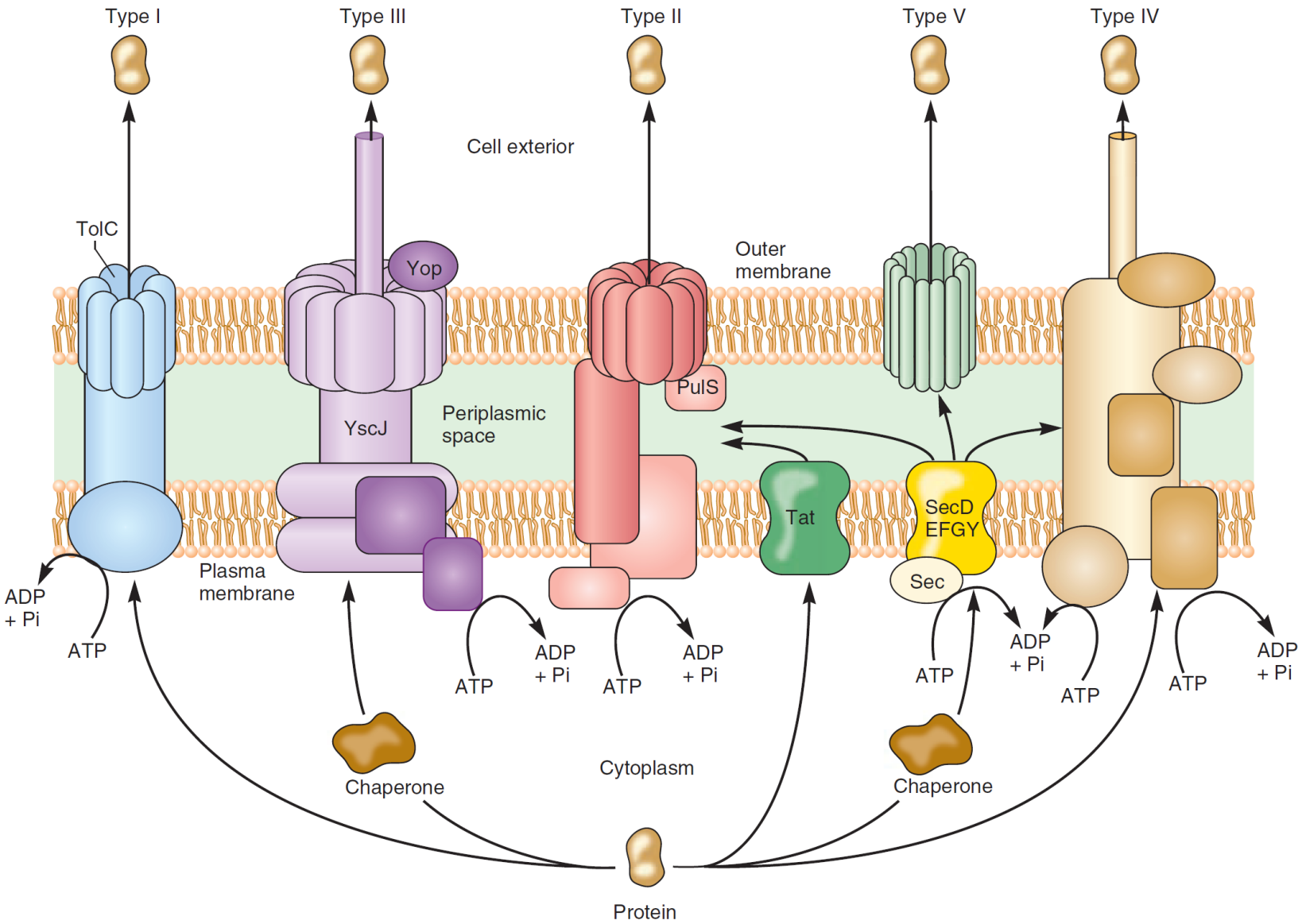
3

Type III secretion pathway is a contact-dependent system. It is activated by contact with a host cell, and then injects a toxin protein into the host cell directly.

1, 4

The type **I and IV secretion systems** have been described in both gram-negative and gram-positive bacteria, but the type **II, III, V, and VI secretion systems have been found only in gram-negative bacteria**.

2, 3, 5, 6


Type I
Type III
Type II
Type V
Type IV
Cell exterior
TolC
Yop
Outer membrane
PulS
YscJ
Periplasmic space
Tat
SecD EFGY
Sec
Plasma membrane
ADP + Pi
ATP
ATP
ADP + Pi
ATP
ADP + Pi
ATP
ADP + Pi
ATP
ADP + Pi
ATP
ADP + Pi
Chaperone
Cytoplasm
Chaperone
Protein

