BACTERIOLOGY - CHAPTER TWENTY

CHLAMYDIA AND CHLAMYDOPHILA

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TEACHING OBJECTIVES

To describe the developmental cycle of chlamydia
To describe the pathogenesis, epidemiology and clinical syndromes associated with chlamydia

KEY WORDS

Elementary bodies
Reticulate bodies
Inclusion
Biovar
Serovar
Trachoma
Inclusion conjunctivitis
LGV
Reiter's syndrome
Psittacosis
Ornithosis
TWAR agent

The family *Chlamydiaceae* consists of two genera. One species of *Chlamydia* and two of *Chlamydophila* are important in causing disease in humans.

- *Chlamydia trachomatis* can cause urogenital infections, trachoma, conjunctivitis, pneumonia and lymphogranuloma venereum (LGV)
- *Chlamydophila pneumoniae* can cause bronchitis, sinusitis, pneumonia and possibly atherosclerosis
- *Chlamydophila psittaci* can cause pneumonia (psittacosis).

Members of the *Chlamydiaceae* are small obligate intracellular parasites and were formerly considered to be viruses. However, they contain DNA, RNA and ribosomes and make their own proteins and nucleic acids and are now considered to be true bacteria. They possess an inner and outer membrane similar to gram-negative bacteria and a lipopolysaccharide but do not have a peptidoglycan layer. Although they synthesize most of their metabolic intermediates, they are unable to make their own ATP and thus are energy parasites.

Physiology and Structure

Elementary bodies (EB)

EBs are the small (0.3 - 0.4 µm) infectious form of the chlamydia. They possess a rigid outer membrane that is extensively cross-linked by disulfide bonds. Because of their rigid outer membrane the elementary bodies are resistant to harsh environmental conditions encountered when the chlamydia are outside of their eukaryotic host cells. The elementary bodies bind to receptors on host cells and initiate infection. Most chlamydia infect columnar epithelial cells but some can also infect macrophages.

Reticulate bodies (RB)

RBs are the non-infectious intracellular from of the chlamydia. They are the metabolically active replicating form of the chlamydia. They possess a fragile membrane lacking the extensive disulfide bonds characteristic of the EB.

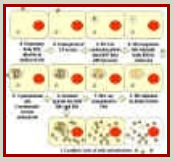

Figure 1 The developmental

Developmental cycle (Figure 1) - The EBs bind to receptors on susceptible cells and are internalized by endocytosis and/or by phagocytosis. Within the host cell endosome the EBs reorganize and become RBs. The chlamydia inhibit the fusion of the endosome with the lysosomes and thus resist intracellular killing. The entire intracellular life cycle of the chlamydia occurs within the endosome. RBs replicate by binary fission and reorganize into EBs. The resulting inclusions may

cycle of chlamydia

contain 100 - 500 progeny (Figure 2). Eventually, the cells and inclusions lyse (*C. psittaci*) or the inclusion is extruded by reverse endocytosis (*C. trachomatis* and *C. pneumoniae*) (Figure 1).

Chlamydia trachomatis

C. trachomatis is the causative agent of *trachoma*, urogenital disease, infant pneumonia and lymphogranuloma venereum.

Biovars

C. trachomatis has a limited host range and only infects human epithelial cells (one strain can infect mice). The species is divided into three biovars (biological variants): trachoma, lymphogranuloma venereum and mouse pneumonitis.

Serovars

The human biovars have been further subdivided in to several serovars (serological variants; equivalent to serotypes) that differ in their major outer membrane proteins and which are associated with different diseases (Table 1)

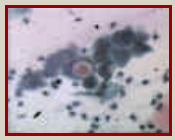

Figure 2
Chlamydial inclusions

Figure 3
Chlamydial inclusions in an endothelial cell

Figure 4
Distribution of trachoma

Table 1		
Serovar	**Disease**	**Distribution**
A B Ba C	Trachoma	Asia and Africa
D - K	Disease of eye and genitals: Conjunctivitis Urethritis Cervicitis Respiratory System: Infant pneumonia	World wide
LGV1 LGV2 LGV3	Lymphogranuloma venerium	Worldwide

Pathogenesis and Immunity

C. trachomatis infects non-ciliated columnar epithelial cells. The organisms stimulate the infiltration of polymorphonuclear cells and lymphocytes which leads to lymphoid follicle formation and fibrotic changes. The clinical manifestations result from destruction of the cells and the host inflammatory response. Infection does not stimulate long lasting immunity and reinfection results in a inflammatory response and subsequent tissue damage.

