Case 2: Bacterial Pathogenesis

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PATH-417

21-year-old Naser G. recently hooked up with a new sexual partner. This morning he noticed a burning pain in his penis during urination followed by a greenish discharge. He immediately goes to the student health clinic. The clinic doctor asks Naser about his recent sexual history and he recounts how he had unprotected sexual intercourse with a new partner about one week ago. The new partner claimed that she did not have any sexually transmitted infections. The doctor asks Naser to provide a urine sample to send to the Microbiology Laboratory. The doctor prescribes antibiotics for him and counsels him on safe sex practices and on the importance of encouraging his new partner to come in for testing too.

Introduction

The patient had unprotected intercourse with a new partner approximately a week before the symptoms began to manifest. Meanwhile, his partner was asymptomatic prior to and after the intercourse. Based on this, it is most likely that he has gonorrhea, caused by *Neisseria gonorrhoeae*, or chlamydia, caused by Chlamydia trachomatis.

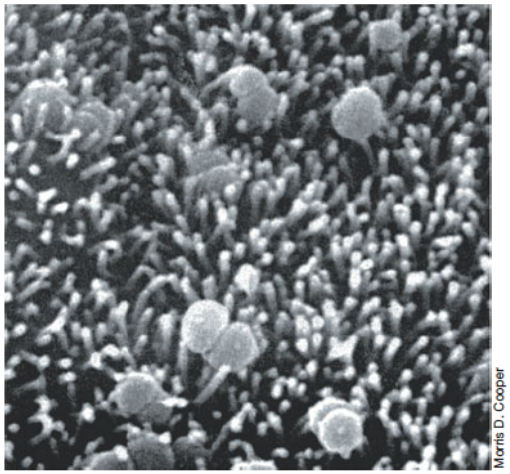
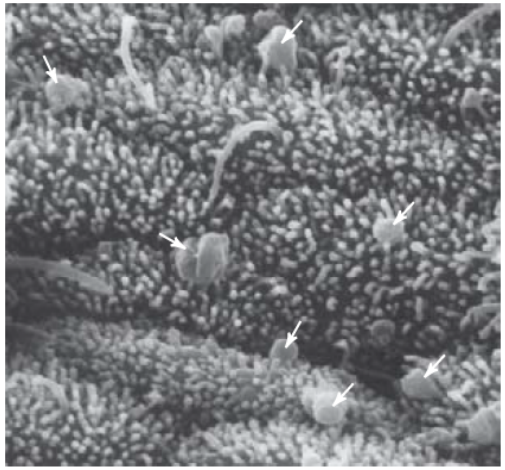
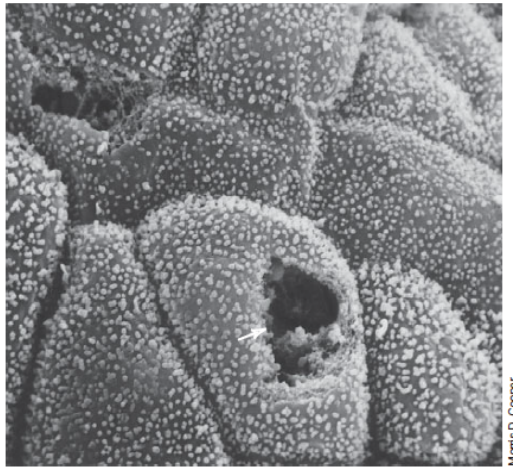


Figure 33.29 **The causative agent of gonorrhea, *Neisseria gonorrhoeae*.** The scanning electron micrograph of the microvilli of human fallopian tube mucosa shows how cells of *N. gonorrhoeae* attach to the surface of epithelial cells. Note the distinct diplococcus morphology. Cells of *N. gonorrhoeae* are about 0.8 μm in diameter.



(a)



(b)

Figure 33.32 **Cells of *Chlamydia trachomatis* (arrows) attached to human fallopian tube tissues.** *(a)* Cells attached to the microvilli of a fallopian tube. *(b)* A damaged fallopian tube containing a cell of *C. trachomatis* (arrow) in the lesion.