Secretion systems

no need to memorize them

Secretion System	Genus Species	Substrate and Role in Pathogenesis
Type 1 (*Sec*-independent)	*Escherichia coli*	α Hemolysin makes holes in cell membranes
	Proteus vulgaris	Hemolysin
	Morganella morganii	Hemolysin
	Bordetella pertussis	Adenylate cyclase which catalyzes synthesis of cAMP
	Pseudomonas aeruginosa	Alkaline protease
	Serratia marcescens	Zn protease yields host cell damage
Type 2 (*Sec* dependent)	*Pseudomonas aeruginosa*	Elastase, exotoxin A, phospholipase C, others
	Legionella pneumophila	Acid phosphatase, lipase, phospholipase, protease, RNAse
	Vibrio cholera	Cholera toxin
	Serratia marcescens	Hemolysin
Type 3 (*Sec*-independent; contact-dependent)	*Yersinia* species	Ysc-Yop system; toxins that block phagocytosis and induce apoptosis
	Pseudomonas aeruginosa	Cytotoxin
	Shigella species	Controls host cell signaling, invasion, and death
	Salmonella enterica subspecies *enterica* serotypes Choleraesuis, Dublin, Paratyphi, Typhi, Typhimurium, and so on	Effectors from *Salmonella* pathogenicity islands I and II (SPI1 and SPI2), which promote attachment to and invasion of host cells
	Escherichia coli	Enterohemorrhagic (EHEC) and enteropathogenic (EPEC); disruption of epithelial barriers and tight junctions
	Vibrio parahaemolyticus	Direct cytotoxicity

Toxins/ Endotoxins

Lipopolysaccharide

The **LPS** (endotoxin) of gram-negative bacteria are **bacterial cell wall components** that are often liberated when the bacteria lyse.

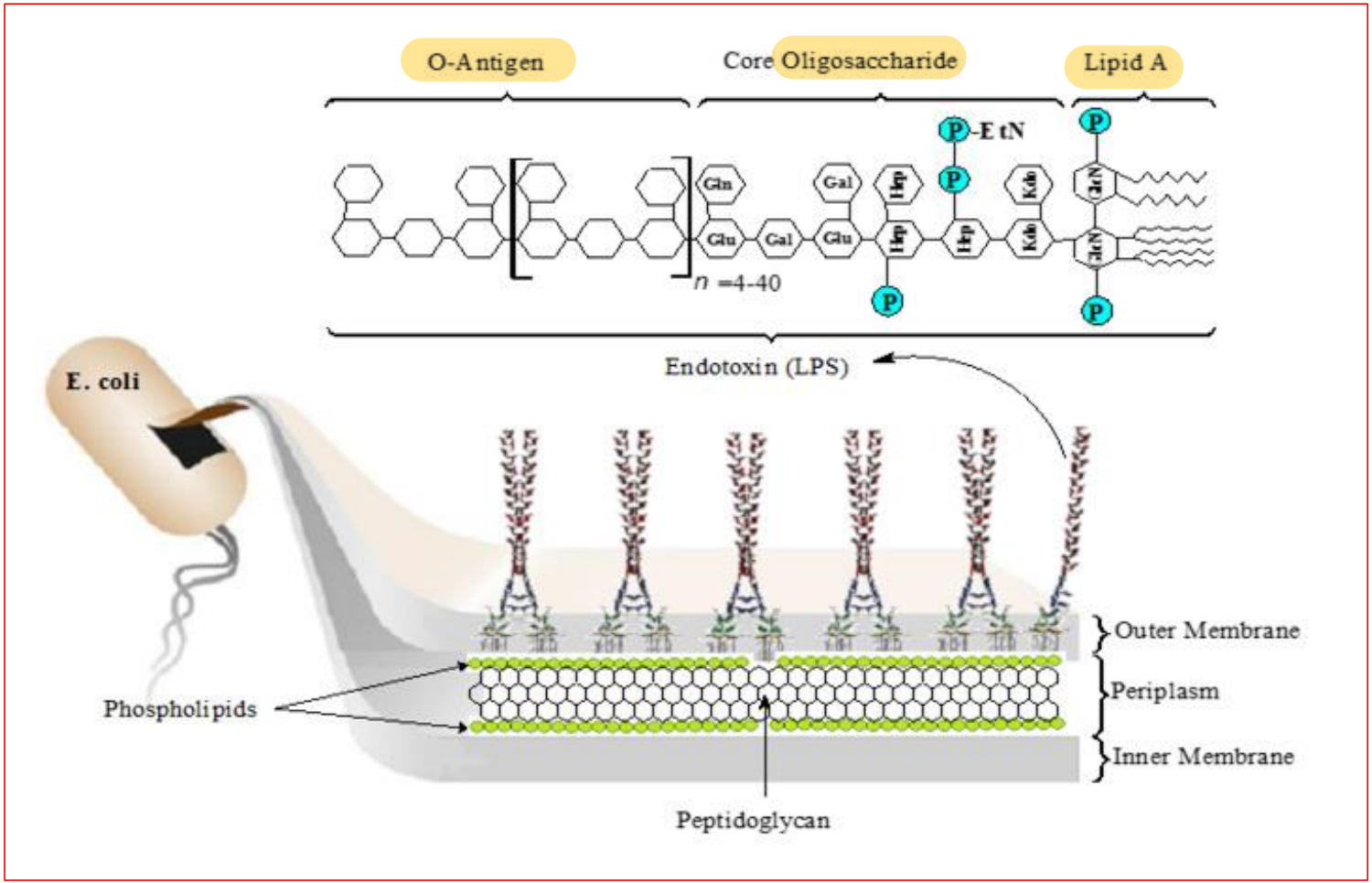
- exotoxin can be produced by gram +/- .

The substances are **heat-stable**.

In response to LPS**, proinflammatory cytokines** such as IL-1, TNF-α **are released**, and the **complement and coagulation cascades are activated**.

