Chlamydial Infections

‘One-half of the troubles of this life can be traced to saying yes to quickly and not saying no soon enough.’

Josh Billings (1818-1885)
Chlamydial Infections--

Classification

• These organisms comprise a single order, Chlamydiales, a single family, Chalmydiaceae, and until 1999, one genus: Chlamydia.
  – C. trachomatis
  – C. pneumoniae
  – C. psittaci

• There are, however, various serovars (subdivisions).
Chlamydial Infections--Classification

• Genus Chlamydia
  – C. trachomatis
  – C. murdarium
  – C. suis

• Genus Chalmydophila
  – C. pneumoniae
  – C. psittaci
  – C. pecorum
  – C. abortus
  – C. caviae
  – C. felis
Physiology and Structure

- Elementary bodies (EBs) are resistant to many harsh environments.
  - MOMP thought to be involved in attachment.
- Energy parasites.
  - use hosts ATP
- Originally thought to be viruses (small size) until the 1960s.
- Histologic stains can readily detect the phagosome with accumulated Reticulate bodies (RBs) called inclusion(s).
- Gram negative with not peptidoglycan layer.
Chlamydia Infectious Cycle

Attachment and entry

Migration to perinuclear area and EB -> RB transition

0h

2h

8-12h

48h

24h

Inclusion biogenesis and bacterial replication

RB -> EB transition and cell lysis

1. Susceptible cell

2. Ingestion

3. Reorganization into RB inside phagosome

4. Growth by binary fission—24 hours

5. Reorganized into EBs

6. Inclusion contains EBs and RBs

7. Continued reorganization

8. Extrusion of mass of EBs by reverse endocytosis

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Inclusions

- Once EB internalized, ineffective lysosomal fusion.
- EB to RB to EB development.
- 100-1000/cell
- Different species differ by inclusion morphology, metabolism, host cell preference.
Chlamydial Infections--
Classification

- *C. pneumoniae*
  - human pathogen
  - important cause of bronchitis, pneumonia, and sinusitis.
  - person-to person
  - 200-300K cases/year
  - Cannot differentiate between *Mycoplasma pneumoniae*, *L. pneumophila*, and respiratory viruses.

- Does not grow on in the cell lines used for the isolation of *C. trachomatis*.

- PCR
Chlamydial Infections-- Classification

- **C. psittaci**
  - Disease first observed in parrots.
  - Reservoirs=all birds.
  - Humans and other mammals can become infected.
  - Organisms present in blood, feces, tissues of infected birds (ill or healthy).
  - <50 cases a year reported in US.
  - Person-to-person rare.
  - Severe disease can include GI symptoms, vomiting, carditis, hepatomegaly, splenomegaly.
  - Diagnosed serologically.
Chlamydial Infections--
Classification

- *C. trachomatis*
  - Made up of 3 biovars
    - Trachoma (14 serovars)
    - Lymphogranuloma venerum (4 serovars)
    - Mouse pneumonitis
  - *C. trachomatis* infects only humans
    » The human biovars and serovars have 87-99% DNA homology with each other.
Chlamydial Infections--Classification

• *C. trachomatis*
  – Classified serologically
  – Based on the Major Outer Membrane Protein (MOMP).

• **Responsible for eye and genital infections.**
  – Trachoma-serovars A-K
  – Lymphogranuloma venereum (LGV)-serovars L1, L2, L2a, L3
  – STIs-serovars D-K
Natural History of Infections

- Genital tract infections not well understood.
- Chlamydiae elicit an immune response that facilitates the resolution of infection in most patients.
- Chronic asymptomatic and persistent infections of the conjunctival and genital mucosa are not easily recognized.
  - 80% women and 30% men are asymptomatic
  - reactivation???????
Chlamydial Infections--
Introduction & History

• The identification of *C. trachomatis* as a cause of genital tract infections was delayed until smear and culture methods became available for detecting *Neisseria gonorrhoeae*.

