Pathogenesis

Part 2

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Organism/Host interaction

II. Antiphagocytic factors

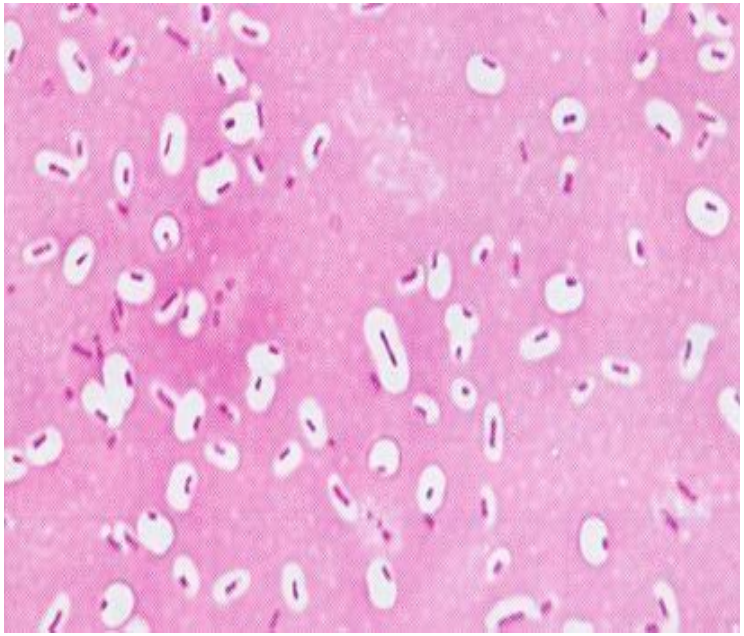
depends on the presence of capsules or slippery slime layer which has the same function as capsule (evading of the immune systems)

1. Evading phagocytosis

Its a strategy of evade: escape from immune cells (mask the receptor so it cannot be identified by immune cells)

- Slippery surface of the capsule is the primary defense mechanism against phagocytosis

- Capsules are highly antigenic
- most of capsules are (exopolysaccharide) and some capsules are (polypeptide) the only difference between them is antigenicity both of them have the same function
- Capsules are highly antigenic



K. pneumoniae

capsulated bacteria are pathogenic (more virulent)
the non capsulated is non pathogenic
EX: streptococcus pneumonia is capsulated bacteria if we remove the capsule (detachment of the capsule) the organism will be converted to non pathogenic

- Prevent phagocytosis
- attachment
- Nutrition

- *Streptococcus pneumoniae*
- *Klebsiella pneumoniae*
- *Haemophilus influenzae*
- *Bacillus anthracis*
- *Streptococcus mutans*

Organism/Host interaction

- Organisms with capsule: S. pneumoniae, K. pneumoniae, H. influenze, P. aeruginosae

for haemophilus influenzae the capsule is the sole virulence factor

2. Avoiding phagocytosis

- Inhibition of phagocyte recruitment: organisms may excrete compounds which interfere with neutrophile motility and chemotaxis e.g: B. pertussis (the causative agent of wooping cough) produces a toxin which paralysis neutrophile
- Its face to face contact of the pathogen and immune system
- different strategies :
- 1)interfering with motility of immune cells : some bacteria secrete chemical material to prevent phagocyte from following the pathogen (causes paralysis).

Organism/Host interaction

- Destruction of phagocyte: some organisms produce toxins which specifically destroy white blood cells, these toxins called leukocidin and produced by *P. aeruginosae* and *S. aureus*

2)bacteria can produce chemicals structures which can kill the immune cells.
#(leukocidin) direct killing of the WBCs.

3. Survivng phagocytosis (the most dangerous pathogens)

- Some organisms do not avoid ingestion by the phagocyte, but they are able to avoid destruction inside these cells

Organism/Host interaction

- The organism may escape from the phagosome and survive in the cell cytoplasm e.g Rickettsia spp.
- The organism may survive in the phagosome by avoiding the killing mechanisms of the phagocyte e.g: Y. pestis, B. abortus
- The organism may excrete toxins which inhibit the fusion of the phagosome and lysozyme, thereby surviving in the phagocyte

- some bacteria can survive inside the phagocyte (the most dangerous pathogene) they have ability to live in the macrophage HOW?
- 1) avoid the killing machinery in the phagocyte of the macrophage EX: Rickettsia
- 2) bacteria that survive inside the phagosome itself.
-
- # the killing machinery in the macrophage includes :
- fusion of (phagosome + lysosome = phagolysosome)
- non fusion : no killing , bacteria prevent the fusion

Organism/Host interaction

Benefits of surviving phagocytosis

1. Survival and multiply of the organism inside the cell for months

2. Transport to other sites

   some intracellular pathogens can use the macrophage as a vehicle then it goes to specific sites & establish an infection .