The following can be observed clinically or experimentally:
fever, leukopenia, and hypoglycemia; hypotension and shock resulting in impaired perfusion of essential organs (eg, brain, heart, kidney); intravascular coagulation; and death from massive organ dysfunction.

On the other hand **peptidoglycan** released from gram-positive bacteria can cause similar immune responses, but much **less potent than endotoxin** (LPS).


O-Antigen
Core Oligosaccharide
Lipid A
P-EtN
P
Gln
Glu
Gal
Glu
Gal
Hep
Hep
Hep
Kdo
Kdo
NP
NP
n =4-40
Endotoxin (LPS)
E. coli
Phospholipids
Outer Membrane
Periplasm
Inner Membrane
Peptidoglycan

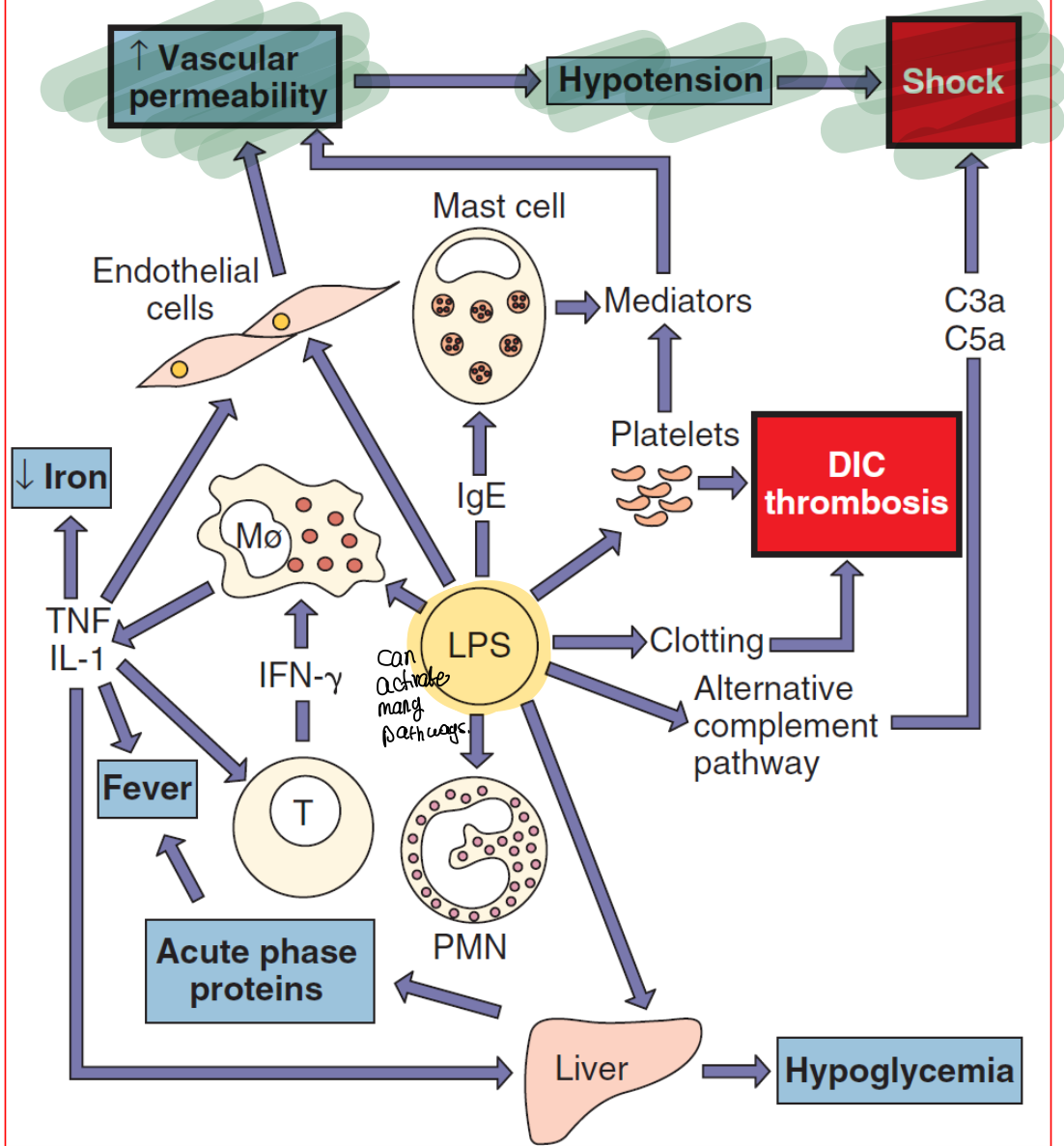

↑ Vascular permeability
Hypotension
Shock
Mast cell
Endothelial cells
Mediators
C3a
C5a
↓ Iron
Mø
IgE
Platelets
DIC thrombosis
TNF
IL-1
IFN-γ
LPS
Clotting
Alternative complement pathway
Fever
T
PMN
Acute phase proteins
Liver
Hypoglycemia

TABLE 9-4 Characteristics of Exotoxins and Endotoxins (Lipopolysaccharides)