Infection summary

Gonorrhea

- Sexually transmitted infection (STI)
- In females:
  - 50% chance of becoming infected after 1 sexual intercourse with an infected man
  - Likely asymptomatic
  - May have vaginal discharge
  - If left untreated, may cause pelvic inflammatory disease (PID), chronic pelvic pain and infertility
- In males:
  - 20% chance of becoming infected after 1 sexual intercourse with an infected woman
  - Symptoms develop 2-7 days after infection
  - Symptoms are urethral discharge and pain on passing urine
- Caused by *Neisseria gonorrhoeae*

Chlamydia

- Sexually transmitted infection (STI)
- Serotypes D-K cause STI's
- In females:
  - Commonly asymptomatic
  - Symptoms include urethritis, cervicitis, bertholinitis, salpingitis, and conjunctivitis
- In males:
  - Symptoms include urethritis, epididymitis, proctitis and conjunctivitis
- Symptoms develop from 1 to 3 weeks after infection
- Caused by *Chlamydia trachomatis*

Encounter

Gonorrhea

- One of the most prevalent STIs in the world
- Approximately 26 million cases reported worldwide in 2012
- Estimated 78 million cases worldwide in 2012

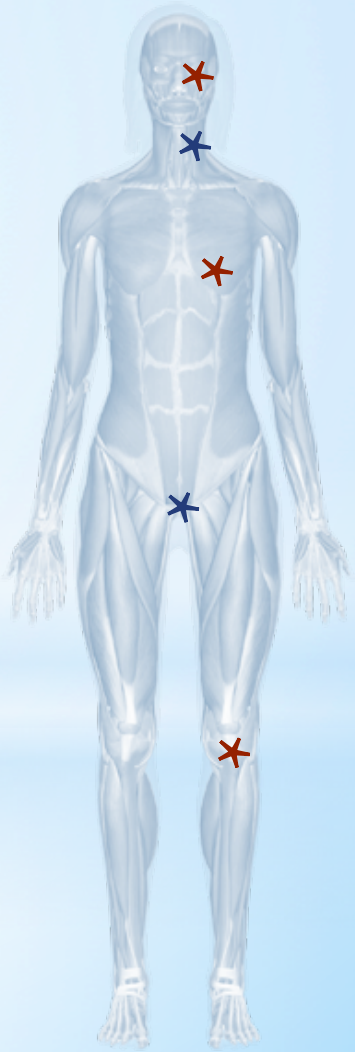
Chlamydia

- Most prevalent STI in the world
- Approximately 128 million cases reported worldwide in 2012
- Estimated 131 million cases worldwide in 2012

Encounter

Neisseria gonorrhoeae

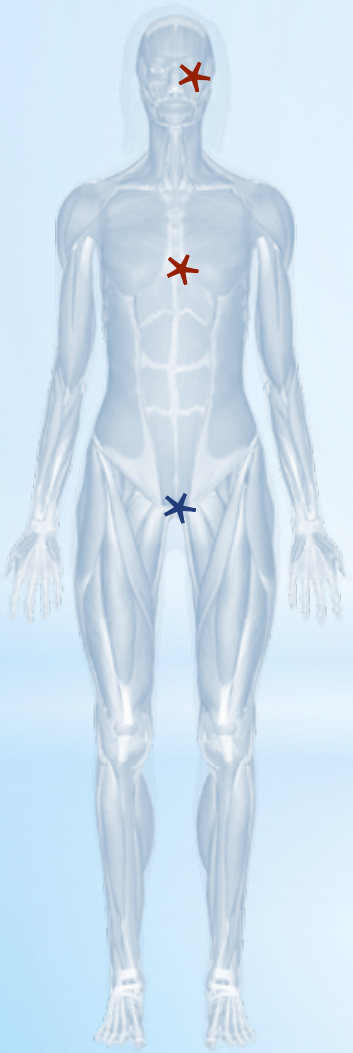
- Commonly found as commensals on mucosal surfaces of animals and humans [1]
  - Nasopharynx
  - Genital epithelium
  - Rectal mucosa [3]
- If left untreated, it can cause damage to heart valves and joint tissues [2]
- May also cause ophthalmia neonatorum in newborns via transmission from mother during birth



Favourite microbiological environments

- Very sensitive to drying, sunlight, UV light, and generally doesn't survive away from host [2]
- Non-sporulating
- Transmission is via direct contact
  - Intercourse
  - Vaginal birth
- Adheres to non-ciliated epithelial cells