3. Avoid specific immune response of the host

   Stealth pathogens : pathogens that are not recognized by the immune system

Organism/Host interaction

III. Toxins

- endotoxin : built in the structure of the bacterial cell
- exotoxin : secreted by pathogen

A. Endotoxins: The lipopolysaccharide endotoxins on Gram-negative bacteria cause:

- fever
- changes in blood pressure low blood pressure
- inflammation, lethal shock, clotting
- and many other toxic events.

Lipopolysaccharide is composed of three components

1. O polysaccharide side chain
2. Core polysaccharide
3. Lipid A: is a part of Gram negative cell membrane, and so all Gram negative bacteria have endotoxin, the endotoxin released when the bacterial cell die.

Lipid A is lethal , chemical, and stable
the most toxicity is caused by these organisms
the majority of these organisms are G- Negative (and some exceptional G positive)
all of the G negative have endotoxin lipopolysaccharide WHY?
lipopolysaccharide is structural part of G-Negative bacteria , how ever G-Positive don't have liposaccharide it has teichoic acid ,polyteichoic acid , and other structures.

Organism/Host interaction

- The effect of endotoxin when it is in an internal site (the blood stream) (Must enter the circulatory system)
- Endotoxin is heat stable . (This is the most important characteristic of lipid A (It can not be denatured)
- Endotoxin cannot be converted to toxoids (vaccines)
- (Toxoid is the conversion of toxic material to toxoid by neutralization or detoxication using heat) (we can not use endotoxin as vaccine)
- Do not produce antitoxic antibodies.(For any material that enters our body, the immune system produces antibodies against it, but endotoxin has no antibody (virulence).
- Induce non-specific reactions in the host such as fever, increased white cells, and vascular permeability.(Endotoxin are not specific for certain structure whereas exotoxins are very specific.)
- Pyrogen free solution: free of endotoxin

- From the previous slide :
- Pyrogen is any chemical that can elevate body temperature (causes fever).
- In order to use a solutions as a vaccine we should ensure that this solution is Pyrogen free solution (safe to be used as a vaccine).
- When you read toxin- like or (endotoxin - like) this indicates that this substance is similar to endotoxin. Ex: Shiga like toxin, is a toxin that is similar to the endotoxin produced by shiglla, but the effect of shiga like toxin is milder than the original toxin. (difference in severity)

Organism/Host interaction

The physical effect of endotoxins

1. Fever: results from the induction of the synthesis of prostaglandin which have direct effect on the fever center of the brain

prostaglandin change the setting of fever center in the brain (hypothalamus) .
Fever is one of the signs & symptoms of bacterial infection , not all bacteria elevate body temperature to the same level.

some bacteria are pyrogenic which elevates body temperature to the max could reach 40–41 C
other bacteria (which has no endotoxins) elevates body temperature to 38.5 – 39 C

Organism/Host interaction

2. Hypotension: results from increasing vascular permeability which leads to shock and consequently to death

   hypotension is more dangerous than hypertension it may lead to shock

3. Dessiminated intravascular coagulation: endotoxin may induce the clotting mechanism and result in clot formation in many of the small vessels leading to local necrosis and tissue damage

   many clots in different small blood vessel causes closure of blood vessel leading to necrosis

From the previous slide :
Bacteria infect inside bloom steam (sepsis), sepsis is related to higher mortality rate (not less than 50%).
The effect of endotoxins is when it is in blood stream and when the bacteria is destroyed, because lipid A is a built in endotoxin (part of the structure of bacteria).
As long as the bacteria is alive, the endotoxin has no effect, but when the bacteria is destroyed (died) it releases lipid A to blood stream and exert its effect. So when you give IV antibiotic, you kill bacteria then lipid A is released to the blood it becomes activated and exert the effect (fever, hypotension, clotting,... etc).
(sepsis) يعني خياراتك محدوده وما بتقدر تعمل اشي في حاله #
It depens on health state , the amount & content of toxin , virulence factor of the organism)