Exotoxins	Endotoxins
Excreted by living cell; high concentrations in liquid medium	Integral part of the cell wall of gram-negative bacteria; released on bacterial death and in part during growth; may not need to be released to have biologic activity
Produced by both gram-positive and gram-negative bacteria	Found only in gram-negative bacteria
Polypeptides with a molecular weight of 10,000–900,000	Lipopolysaccharide complexes; lipid A portion probably responsible for toxicity
Relatively unstable; toxicity often destroyed rapidly by heating at temperatures above 60°C	Relatively stable; withstand heating at temperatures above 60°C for hours without loss of toxicity
Highly antigenic; stimulate formation of high-titer antitoxin; antitoxin neutralizes toxin	Weakly immunogenic; antibodies are antitoxic and protective; relationship between antibody titers and protection from disease is less clear than with exotoxins
Converted to antigenic, nontoxic toxoids by formalin, acid, heat, and so on; toxoids are used to immunize (eg, tetanus toxoid)	Not converted to toxoids
Highly toxic; fatal to animals in microgram quantities or less	Moderately toxic; fatal for animals in tens to hundreds of micrograms
Usually bind to specific receptors on cells	Specific receptors not found on cells
Usually do not produce fever in the host	Usually produce fever in the host by release of interleukin-1 and other mediators
Frequently controlled by extrachromosomal genes (eg, plasmids)	Synthesis directed by chromosomal genes

Iron uptake mechanisms

* we will talk about some pathogenic mechanisms :- (types of virulance factors)

bacteria can produce siderophores they can strip iron from iron carrier (ferrin).

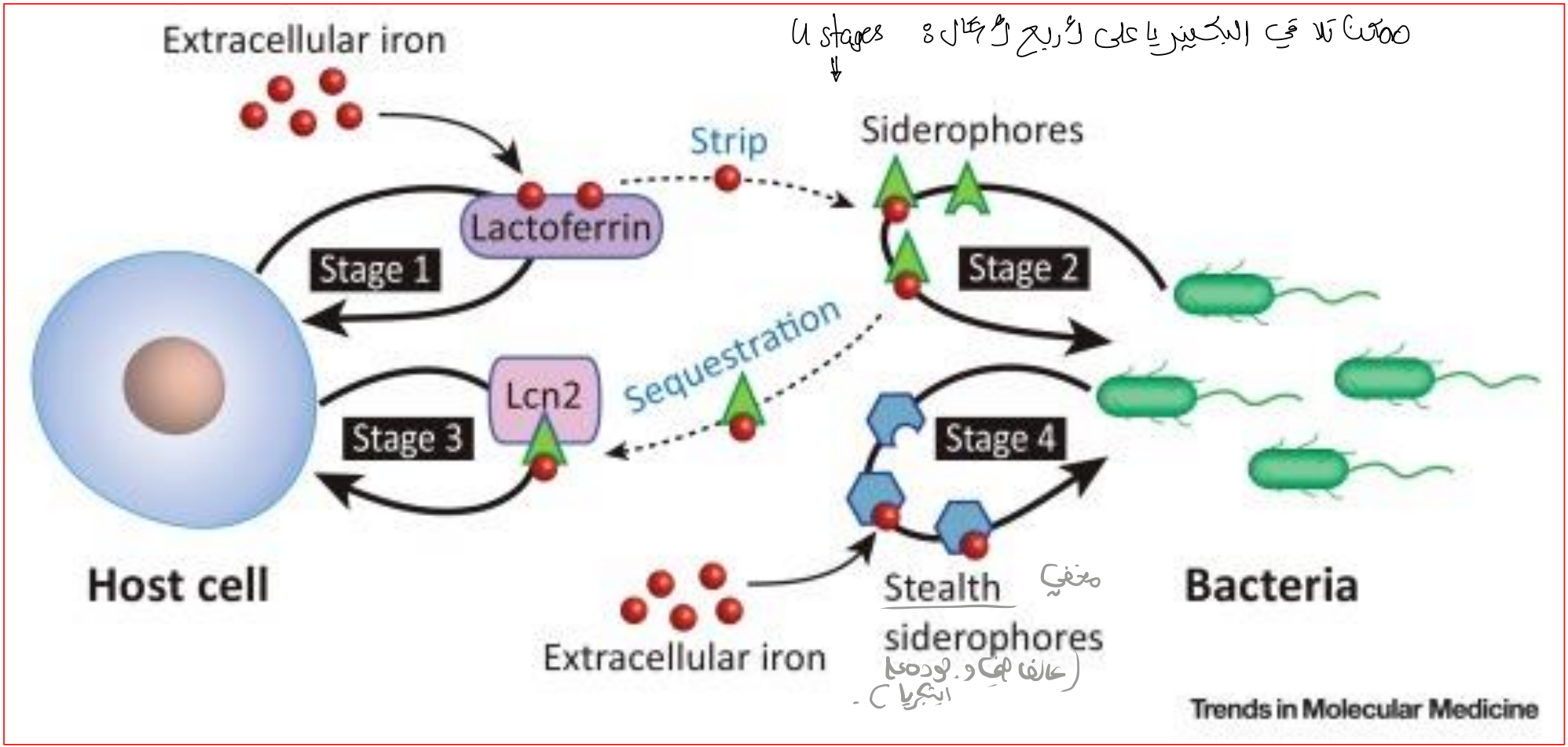
important for bacteria growth

- Most of the iron in a mammalian body is complexed with various proteins. Moreover, **in response to infection, iron availability is reduced** in both extracellular and intracellular compartments.

- **Bacteria need iron for growth** and successful bacterial pathogens have therefore evolved to compete successfully for iron in the highly iron-stressed environment of the host's tissues and body fluids, for example, through production of **siderophores**.