• Once *N. gonorrhoeae* was excluded as a cause of a variety of infections there were suspicions that a unique infectious agent caused these diseases.
Chlamydial Infections--Introduction & History

• 1907-First visualization of intracytoplasmic inclusions of Chlamydia in conjunctival scrapings.
• 1920- *C. psittaci* isolated
• 1935- LGV
• 1950s- Trachoma agent
  – in 1959, a genital strain of *C. trachomatis* was finally isolated.
  – facilitated by developing tissue culture techniques.
Chlamydia
Epidemiology-Genital Infections

• Found worldwide
• Most common bacterial STI in the world.
• In 2003, estimated 2.8 million American infected each year and as many as 50 million new infections occur annually worldwide
Chlamydia — Rates by state: United States and outlying areas, 2005

Rate per 100,000 population
- <=150.0 (N= 3)
- 150.1-300.0 (N= 26)
- >300.0 (N= 25)
Chlamydia — Rates by county: United States, 2005
Epithelium and Infection--

Junctions

- Affect a limited number of cell types
  - nonciliated columnar
  - cuboidal
  - transitional

- Found on the mucous membranes of the urethra, endocervix, endometrium, fallopian tubes, anorectum, respiratory tract, and the conjunctivae.
Epithelium and Infection

Columnar epithelium
Epithelium and Infection

Transitional epithelium
Epithelium and Infection

Pseudostratified epithelium
Epithelium and Infection

Squamous epithelium
Epithelium and Infection--

Junctions

Squamocolumnar junction
Chlamydia — Age- and sex-specific rates: United States, 2005
Chlamydia
Epidemiology-Genital Infections

• A large number of studies have focused on the prevalence of, and risk factors for, infection among women (majority of cost [80%] goes to treating women).
  – few studies have addressed these problems in men.

• The highest prevalence rates of infection are among sexually active adolescent women (exceeding 10%) and for women attending STD clinics the rates are 15-20%.

• Young age (<25 years) is the strongest and most consistent association with chlamydial STDs among women. Why???
Chlamydia--Clinical Features

• The syndromes attributed to chlamydiae most closely resemble *N. gonorrhoeae*.

• Sites of infection: Epididymis, endocervix, endometrium, salpinx, adnexae, Bartholin’s duct, perihepatic region, and rectum.
  - Cervix and urethra primary sites in women.

• There is some evidence that chlamydial infections of the cervix enhance the acquisition and transmission of HIV.
  - Of the few in vivo studies, one demonstrated significant HIV seroconversion among female prostitutes infected with *C. trachomatis*.
  - Public health control measure for HIV spread.
Chlamydia--Symptoms (women)

- dysuria
- pelvic pain
- dyspareunia
- cervicitis
- pyuria
- Fitz-Hugh-Curtis Syndrome
  - liver

- Reproductive consequences more likely among women with chlamydial PID than women with gonococcal PID

- PID (pelvic inflammatory disease)
  - severe pelvic and/or lower abdominal pain
  - fatigue
  - fever
  - adnexal tenderness
  - salpingitis
  - infertility
  - ectopic pregnancy
    - viable chlamydial organisms, antigens, DNA recovered from damaged fallopian tubes of infertile women
Chlamydia--Symptoms (men)

- urethritis
  - Chlamydia coinfect 20% of patients with GC urethritis.
  - most common symptoms are urethral discharge, itching, and dysuria.
  - symptoms more prolonged than with GC infection.
    - 7-14 day incubation period compared to 3-4 days for GC infection.
- epididymitis
- oligospermia
- proctocolitis
Cervicitis

Urethritis

Epididymitis
Time Course of Untreated Chlamydial Urethritis in Men
Diagnostic Tests

• Tissue culture (gold standard)
  – can take 3-7 days

• Fluorescent antibodies
  – smear of tissue on slide

• PCR
Lymphogranuloma Venerum

‘Do not trifle with love.’
Alfred de Musset (1810-1857)

‘For my loins are filled with a loathsome disease; and there is no soundness in my flesh.’
Psalms 41:8
Lymphogranuloma Venerum

- tropical bubo
- strumous bubo
- climatic bubo
- Durand-Nicolas-Favre disease
- poradenitis inguinalis
Lymphogranuloma Venerum

• Occurs sporadically in North America, Australia, and Europe.
  – 200-500 cases annually in the USA over the last decade.