Endotoxin effect depends on its concentration, so there is a minimum amount which is similar to "infection dose" to exert the effect.
Treatment of sepsis is very difficult . You can only give an antibiotic and it will kill the organism ⟶ release of Lipid A ⟶ active the pathogenesis

The best choice is to prevent reaching sepsis stage, يعني انه نسيطر على البكتيريا قبل ما تدخل على الدم

Organism/Host interaction

dealing with a protein is much easier than lipopolysaccharide we can denaturate the protein by (temperature, acidity , salt)

B. Exotoxins

- Excreted proteins have specific targets and actions, some of these toxins may cause sever tissue damage and may represent the sole virulence factor of an organism (Cholera, Diphtheria, Tetanus).
- could be sole causative agent of diseases or it could be a co-Factor
- Other exotoxins are part of the virulence factors e.g:
  S. aureus (hemolysin, lekocidin, nuclease)
  these exoenzymes or exotoxin are co-factor of infectious disease not the main cause causative agent

Organism/Host interaction

General properties of exotoxins

1. Protein: can be easily destroyed by heat and denaturing compounds

   any small amount of exotoxin can exert the effect

   lipopolysaccharide may have minimum concentration to exert the effect

2. Exotoxins act as an enzymes and therefore very small amounts required to exert major effects
3. Specific action: exotoxins are very specific in their targets and their mechanism of action

each protein (Exotoxin) has a specific substance so it will exert the effect on specific component of the bacterial cell .

Organism/Host interaction

4. Converted to toxoids: exotoxins can be chemically modified so that they are no longer toxic but retain their antigenecity, these toxoids are used as vaccines (diphtheria, tetanus)

5. Stimulate antitoxin antibody production: exotoxins are potent stimulators of protective antitoxin antibody

Organism/Host interaction

Mechanisms of action

1. Cytolytic (cell lysis): hydrolyze membrane phospholipids or cholesterol e.g., phosphlipase C toxin of Clostridium perfringes (gas gangrene)

(this enzyme causes diffusion to live tissue , it kills the live tissue then the bacteria follow the enzyme)

1. Inhibit intracellular metabolic functions: affect the adenylate cyclase enzyme system which leads to altered levels of cAMP and therefore altered ion transport (enterotoxins in gastrointestinal tract leading to watery diarrhea e.g., V.cholera, E.coli)

Organism/Host interaction

3.Neurotoxic: blocks the neurotransmitters at myoneural junction leading to paralysis (C. botulinum, C.tetani)

Neurotoxic exotoxins that blocks neurotransmitters either by convolution or paralysis or (flaccid paralysis).

C.tetani patient with convulsion (rigid body) blocked neurotransmitter at contraction state .

C.Botulinum: causes flaccid paralysis prevent the transport block neurotransmitters when the patient is in the relaxation state.

Now we have vaccine for C.tetani (except for countries which don't have the national program of vaccination or those who still work in field)

C.Tetani is common soil bacterium.

3. Toxic to specific tissue components

Specific target (mitochondria or plasma membrane)

Organism/Host interaction

IV. Exoenzymes

hyaluronic acid is the cement material that link cells to each other .
And its Maintains the shape of the cells & signals between cells

- Hyaluronidase: breaks hyaluronic acid (the tissue component which cements cells together), destruction of hyaluronic acid aids in the spread of infection (S. aureus, C. perfringes, S. pyogenes
- Deoxyribinucease: hydrolyze nucleic acids (S.aureus, S. pyogenes)
- Lecithinase: hydrolyze membrane lipids

- Collagenase: hydrolyzes collagen, the primary connective tissue fiber, therefore promoting spread of bacteria (C. perfringes)

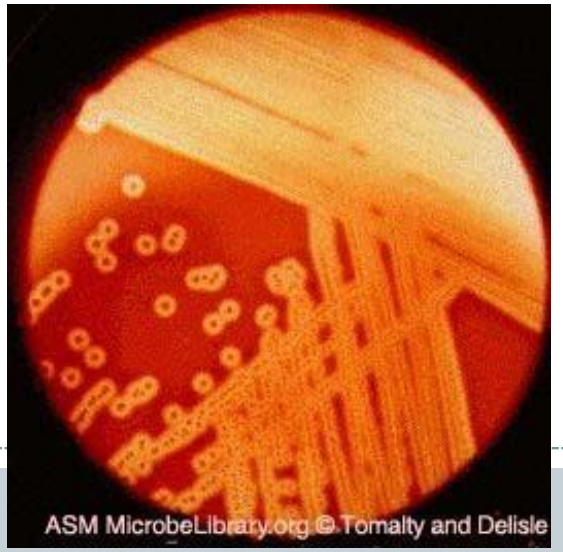
- Leukocidin: destroys leukocytes, thereby destroying the first line of host defense (S. aureus)