- **Siderophores** (Greek: "iron carrier") are small, high-affinity **iron-chelating compounds** secreted by microorganisms such as bacteria and fungi .

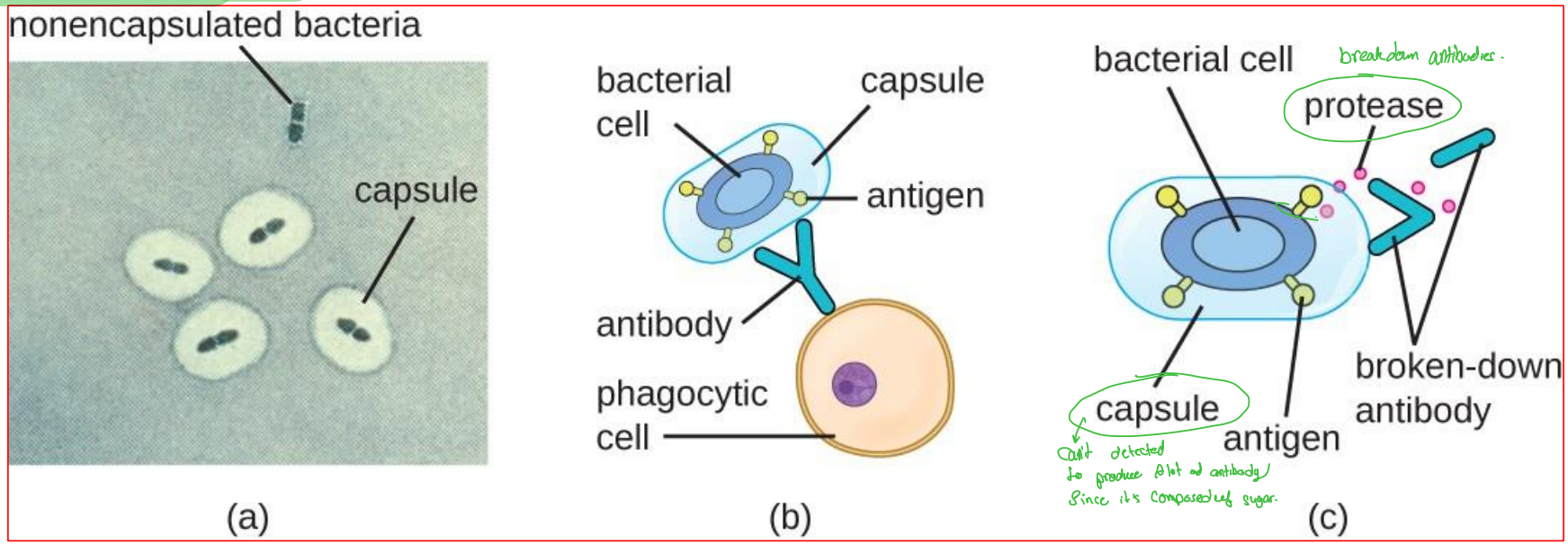
سبحان الله وبحمده سبحان الله العظيم


Extracellular iron
4 stages
Strip
Siderophores
Lactoferrin
Stage 1
Stage 2
Sequestration
Lcn2
Stage 3
Stage 4
Host cell
Bacteria
Stealth siderophores
Extracellular iron
Trends in Molecular Medicine

Evasion of the host immune system

different mechanisms for bacteria to overcome the immune system :- (How can theg escape from immung system).

Pathogenic bacteria can evade phagocytosis in many ways, examples include **capsule production**, **Protein A in Staph aurues binds antibodies in an inactive manner.** Some bacteria produce proteins that **inhibit complement activation,** therby decresing immune signaling and opsonization* of bacteria**.** Intracellulaly some bacteria **inhibit phagolysosome fusion.**



* **Opsonization** is the process in which bacteria is covered by substances to enhance phagocytosis. For example, antibodies bound on bacterial surface, as well as activated complement components depositing on bacterial surfaces are considered ”opsonins” since the make the bacteria easier to phagocytose.

Enzyme production

Pathogenic bacteria produce enzymes to degrade tissues and spread infection. E.g **Hyaluronidase and collagenase** are enzymes that hydrolyze hyaluronic acid and collagen respectively, constituents of the ground substance of connective tissue.