• Prevalent in Africa, Asia, and South America.
Lymphogranuloma Venerum--
3 Stages of Disease

- **First stage**--primary lesion is a small and inconspicuous genital papule or herpetic-form ulcer.
- 3-12 days to form.
- Short lived.
- In women, lesion is primarily on the posterior vaginal wall, cervix, and vulva.
- Differential with canchroid, syphilis or Herpes simplex infections.
Lymphogranuloma Venerum--
3 Stages of Disease

- **Second stage**--acute lymphadenitis with buboes.
- 10-30 days after primary lesion.
- Bubo begins as a firm, slightly painful and gradually enlarging mass that is unilateral in 2/3 of patients.
- Within 1-2 weeks, bubo becomes more tender and fluctuant.
- Ruptures 1/3 of the time.
  - Relieves pain and fever
- Numerous sinus tracts form after rupture, which drain thick pus for several months.
Lymphogranuloma Venerum--3 Stages of Disease

• In men, healing of the bubo usually predicts the end of disease.
• Relapse in 20% of patients.
• Third stage--Important subacute manifestation is the anogenitorectal syndrome which includes:
  – proctocolitis, perirectal abscesses, rectovaginal fistulas, anal fistulas, and rectal stricture, ‘esthiomene.’
Lymphogranuloma Venerum--
3 Stages of Disease

- **Esthiomene**-derived from the Greek word for ‘eating away.’
- Fibrosis of the subcutaneous tissues causing elephantiasis of the affected parts.

- **DIAGNOSIS**-ideally made by the isolation of the LGV serovar from the bubo.
  - only culture positive 30% of the time.
- **Fluorescent antibodies**
- **Excluding other infectious agents.**
  - herpes, granuloma inguinale, syphilis
Trachoma

‘Let there be sight to heal the soul of man.’

Sanskrit proverb
Introduction and History

• First report from China in the 27th century B.C.
• Later there was a mention of a conjunctival disease similar to trachoma in the Ebers Papyrus from Egypt that dates to 1800 B.C.
• In the first century B.C., the name trachoma appeared, which meant ‘rough swelling’ in Greek.
• Not until the Napoleonic era did trachoma become a significant blinding disease.
Trachoma—Epidemiology

- Leading cause of preventable blindness.
- More than 500 million people affected worldwide.
- Of those 100 million have severe visual deficits and 9 million are blind.

- Estimated that by the year 2020 those with blinding disease will reach 12 million.
Trachoma--Epidemiology

- Infection vs. symptoms
- In Tanzania, 43% of patients with trachomatous follicles and 23% with intense trachoma were negative for chlamydia.
- Also in Tanzania, 24% of the children who had no evidence for clinical disease were positive for *C. trachomatis* by PCR.
- Eye-to-hand contact most common route of transmission.
- Risk factors
  - crowding, poverty, children in the household, >1 child/sleeping room, lack of water use or lack of water and poor hygiene.
Trachoma--Epidemiology

- Flies may be an important vector for transmission.
- Study: a child’s ocular lesions were stained with fluorescein.
  - subsequently, fluorescein was detected on the legs and bodies of flies in the study household and in the eyes of children in the same family within 15-30 min.
  - Ability of chlamydia to survive long outside the host??
Trachoma—Clinical Features

• Defined as a chronic follicular conjunctivitis that has persisted for at least 15 days.

• Early in the disease, it is characterized by a follicular conjunctivitis that is indistinguishable from that caused by *C. trachomatis* sexually-transmitted serovars or *C. psittaci* or *C. pneumoniae* strains.
Trachoma--**Clinical Features**

- Later it becomes a cicatricial (or scarring) conjunctivitis.
- Can be acute or insidious.
- Patients present with a foreign body sensation.
- Entire upper tarsal epithelium typically is involved and contains developing lymphoid follicles.
Some Eye Anatomy
Trachoma--Clinical Features

• Entire upper tarsal epithelium typically is involved and contains developing lymphoid follicles.

• Follicles appear as clear, yellowish, or gray-white avascular lesions.