Encounter



Chlamydia trachomatis

- Not part of the human normal microbiota
- Obligate intracellular pathogen in humans
- If left untreated, it can cause pelvic inflammatory disease in women
- May cause conjunctivitis and blindness
- In newborns, it may cause pneumonia

Favourite microbiological environments

- Adhere to columnar and transitional epithelial cells
- Transmission via direct contact:
  - Intercourse
  - Vaginal birth

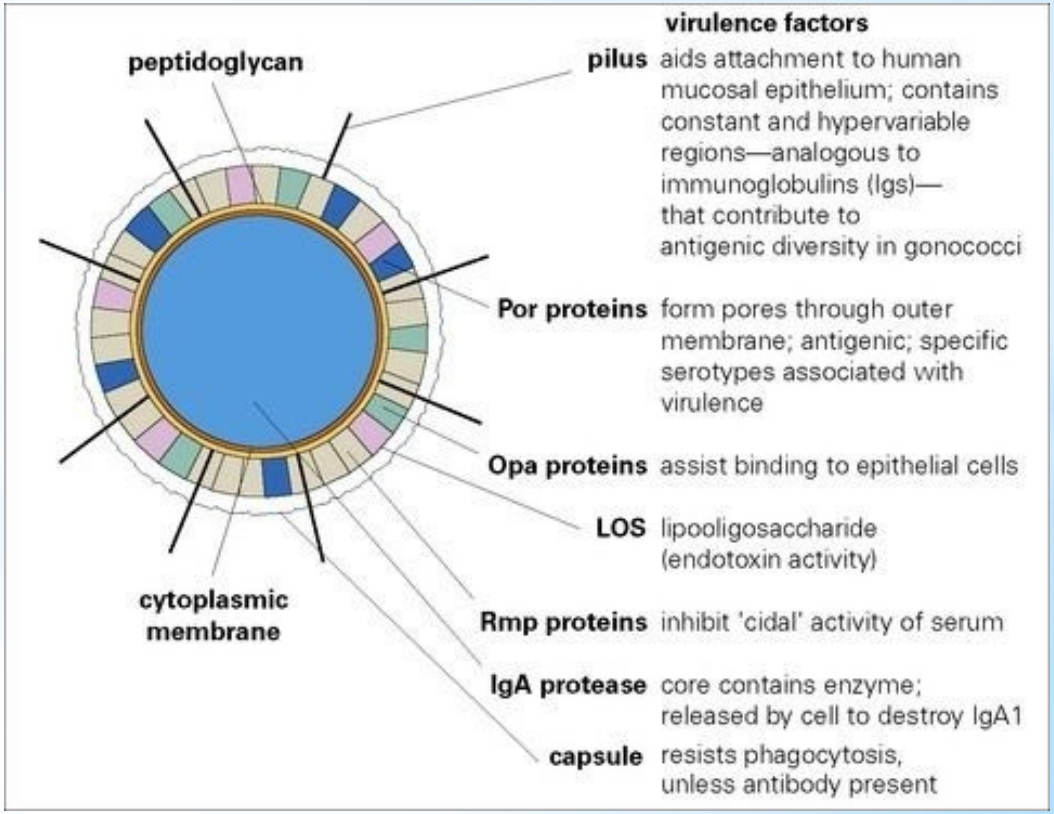
Entry into host cells~ *Neisseria gonorrhoeae*

Bacterial structure and overview

- Gram negative, diplococci
- Enters via vagina or urethral mucosa of the penis
- May also be deposited in the throat or on the rectal mucosa
- Adhere and invade non-ciliated epithelial cells

Bacterial structures aiding in entry

1. Pilus
2. Opa proteins
3. Por proteins



Entry into host cells~ *Neisseria gonorrhoeae*

1. Pilus

- Has a highly variable structure (antigenic variation)
- Pilin locus consists of 1 or 2 expressed genes at a time, and 10 to 20 silent genes
- Expressed pili are less likely to be detected by antibodies
- Type IV:
  - Used for twitching motility and adhesion
  - 6nm in diameter
  - Mediates genetic transfer (transformation)
- Twitching motility via pili allow gonococci to find a suitable location for adhesion