Epidemiology

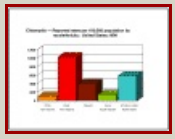

Figure 4A
Chlamydia - Reported rates per 100,000 population by race/ethnicity: United States,1999 CDC

Figure 4B
Chlamydia - Age-and gender-specific rates: United States,1999 CDC

- Ocular infections

  a. *C. trachomatis* (biovar: trachoma) is found worldwide primarily in areas of poverty and overcrowding (Figure 4). It is estimated that 500 million people are infected worldwide and 7 - 9 million people are blind as a consequence. *C. trachomatis* biovar: trachoma is endemic in Africa, the Middle East, India and Southeast Asia. In the United States, Native Americans are most commonly infected. Infections occur most commonly in children. The organism can be transmitted by droplets, hands, contaminated clothing, flies, and by passage through an infected birth canal.

- Genital tract infections

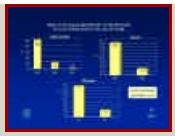
Figure 5
Results of trachoma-specific interventions in three countries in the last 30 years

a. *C. trachomatis* (biovar: trachoma) is the most common sexually transmitted bacterial disease in the United States (4 million new cases each year) and 50 million new cases occur yearly worldwide. In the United States, the highest infection rates occur in Native and African Americans (Figure 4A) with a peak incidence in the late teens/early twenties (Figure 4B).

b. *C. trachomatis* (biovar: LGV) is a sexually transmitted disease that occurs sporadically in the United States but is more prevalent in Africa, Asia and South America. Humans are the only natural host. Incidence is 300 - 500 cases per year in the United States with male homosexuals being the major reservoir of the disease.

Clinical Syndromes

- Trachoma

  Chronic infection or repeated reinfection with *C. trachomatis* (biovar: trachoma) results in inflammation and follicle formation involving the entire conjunctiva (Figure 7 and 8). Scarring of the conjunctiva causes turning in of the eyelids and eventual scarring, ulceration and blood vessel formation in the cornea, resulting in blindness. The name trachoma comes from 'trakhus' meaning rough which characterizes the appearance of the conjunctiva. Inflammation in the tissue also interferes with the flow of tears which is an important antibacterial defense mechanisms. Thus, secondary bacterial infections occur.

- Inclusion conjunctivitis

  Inclusion conjunctivitis is caused by *C. trachomatis* (biovar: trachoma) associated with genital infections (serovars D - K). The infection is characterized by a mucopurulent discharge, corneal infiltrates and occasional corneal vascularization. In chronic cases corneal scarring may occur. In neonates infection results from passage through an infected birth canal and becomes apparent after 5 - 12 days. Ear infection and rhinitis can accompany the ocular disease.

- Infant pneumonia

  Infants infected with *C. trachomatis* (biovar: trachoma; serovars: D - K) at birth can develop pneumonia. The children develop symptoms of wheezing and cough but not fever. The disease is often preceded by neonatal conjunctivitis.

- Ocular lymphogranuloma venereum

  Infection with the LGV serovars of *C. trachomatis* (biovar: LGV) can lead to oculoglandular conjunctivitis. In addition to the conjunctivitis, patients also have an associated lymphadenopathy.

- Urogenital infections

  In females, the infection is usually (80%) asymptomatic but symptoms can include cervicitis, urethritis, and salpingitis. Postpartum fever in infected mothers is common. Premature delivery and an increased rate of ectopic pregnancy due to salpingitis can occur. In the United States, tubal pregnancy is the leading cause of first-trimester, pregnancy-related deaths. In males, the infection is usually (75%) symptomatic

  After a 3 week incubation period patients may develop urethral discharge, dysuria and pyuria. Approximately 35 - 50% of non-gonococcal urethritis is due to *C. trachomatis* (biovar: trachoma). Post-gonococcal urethritis also occurs in men infected with both *Neisseria gonorrhoeae* and *C. trachomatis*. The symptoms of chlamydial infection occur after treatment for gonorrhea because the incubation time is longer.