• In children <2 years of age thickening of the epithelium may be the only symptom.
  – follicle formation less common.
Trachoma--Clinical Features

• The intensity of the infiltrates tends to increase in children up to 6-8 years.
Trachoma--Clinical Features

- Lymphoid follicles at the limbus are a characteristic feature of trachoma that lead to the formation of Herbert’s pits.
Trachoma—Clinical Features

- As scarring progresses, the upper tarsus becomes distorted, leading to trichiasis.
- These inturned eyelashes can produce corneal abrasions that become superinfected with bacteria.
- Abrasions heal by scarring.
  - varying degrees of corneal opacity.
Trichiasis and Distichiasis

- Normal lashes

- Trichiasis

- Distichiasis
Trachoma-Clinical Features

• **Ophthalmia neonatorum**
  – newborns (1-3 weeks post)
  – infected in birth canal
  – infected caregivers
  – 44% develop this condition
  – Prophylaxis does not work.

  – Pneumonitis
Trachoma--Clinical Features

- Although trachoma is one disease that causes a chronic follicular conjunctivitis, there are other conditions that meet the definition of disease.
  - toxic follicular conjunctivitis
  - inclusion conjunctivitis form sexually transmitted *C. trachomatis.*
  - *H. influenzae*
  - *H. aegyptius*
  - *Moraxella* spp.
  - *Neisseria meningitidis*
  - *N. gonorrhoeae*
  - *S. pneumoniae*
Trachoma--Diagnosis

- Same as for other Chlamydial infections.
- Conjunctival smears.
Neisseria and Related Genera

‘A young man wishes to faithful, but cannot. A old man wishes to faithless, but cannot.’

Oscar Wilde
Neisseria

- Gram negative
- Non spore forming
- Usually non motile
- *N. gonorrhoeae*
  - fastidious
  - culture depends on high humidity
  - utilizes glucose but not maltose, lactose nor sucrose
  - Referred to as the “clap” (middle French *clapoir*, “bubo”)

*Image of Neisseria gonorrhoeae*
N. gonorrhoeae--Introduction and History

• Numerous references to gonococcal urethritis in Chinese writings dating back 2500 years.
• Biblical references to NG infection.
• The term gonorrhea, meaning “flow of seed” (gonos, seed; rhoia, flow) was introduced by Galen in about 130 AD, who confused the purulent urethral exudate from infected men with semen.
N. gonorrhoeae--Introduction and History

• Additional descriptions of gonorrhea can be found in the Papyrus of Ebers and the writings of Hippocrates.

• Causative agent first described by Neisser in 1879.
N. gonorrhoeae--Epidemiology

- In the U.S. it remains the most frequently reported STI.
- Many more infections reported in men than in women.
  - easier to diagnose
  - trends are evening out
- Transmission is almost exclusively be sexual contact.
  - nonsexual transmission i.e., skin-to-skin, skin to mucus membrane, autoinoculation, fomite transmission have not been reported.
N. gonorrhoeae--Epidemiology

- Highest risk factor group: <25 years.
- Risk following 1 sexual contact is 50-60% (man to uninfected woman).
- Risk following 1 sexual contact is 22% (woman to uninfected man).
- Presence and survival of NG in fresh and frozen semen have been documented.
- Antibiotic-resistant strains are on the rise.
Gonorrhea — Rates: United States, 1941–2005 and the Healthy People 2010 target
Gonorrhea — Rates by state: United States and outlying areas, 2005
Gonorrhea — Rates by County: United States and outlying areas, 2005
Gonorrhea — Rates: Total and by sex: United States, 1986–2005 (per 100,000)
N. gonorrhoeae--Biology and Pathogenesis

• Prefer columnar and transitional epithelium.
• Outer membrane contains lipooligosaccharide (LOS).
  – endotoxic properties
  – lethal to experimental animals
  – mediates cellular destruction
  – LOS form the basis of an alternative serologic typing system.
• Porins
  – major protein antigen used in serologic typing systems
• Opacity proteins
  – increase adhesion of gonococci to each other.
• Pili play an important role in infection
  – more than 50 serotypes of pili
  – better able to attach to mucosal surfaces--INFECTION
**N. gonorrhoeae—Clinical Features—Men**

- Most common symptom is acute urethritis, presenting with urethral discharge.
  - 2-5 days post
- If untreated, most infections will resolve after several weeks.
  - epididymitis
- Rare complications include penile edema referred to as “bullheaded clap.”
N. gonorrhoeae--Clinical Features-Women

• Endocervix is the primary site of genital tract gonococcal infection.