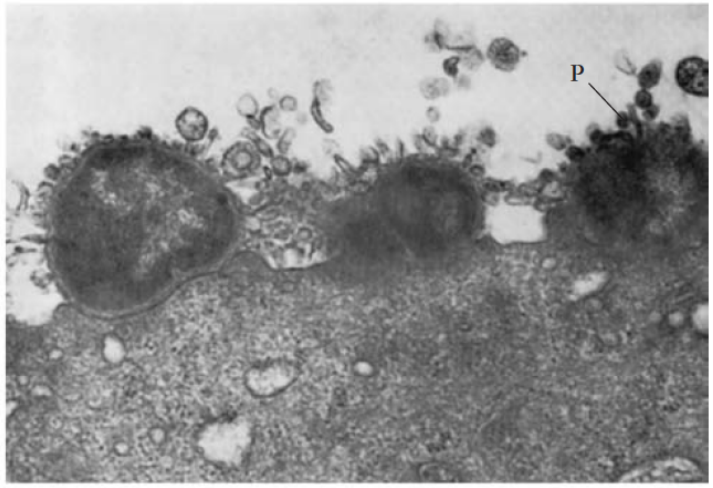


FIGURE 17-6 Electron micrograph of *Neisseria gonorrhoeae* attaching to urethral epithelial cells. Pili (P) extend from the gonococcal surface and mediate the attachment. *[Source: M. E. Ward and P. J. Watt, Adherence of* Neisseria gonorrhoeae *to urethral mucosal cells: an electron microscope study of human gonorrhea. 1972,*

Entry into host cells~ *Neisseria gonorrhoeae*

2. Opa proteins

- Opacity Associated protein
- Located on the surface of the bacteria
- Binds specifically to host protein CD66
  - CD66: found only on the surface of epithelial cells
- Allows bacteria to adhere to host cells
- Triggers cytoskeletal rearrangement and endocytosis