degrade the tissue

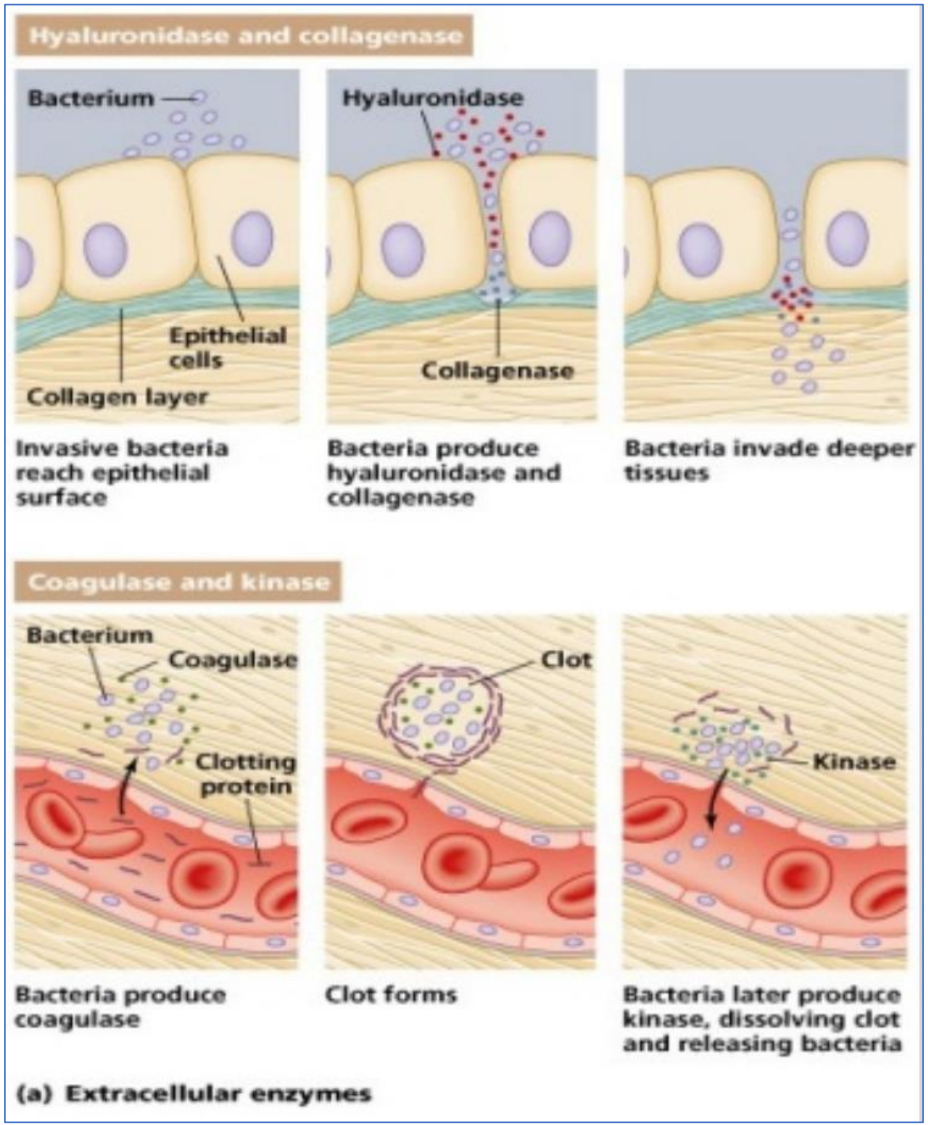
forming Clot so WBC can't exit the blood vessels.

Bacteria produce **cytolysins which directly kill cells** usually by forming pores in their membranes **(e.g. hemolysins, leukocidins)**.

directly kill the cell

kill RBC

kill WBC



اللهم منزل الكتاب ، مجري السحاب هازم الأحزاب ، اهزمهم واهزمهم وانصرنا عليهم

Pathogenicity islands

Chromosomal or extra chromosomal discrete genetic units that encode genes that aid in the virulence of a bacteria by coding for **adhesins, secretion systems (like type III secretion system), toxins, invasins, capsule synthesis, iron uptake systems** .

Absent in non-pathogenic bacteria. Virulence genes are **usually activated by environmental cues (e.g. Temperature change).**

Commonly found on mobile genetic elements **(passed through plasmids, transformation, transduction, transposons**), the **G-C content** of pathogenicity islands is usually different from the rest of the genome.

TABLE 9-2 Examples of Virulence Factors Encoded by Genes on Mobile Genetic Elements

Genus and Species	Virulence Factor and Disease
Plasmid encoded	
Escherichia coli	Heat-labile and heat-stable enterotoxins that cause diarrhea
Escherichia coli	Hemolysin (cytotoxin) of invasive disease and urinary tract infections
Escherichia coli and *Shigella* species	Adherence factors and gene products involved in mucosal invasion
Bacillus anthracis	Capsule essential for virulence (on one plasmid) Edema factor, lethal factor, and protective antigen are all essential for virulence (on other plasmids)
Phage encoded	
Clostridium botulinum	Botulinum toxin that causes paralysis
Corynebacterium diphtheriae	Diphtheria toxin that inhibits human protein synthesis
Vibrio cholerae	Cholera toxin that can cause a severe watery diarrhea