• Most common symptoms include cervicitis, urethritis, vaginal discharge.
  – examination reveals mucopurulent cervical discharge.

• PID
  – chronic complication--ascending infection
  – infertility more likely with C. trachomatis because NG causes more severe clinical manifestations.
**N. gonorrhoeae—Other Infections**

- **Anorectal Infection**
  - 40% of women and homosexual men have positive rectal cultures for the gonococcus.
  - In 40% of homosexual men and 5% of women with gonorrhea, the rectum is the only site found to be infected.
  - Most asymptomatic
  - Symptomatic
    - tenesmus
    - puritis
    - bleeding

- **Pharyngeal Infection**
  - Majority of patients are asymptomatic.
  - Major risk factor for infections is having oral-genital sexual exposure with an infected partner.
N. gonorrhoeae—Pregnancy and Neonatal Infections

• Pregnancy
  – poor obstetric outcome
  – spontaneous abortion
  – premature labor
  – perinatal infant mortality

• Neonatal Infections
  – ophthalmia neonatorum
    • most frequent clinical manifestation of neonatal infection.
    • At one time in the US, it was the most common cause of blindness and remains a pediatric public health problem in many developing nations.
**N. gonorrhoeae**--Diagnosis and Treatment

- Culture
- Demonstration of intracellular gram-negative diplococci in Gram-stained smears.
- Fluorescent antibody
- DNA
- Accu Probe

- Antibiotics while they last.
Meningococcal Infections

“Acute pain of the ear with continual and strong fever is to be dreaded; for there is danger that the man may become delirious and die.”

Hippocrates, *Book of Prognostics*, 22
N. meningitidis - Epidemiology

- Colonize the oropharynx.
- Can colonize 2-15% of healthy individuals but in crowded or confluent populations colonization is so common that it could arguably be considered part of the normal human oral flora.
- Transmission is by direct contact with contaminated respiratory secretions or airborne droplets.
- Sexual transmission has been reported.
  - creates a ‘carrier’ population
**N meningitidis - Epidemiology**

- 13 serotypes are currently recognized based on capsular polysaccharides: A, B, C, D, 29E, H, I, K, L, W135, X, Y, Z.
- Strains belonging to groups A, B, C, Y, and W135 most frequently cause systemic disease.
- Classically, groups A and C cause epidemic meningococcal disease.
In Africa, epidemic meningitis is in a wide band of countries lying south of the Sahara in the so-called “meningitis belt.”
N meningitidis-Pathogenesis

• Major toxic factor is LOS
• Piliation appears to be required for colonization of host mucosal surfaces.
• LOS is a potent activator of complement.
  – double-edged sword
    • disseminated intravascular coagulation (DIC)
**N meningitidis-Clinical Manifestations**

- Manifestations dominated by fulminating, rapidly progressive septicemia with fever, vascular collapse, and DIC manifested by petechial or purpuric skin lesions.
- Course of the infection may be brief with death in a few hours of onset.
  - arthritis
  - endocarditis
N meningitidis - Clinical Manifestations

- Purpura fulminans
  - Catastrophic febrile illness with initial hemorrhagic skin lesions that progress to gangrene.
  - Amputation maybe necessary.
  - Other pathogens that can cause hematogenous infections such as E. coli, S. pneumoniae and viruses like varicella and rubella
**N meningitidis—Clinical Manifestations**

- **Waterhouse-Friderichsen Syndrome**
  - Classically associated with meningococcal septicemia.
  - W-FS has an abrupt onset in a previously healthy patient.
    - septicemia
    - shock
    - cutaneous petechiae
    - hemorrhage to both adrenal glands
    - adrenal gland hemorrhage
N meningitidis - Diagnosis and Treatment

- Hallmark (unfortunately) is its rapid fulminating course.
  - early diagnosis is essential
- Blood cultures positive in about 1/3 of patients
- 90% of patients have positive CSF cultures.
- Kits for rapid detection available.

- Penicillin G
  - resistant strains exist
N meningitidis- Prophylaxis

• Quadrivalent vaccine is commercially available (groups A, C, W, W135).