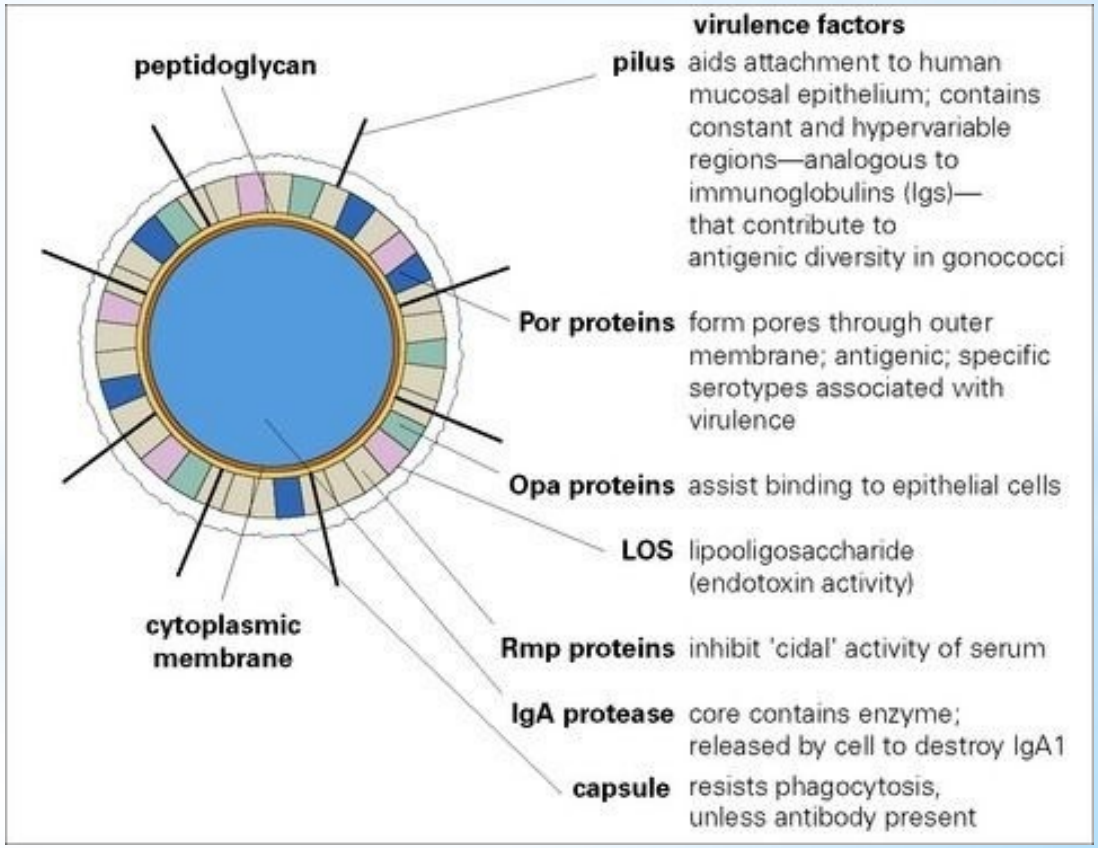
3. Por proteins

- Major porin protein “P.I”
- Invasin that mediates penetration of a host cell
- May prevent phagolysosome formation in neutrophils
- May reduce oxidative burst

Entry into host cells~ *Neisseria gonorrhoeae*

Bacterial structures aiding in evasion of host responses

1. IgA proteases
2. Rmp proteins
3. Lipooligosaccharide (LOS)
4. Capsule



Entry into host cells~ *Neisseria gonorrhoeae*

1. IgA Proteases

- Secreted enzyme that breaks down Immunoglobulin A dimers (IgA)
- Cleaves the heavy chain (non-variable) region of the antibody
- Recall, IgA:
  - Secreted by B-cells (part of the adaptive immune response)
  - Major isotype found in secretions (mucus in gut, milk in mammary glands, tears, saliva)
  - Does not fix a complement, therefore does not drive inflammation

2. Rmp proteins

- Found on the outer membrane of the N. gonorrhoeae
- Does not undergo antigenic variation
- Found in a complex with Por proteins and lipooligosaccharides (LOS)
- Block bactericidal antibodies directed against the Por and LOS

Entry into host cells~ *Neisseria gonorrhoeae*

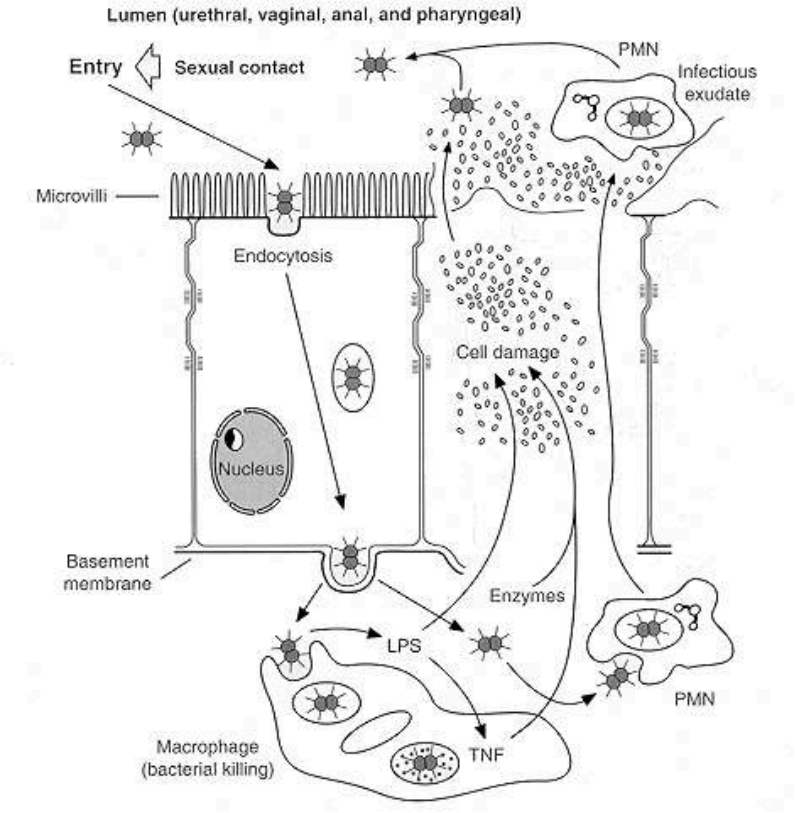
3. Lipooligosaccharides (LOS)

- Released after the autolysis of host cells
- Undergoes antigenic variation to prevent host defenses from detecting the bacteria
- Has been shown to be involved in the resistance of bactericidal activity of normal human serum
- Similar to antigens found on human erythrocytes, therefore less likely to cause an immune response