- Haemolysin: cause damage to host RBCs

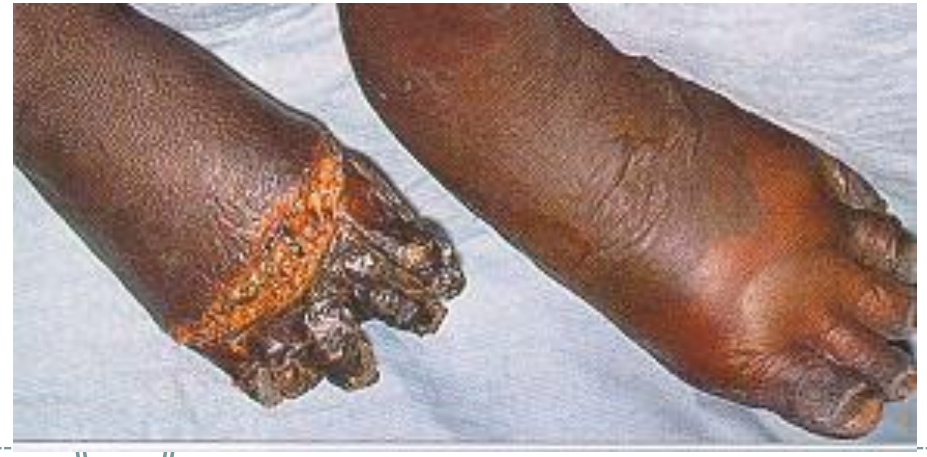
- Kinases: lyse the clots, so the organism can dissolve the clots and escape from the clots

Kinases : important in medicine (dissolves clots) , we have 2 types of kinases

1) Streptokinase : produce by streptococcus
2) Staphylokinase : produce by staphylococcus

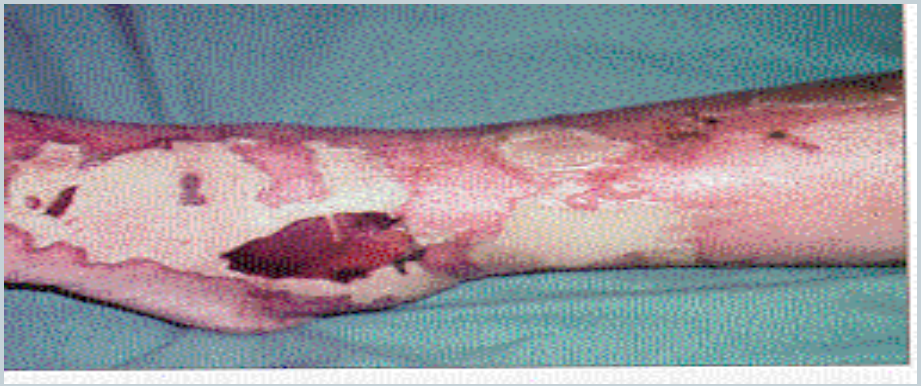


Complete Lysis of RBC



Tissue Damage Caused by Microbial Enzymes of *Clostridium perfringens*

Gas gangrene ممكن تبدأ من اي مكان مش شرط الاصابع



“Flesh Eating Bacteria”

Necrotizing fasciitis

آكلة لحوم البشر

invade muscles

Cellulitis : it’s a very simple bacteria (streptococcus group A, which cause tonelitis & other strains of this bacteria cause (flesh eating bateria

Organism/Host interaction

Virulence factors help bacteria to

1. Invade the host

2. Cause disease

3. Evade host defenses

Mechanisms by Which Pathogens Escape Immune Responses

1. Antigenic Variation

Some pathogens are able to periodically change their surface antigens, a phenomenon known as **antigenic variation**

2. Camouflage and Molecular Mimicry

Some organisms are able to conceal their foreign nature by coating themselves with host proteins—a sort of camouflage.

In molecular mimicry, pathogens cover their surface antigens with host proteins, so the pathogens will not be recognized as being foreign.