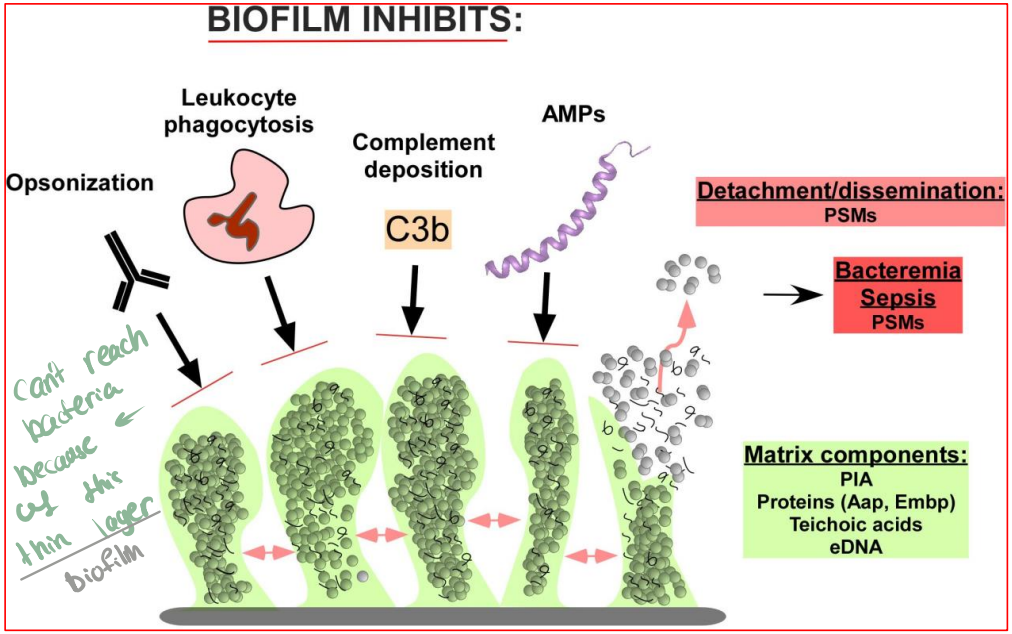
regions of bacterial genomes that carry genes responsible for the virulence (ability to cause disease) of the bacteria. These islands are often found on mobile genetic elements and can be transferred between bacteria through mechanisms such as plasmids, transformation, transduction, and transposons. Additionally, they typically have a different G-C content compared to the rest of the bacterial genome. G-C content refers to the percentage of nitrogenous bases in DNA that are guanine (G) and cytosine (C).

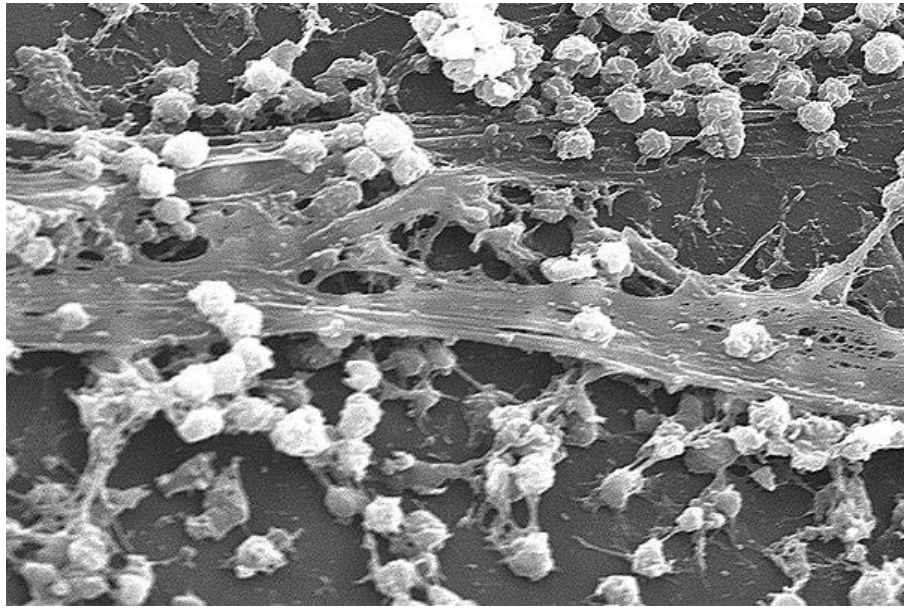
Bacterial communities / Biofilm and pathogenesis

Structure made of different macromolecules ← property for collective of bacteria, when bacteria found together will form Biofilm.

A biofilm is an aggregate of interactive bacteria attached to a solid surface or to each other and encased in **EPS**.
The cells within the biofilm produce the EPS (extracellular polymeric substances) components, which are typically a polymeric conglomeration of **extracellular polysaccharides, proteins, lipids and DNA**
Biofilms may form on living or **non-living surfaces** and can be prevalent in natural, industrial **and hospital settings**.
Helps in persistence on surfaces, evasion of the immune response and antimicrobial resistance and dissemination.