4. Capsule

- Made up of polysaccharides
- Functions as a defense mechanism under stressful conditions

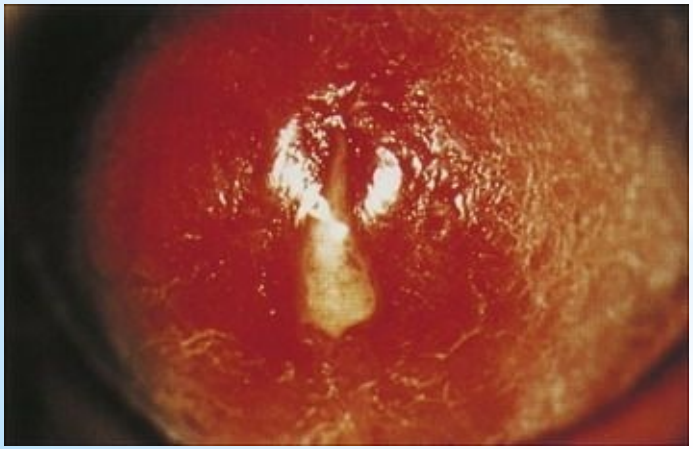
Multiplication and Spread ~ *Neisseria gonorrhoeae*



- After endocytosis, *N. gonorrhoeae* replicate within the host cell
  - Aids in evading phagocytosis and antibodies
- Infected vacoules move from the apical to the basolateral side of the cell
- Bacteria are released via exocytosis into the subepithelial connective tissues
- The LOS activates the host's alternative complement pathway and production of the tumor necrosis factor (TNF)
- Phagocytosis may occur, but the bacteria can survive within the phagocytes
  - Once phagocytosed, the bacteria can multiply again, exocytose and spread
- Infection is usually localized
- Infection is able to spread to other parts of the body via bloodstream
  - Cause of bacteremia
- Twitching motion of the gonococci allows them to "jump" distances of 1-5um

Bacterial Damage~ *Neisseria gonorrhoeae*

- The LOS activates the host's alternative complement pathway and production of the tumor necrosis factor (TNF)
- As bacteria are lysed by host's leukocytes, soluble LOS are released (endotoxin)
- Release of TNF and enzymes such as proteases and phospholipases are responsible for host tissue damage



In this case, Naser shows the symptoms of urethritis and a green discharge. These are indicative of the localized infection by the Neisseria gonorrhoeae bacteria. In particular, the localized immune response and tissue damage would lead to Naser's observable symptoms.

Entry into host cells~ *Chlamydia trachomatis (serotypes D-K)*

Bacterial structure and overview

- Gram negative, diplococci
- Has both DNA and RNA
- Divides by binary fission
- Contains genes for peptidolycan synthesis, but does not actually express those genes
- Infect non-ciliated columnar cells and macrophages
- Lacks muramic acid usually found on other bacteria
  - Lactam antibiotics have no impact on this bacteria
- Polymorphic:
  - Elementary body:
    - adapted for extracellular survival and initiation of infection
    - relatively resistant to drying
    - non-multiplying
  - Reticulate body:
    - adapted for intracellular multiplication in order to make a large inoculum for further transmission
    - vegetative (non-infectious) form

Entry into cells: Parasite-induced endocytosis

- Elementary body of C. trachomatis binds to clathrin expressed on host cells
- Clathrin triggers endocytosis of the bacteria
- C. trachomatis can also bind to host's dynamin-2 receptor, and promote endocytosis
- May induce endocytosis via a secreted type III secreted effector