  Up to 40% of women with untreated (undiagnosed) chlamydia will develop pelvic inflammatory diseases and about 20% of these women will become infertile. Many untreated cases (18%) result in chronic

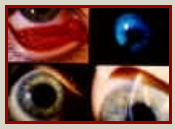
Figure 7
Chlamydial kerato-conjunctivitis

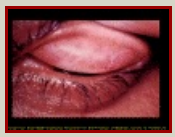
Figure 8
Tracomatous SCARRING : the presence of scarring in the tarsal conjunctiva. Scars are easily visible as white lines, bands, or sheets in the tarsal conjunctiva. They are glistening and fibrous in appearance. Scarring, especially diffuse fibrosis, may obscure the tarsal blood vessels.


Tracomatous TRICHIASIS : at least one eyelash rubs on the eyeball


CORNEAL OPACITY : easily visible corneal opacity over the pupil. The pupil margin is blurred viewed through the opacity. Such corneal opacities cause significant visual impairment (less tah 6/18 or 0.3 vision)

pelvic pain.

Women infected with chlamydia have a 3 - 5 fold increased risk of acquiring HIV.

- Reiter's syndrome

  Reiter's syndrome is a triad of symptoms that include conjunctivitis, polyarthritis and genital inflammation. The disease is associated with HLA-B27. Approximately 50 - 65% of patients have an acute *C. trachomatis* infection at the onset of arthritis and greater than 80% have serological evidence for *C. trachomatis* infection. Other infections (shigellosis or *Yersinia enterocolitica*) have also been associated with Reiter's syndrome.

- Lymphogranuloma venereum (*C. trachomatis* biovar: LGV)

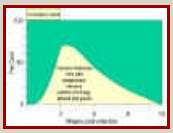
Figure 9 Chlamydial urogenital infection in men. After an incubation of 3 weeks, up to 75% of patients show symptoms such as urethral discharge, dysuria and pyuria

The primary lesion of LGV is a small painless and inconspicuous vesicular lesion that appears at the site of infection, often the penis or vagina. The patient may also experience fever, headache and myalgia. The second stage of the disease presents as a marked inflammation of the draining lymph nodes. The enlarged nodes become painful 'buboes' that can eventually rupture and drain. Fever, headache and myalgia can accompany the inflammation of the lymph nodes. Proctitis is common in females; lymphatic drainage from the vagina is perianal. Proctitis in males results from anal intercourse or from lymphatic spread from the urethra. The course of the disease is variable but it can lead to genital ulcers or elephantiasis due to obstruction of the lymphatics.

Laboratory diagnosis

There are several laboratory tests for diagnosis of *C. trachomatis* but the sensitivity of the tests will depend on the nature of the disease, the site of specimen collection and the quality of the specimen. Since chlamydia are intracellular parasites, swabs of the involved sites rather than exudate must be submitted for analysis. It is estimated that as many as 30% of the specimens submitted for analysis are inappropriate.

- Cytology

  Examination of stained cell scrapings for the presence of inclusion bodies (Figures 2 and 3) has been used for diagnosis but this method is not as sensitive as other methods.

- Culture

  Culture is the most specific method for diagnosis of *C. trachomatis* infections. Specimens are added to cultures of susceptible cells and the infected cells are examined for the presence of iodine-staining inclusion bodies. Iodine stains glycogen in the inclusion bodies. The presence of iodine-staining inclusion bodies is specific for *C. trachomatis* since the inclusion bodies of the other species of chlamydia do not contain glycogen and stain with iodine.

- Antigen detection

  Direct immunofluorescence and ELISA kits that detect the group specific LPS or strain-specific outer membrane proteins are available for diagnosis. Neither is as good as culture, particularly with samples containing few organisms (*e.g.* asymptomatic patients).

- Serology

  Serological tests for diagnosis are of limited value in adults, since the tests do not distinguish between current and past infections. Detection of high titer IgM antibodies is indicative of a recent infection. Detection of IgM antibodies in neonatal infection is useful.

- Nucleic acid probes

  Three tests based on nucleic acid probes are available. These tests are sensitive and specific and may replace culture as the method of choice.