1. Prevent many immune mechanic to reach bacteria
2. protect bacterica from antibiotic.
3. helping in adhesion.



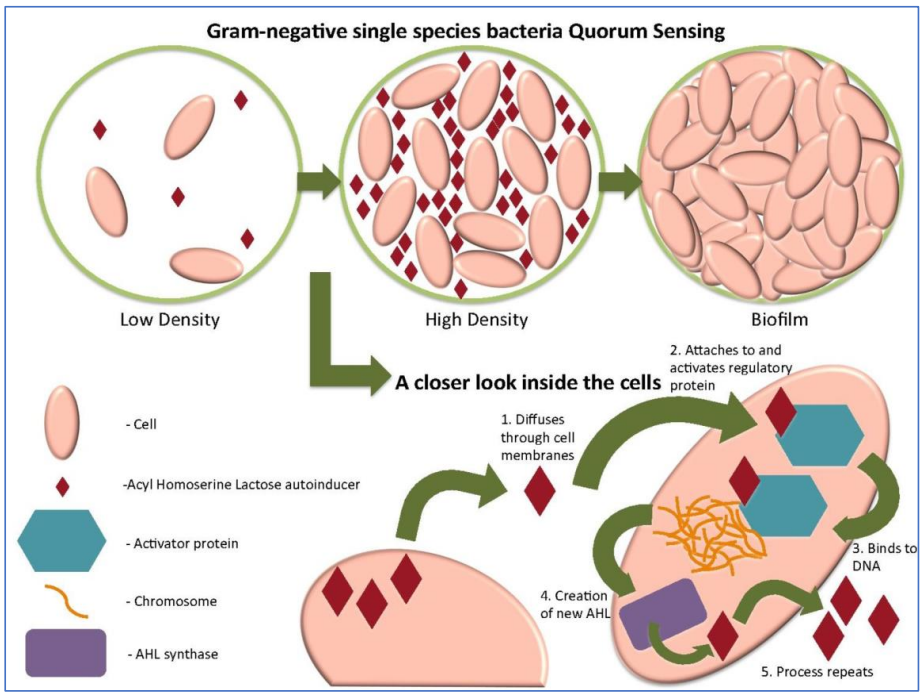


Bacterial communities / Quorum sensing and pathogenesis

property of bacteria ,

Quorum sensing is the regulation of gene expression in response to fluctuations in cell-population density. Quorum sensing bacteria produce and release chemical signal molecules called autoinducers that increase in concentration as a function of cell density

Quorum sensing allows bacteria to "sense" the population density through chemical signals called autoinducers. When the population reaches a critical density, the autoinducers activate gene expression that leads to coordinated behaviors like biofilm formation or toxin production. This system is crucial for bacterial survival and pathogenicity,



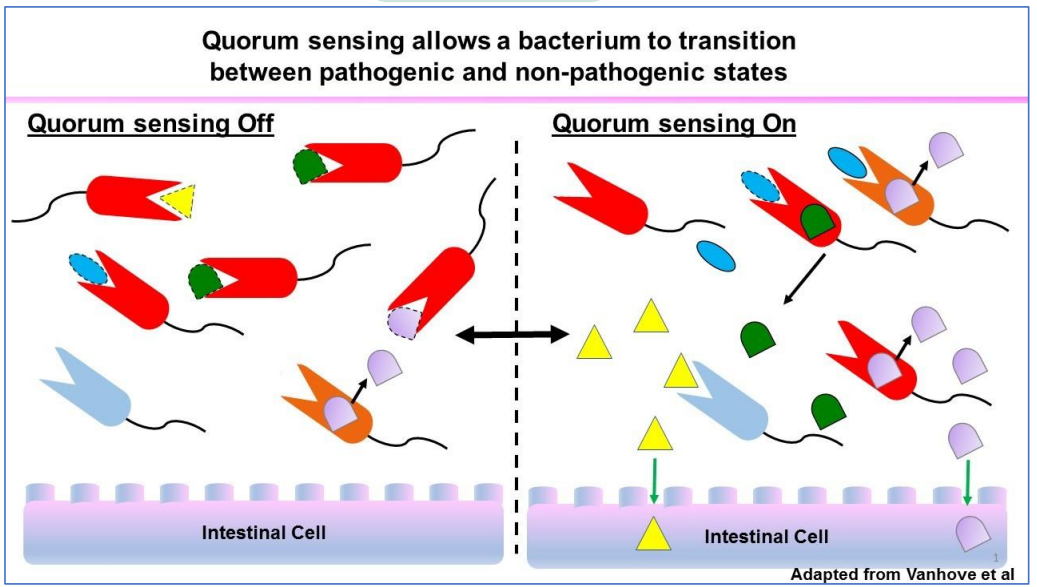


TABLE 9-1 Guidelines for Establishing the Causes of Infectious Diseases

Koch's Postulates	Molecular Koch's Postulates	Molecular Guidelines for Establishing Microbial Disease Causation
1. The microorganism should be found in all cases of the disease in question, and its distribution in the body should be in accordance with the lesions observed. 2. The microorganism should be grown in pure culture in vitro (or outside the body of the host) for several generations. 3. When such a pure culture is inoculated into susceptible animal species, the typical disease must result. 4. The microorganism must again be isolated from the lesions of such experimentally produced disease.	1. The phenotype or property under investigation should be significantly associated with pathogenic strains of a species and not with nonpathogenic strains. 2. Specific inactivation of the gene or genes associated with the suspected virulence trait should lead to a measurable decrease in pathogenicity or virulence. 3. Reversion or replacement of the mutated gene with the wild-type gene should lead to restoration of pathogenicity or virulence.	1. The nucleic acid sequence of a putative pathogen should be present in most cases of an infectious disease and preferentially in anatomic sites where pathology is evident. 2. The nucleic acid sequence of a putative pathogen should be absent from most healthy control participants. If the sequence is detected in healthy control participants, it should be present with a lower prevalence as compared with patients with disease and in lower copy numbers. 3. The copy number of a pathogen-associated nucleic acid sequence should decrease or become undetectable with resolution of the disease (eg, with effective treatment) and should increase with relapse or recurrence of disease. 4. The presence of a pathogen-associated nucleic acid sequence in healthy subjects should help predict the subsequent development of disease. 5. The nature of the pathogen inferred from analysis of its nucleic acid sequence should be consistent with the known biologic characteristics of closely related organisms and the nature of the disease. The significance of a detected microbial sequence is increased when microbial genotype predicts microbial morphology, pathology, clinical features of disease, and host response

Further reading and material:

- Jawetz, Melnick & Adelberg's Medical Microbiology, 26th edition-
  Section 3: Bacteriology
  Chapter 9: Pathogenesis of bacterial infections