Entry into host cells~ *Chlamydia trachomatis (serotypes D-K)*

Entry into cells: Parasite-induced endocytosis

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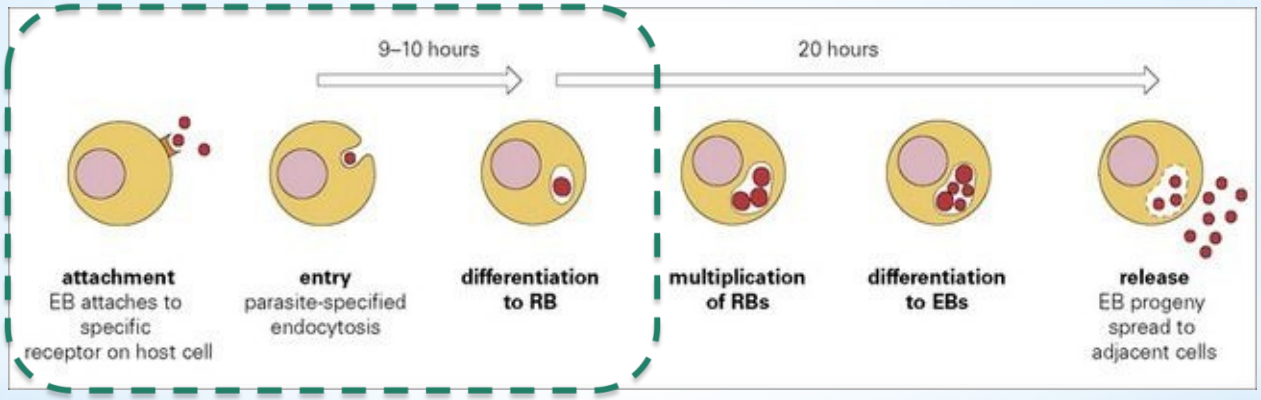
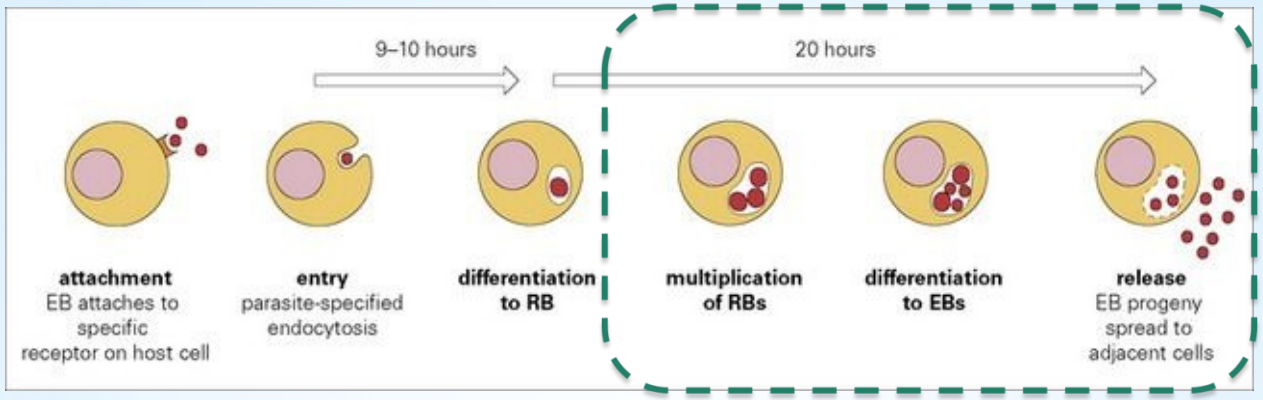


- Fusion of infected vesicle with lysosomes and endosomes is inhibited
  - Mechanism of this step is unknown
- Elementary bodies mature and differentiate into reticulate bodies
  - Within 9-10 hours
  - Reticulate bodies are metabolically active

Multiplication and Spread ~ *Chlamydia trachomatis (serotypes D-K)*



- Reticulate bodies replicate via binary fission
- New progeny of elementary bodies is formed
- Elementary bodies are released into the extracellular environment
  - Within another 20 hours
- Newly released elementary bodies can invade nearby cells (localized infection)
- Distant cells can be infected if bacteria enter lymph or blood

Bacterial Damage~ *Chlamydia trachomatis (serotypes D-K)*

- Host cells disintegrate after release of elementary bodies
- Lysis of *C. trachomatis* releases a soluble lipopolysaccharide (endotoxin)
  - Endotoxin causes an immune response, cell and tissue damage
- Clinical effects seem to result because of cell destruction and host's inflammatory response

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Naser shows the symptoms of urethritis and discharge after urinating. These symptoms can be explained by localized infection by Chlamydia trachomatis. Due to the large bacterial inoculum that develops relatively quickly, and the immune response that would follow, the symptoms would match the bacterial pathogenesis of C. trachomatis.

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