3. Destruction of Antibodies

N. gonorrhoeae, and *streptococci,* produce an enzyme (IgA protease) that destroys IgA antibodies.

Several bacterial pathogens, including *H. influenzae,*

- phagocyteS have a specific marks (Opsinins) if it doesn't find this marks it assumes that as false notification this happens as a result of antigenic variation.

or

- the other method: they cover their own antigens with proteins of the host cell, this is what we call (camouflage)

-the last strategy is distrcution of antibodies some cells secrete enzymes especially in fluids, it secrete immunoglobulin IGAs present fluid

- when bacterial cell come IGAs destroys immunoglobulin a the organism become more virulent

Epidemiology

DR. WALEED AL MOMANI, MLT, PHD

Epidemiology:

useful to know the source of infection as well as enables following up of infection.

Is the study of the determinants, occurrence, and distribution of disease in a defined population and the application of this study to control of health problems

-the important of epidemiology is to control and follow up the infection .
-there are many diseases that have unknown source .
-molecular epidemiology is used to determine the source of disease and describe it as endemic and exotic .
-molecular epidemiology is useful to study genetic diversity and similarity between organism endemic & exotic organism.

Uses of Epidemiology to:

- Determine, describe, and report on the natural course of disease, disability, injury, and death
- Aid in the planning and development of health services and programs
- Provide administrative and planning data

- Study the cause (or etiology) of disease(s), or conditions, disorders, disabilities, etc.

- Determine the primary agent responsible or ascertain causative factors

- Determine the characteristics of the agent or causative factors

- Determine the mode of transmission
- Determine contributing factors
- Identify and determine geographic patterns
- Provide a basis for developing disease control and prevention measures for groups at risk

Definitions

-when the organism is released to environment it's becomes much easier for transmission
-the organism must enter the host cell and multiple (infection)

- Infection: is the replication of organisms in host tissue, which may cause disease.

- Dissemination: is the spread of the organism in the environment.

-inflammation could be without organisms ex: physical inflammation
-inflammation could develop to become infection if it involve orgasms infection is an inflammation ex: swelling, hotness, tenderness
كل الاعراض الي موجوده في الالتهاب توجد في العدوى ولكن
inflammation is not infection

Definitions

- Reservoir: the reservoir is any site where the pathogen can survive and multiply until it is transferred to a host

Reservoir any site is described as survival place for the microorganism until there is a portal of entry & portal of exit from reservoir itself and portal of entry to the susceptible

- Source: the immediate location from which the infecting organism has been transmitted

ex: bacteria in shawarma majority of infection is caused by salmonella
salmonella lives in chicken and eggs, chicken is receiver the source is the sandwich

- Carrier: hosts that harbour a pathogen without clinical symptoms and transmit the infection

- Vector: a biological source that aids in the transmission of infection from one host to another

-transmit the microorganism from the reservoir to susceptible host vector cutting be biological or mechanical
1) live (mosquito which transmit malaria)
2) physical mechanism
3) Biological rat has bacteria , it bite a susceptible host and transmit this bacteria

- Zoonosis: an infection where the disease is transmissible from vertebrate animals to human

one-way disease transmitted from animal to Human

- Incidence: the number of new cases of a disease in a defined population over a specific period
- the incidence of malaria: the new cause registered in a specific area within a specific time

- Prevalence: the number of cases of the disease existing in a given population during a specific period

- Mortality: the ratio of the number of people who died of a particular disease during a specified period per a specified population

- Contagious: if the agent is highly transmissible it is said to be contagious

the fast transmission of a disease the most dangerous microorganism are contagious.
Ex: conjunctivitis التهاب العين highly contagious must be isolated

- Sporadic: occasional occurrence (few cases randomly distributed geographically)

when there is sharp increase of endemic it becomes epidemic
this becomes epidemic = في 2019 سجلت 20000 حاله من الملاريا

- Endemic: regular, continuing occurrence (a constant number of cases in one geographic area)

ex: malaria is endemic in africa
دائما نسبه الملاريا ثابته في افريقيا كل سنه 10000 حاله

- Epidemic: significantly increased occurrence (if the incidence of disease is greater than expected or greater than normal sporadic or endemic disease)

- Pandemic: epidemic occurrence in multiple countries (the incidence of a disease is spread across continents)

pandemic :occurs in multiple countries (Asia ,Europe , Africa)
Epidemic : occurs in specific area geographical area
ex: AIDS is a pandemic disease (HV virus)
- zika virus is pandemic , its originated from Africa and transmitted to other countries.