Treatment and prevention

Tetracyclines, erythromycin and sulfonamides are used for treatment but they are of limited value in endemic areas where reinfection is common. Vaccines are of little value and are not used. Treatment coupled with improved sanitation to prevent reinfection is the best way to control infection. Safe sexual practices and prompt treatment of symptomatic patients and their sexual partners can prevent genital infections.

Chlamydophila psittaci

C. psittaci is the causative agent of psittacosis (parrot fever). Although the disease was first transmitted by parrots, the natural reservoir for *C. psittaci* can be any species of bird. Thus, the disease has also been called ornithosis from the Greek word for 'bird'.

Pathogenesis

The respiratory tract is the main portal of entry. Infection is by inhalation of organisms from infected birds or their droppings. Person-to-person transmission is rare. From the lungs the organisms enter the blood stream and are transported to the liver and spleen. The bacteria replicate at these sties where they produce focal areas of necrosis. Hematogenous seeding of the lungs and other organs then occurs. A lymphocytic inflammatory response in the alveoli and interstitial spaces leads to edema, infiltration of macrophages, necrosis and sometimes hemorrhage. Mucus plugs may develop in the alveoli causing cyanosis and anoxia.

Epidemiology

Approximately 50 - 100 cases of psittacosis occur annually in the United States with most infections occurring in adults. The organism is present in tissues, feces and feathers of infected birds that are symptomatic or asymptomatic. There may also be reservoirs in other animals such as cats and cattle. Veterinarians, zoo keepers, pet shop workers and poultry processing workers are at increased risk for developing the disease.

Clinical Syndromes

The illness develops after an incubation time of 7 - 15 days. Symptoms include fever, chills, headache, a non-productive cough and a mild pneumonitis. In uncomplicated cases the disease subsides by 5-6 weeks after infection. Asymptomatic infections are common. In complicated cases convulsions, coma and death (5% mortality rate) can occur. Other complications include carditis, hepatomegaly and splenomegaly (Figure 10).

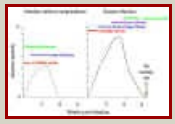
Figure 10 Course of psittacosis. In severe disease there is a 5% mortality rate

Laboratory diagnosis

Laboratory diagnosis is based on a serological tests. A four-fold rise in titer in paired samples in a complement fixation test is indicative of infection.

Treatment and prevention

Tetracycline or erythromycin are the antibiotics of choice. Control of infection in birds by feeding of antibiotic supplemented food is employed. No vaccine is available.

Chlamydophila pneumoniae

Chlamydophila pneumoniae is the causative agent of an atypical pneumonia (walking pneumonia) similar to those caused by *Mycoplamsma pneumoniae* and *Legionella pneumoniae*. In addition it can cause a pharyngitis, bronchitis, sinusitis and possibly atherosclerosis. The organism was originally called the TWAR strain from the names of the two original isolates - Taiwan (TW-183) and an acute respiratory isolate designated AR-39. It is now considered a separate species of chlamydia.

Pathogenesis

The organism is transmitted person- to-person by respiratory droplets and causes bronchitis, sinusitis and pneumonia.

Epidemiology

The infection is common with 200,000 - 300,000 new cases reported annually, mostly in young adults. Although 50% of people have serological evidence of infection most infections are asymptomatic or mild. The disease is most common in military bases and college campuses (crowding). No animal reservoir has been identified.

> Potential link to atherosclerosis: A report in the *Journal of the American College of Cardiology* documented a high incidence of *C. pneumoniae* in the arteries of patients with atherosclerosis (79% compared with 4% in the control group). It is still unproven that the link is causal. However, previous reports show a high association between presence of antibodies to *C. pneumoniae* in serum of patients with atherosclerosis as well as the presence of the organisms in the coronary and carotid arteries.

Clinical Syndrome

Symptoms include a pharyngitis, bronchitis, a persistent cough and malaise. More severe infections can result in pneumonia, usually of a single lobe.

Laboratory diagnosis

Culture is difficult so serological test are most common. A four-fold rise in titer in paired samples is diagnostic.

Treatment and prevention

Tetracycline and erythromycin are the antibiotics of choice. No vaccine is available.

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