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Chlamydiosis in Human

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INTRODUCTION

Chlamydiae species are the causative agent for the disease chlamydiosis. A according to their antigenic content, intracellular inclusions, sulfadiazine susceptibility, plus the ability to cause sickness, three forms of chlamydiae that infect humans are *C. trachomatis*, *C. pneumoniae* and *C. psittaci* belonging to the genus *Chlamydia* (Carroll et al. 2016). Therefore, different chlamydiae may infect animals, but seldom or never humans. All chlamydiae share a group antigen, have a similar morphology, and reproduce inside the cytoplasm of their host cells through a certain growing cycle (Al-Barzanji 2020). Chlamydiae are the gram-negative bacteria that lack systems for generating metabolic energy and are unable to manufacture adenosine triphosphate (ATP). Chlamydiae are strictly intracellular pathogens due to the restriction inside the cells. Thus, the host cell provides intermediates that are rich in energy (Tille 2017). Cervix inflammation, pelvic inflammatory disease (PID), urethral inflammation, inflammation of the epididymis, LGV and inflammation of the rectum are the sexually transmitted diseases caused by *C. trachomatis*. When it infects pregnant women, it can also lead to fetal conjunctivitis and eosinophilia pneumonia (Workowski et al. 2021). Numerous upper and lower respiratory tract infections are produced by *C. pneumoniae*. About 5% of acquired pneumonia is caused by common and atypical pneumonia pharyngitis, which resembles *Mycoplasma pneumoniae* (Hammerschlag et al. 2015). Dealing with birds such as parrots, pigeons, and different household avian species can lead to an acquisition of *C. psittaci*. Psittacosis may be unnoticed or moderate, but it has also been reported to cause severe pneumonia and sepsis, both of which have a higher fatality rate (Zhang et al. 2022).

History of *Chlamydia*

Conjunctival scraping samples from trachoma patients were found to include intracytoplasmic inclusions in 1907 by Halberstaedter and von Prowazek, two of Albert Neisser's assistants leading to the discovery of the infectious agent. These inclusions suggested the term "Chlamydozoa" since they were draped around the nucleus (Greek chlamys meaning a cloak). This supposed organism believed for protozoa, then a virus, but it was actually a bacterium adapted to live within cells. (Haider 2009; Taylor-Robinson 2017).
During a human psittacosis outbreak in 1930, "Bedson and Western" identified a minute basophilic particle from the blood and tissues of affected birds and humans; than in the same year, the Lymphogranuloma Venereum (LGV) causative agent was isolated from human tissue. These particles were categorized as viruses in the psittacosis-LGV group because they were not inhibited by bacterial filters and could not be cultivated on artificial media (Al-Barzanji 2020). Over the course of the next 50 years, numerous attempts to cultivate these uncommon organisms were made, but it wasn't until 1957 that the trachoma factor was isolated from chicken-embryo yolk sacs after inoculating them with material from affected human eyes (Jones et al. 1964; Taylor-Robinson 2017).
For almost ten years following their initial isolation, chlamydiae were initially believed to be large viruses due to their obligate intracellular existence. It wasn't until chlamydiae were finally discovered to be a closely related group of gram-negative intracellular bacteria that they had been given their own order, Chlamydiales, one family, *Chlamydiaceae*, and a single genus, *Chlamydia* (Moulder et.al. 1984; Satterwhite and Douglas 2013). The infection was not recognized as a sexually transmitted disease until 1976 because chlamydial disease was first identified in the eye and has a wide variety of symptoms or lack of symptoms that are identical to other diseases or syndromes (Schachter et al. 1976; Balogh 2014).

Etiology

Members of the Chlamydiales order and *Chlamydiaceae* family are the *Chlamydia* spp. *Chlamydiaceae* members had been first grouped by Everett et al. (1999). Based on variations in phenotypic, 16S ribosomal ribonucleic acid (rRNA), and 23S rRNA, *Chlamydia* was split into two genera, *Chlamydia* and *Chlamydophila*. Recent taxonomy of all presently identified *Chlamydiaceae* species into a single genus, the genus *Chlamydia*, has proposed by Sachse et al.

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(2015). Because of their tiny size that may pass through 0.45µm filters, the *Chlamydiaceae* were previously misidentified for viruses. The Chlamydiae are obligate intracellular parasites that depend on their eukaryotic hosts' metabolic resources to give energy for their own metabolism for development and copying by giving it high-energy substances like adenosine triphosphate (ATP) (Balogh 2014; Arif et al. 2020).

The outer cell wall of chlamydiae is similar to that of gram-negative bacteria. This bacterium's center dense core is encircled by a cytoplasmic membrane and a double-layer outer membrane, despite the absence of the stiff peptidoglycan layer seen in the majority of other bacteria. All members of the family share a lipopolysaccharide (LPS) in their cell walls. There is very little endotoxin action in LPS. The major outer membrane protein (MOMP), which is specific to each species, is an essential structural element of the outer membrane (Arif et al. 2022).

There are 18 serological variations (also known as serovars) in *C. trachomatis* due to variable sections in the gene encoding this protein (Witkin et al. 2017). The *C. pneumoniae* MOMP is homogenous, and only one serovar has been described, in contrast to the *C. psittaci* MOMP, which has similar variable areas. All members of the *Chlamydiaceae* family possess OMP 2, a second highly conserved outer membrane protein. This cysteine-rich protein is in charge of creating the many disulfide cross-links that give elementary bodies their stability (Schlossberg 2015).

Morphology and Developmental Cycle

Chlamydiaceae, unlike other bacteria, have a distinct developmental cycle that results in the formation of metabolically active, non-infected shapes termed reticulate bodies (RBs) and metabolically inactive, infectious forms called elementary bodies (EBs). "EB" is a tiny, 0.3 µm diameter cell that resembles spores in size and has an electron-dense nucleoid. The EBs can connect to receptors on host cells and induce absorption by the infected cell despite the fact that they cannot reproduce and are resistant to many harsh environmental stressors (Haider 2009; Arif et al. 2022). In this intracellular site, EBs changes into RBs, a replicating, metabolically active form without an electron-dense nucleoid that is roughly 0.5–1 µm in size. This type is osmotically weak since the vast cross-linked proteins are not present in RBs, but they are safeguarded by their intracellular location (Schlossberg 2015).

There are five main stages in *Chlamydia* developmental cycle. Following the EB's attachment and uptake, the metabolically inactive EB is then taken up by metabolically active RB. Then the RBs begin to multiply and proliferate, maturing from noninfectious RB into infectious EB. Finally, this host cell releases new EBs (Whittum and Hudson 2005; Al-Barzanji 2020).

An acute infection occurs with the EB's attachment to the surface of the eukaryotic cell. Surface microvilli are the site where binding occurs most frequently. The attachment to these sites may facilitate a quick and effective entry since the base of the microvilli serves as active transport sites for extracellular components into the host cells (Escalante et al. 1998).

Upon binding, the EBs is internalized in small, endocytic vesicles known as inclusions, however the method by which the EBs adhere to and enter cells is yet unknown. Since then, a number of unique mechanisms have been suggested (Wyrick et al. 1989). These mechanisms include microfilament-dependent phagocytosis, pinocytosis in non-clathrin-coated pits, and receptor-mediated endocytosis in clathrin-coated pits (Prain and Pearce 1989).

Two hours after infection, the new kinds of inclusions successfully avoid fusion with cellular lysosomes, and EBs begins to develop into RBs. Eight hours after infection, these RBs travel to the edge of the inclusion and begin replicating. The inclusion quickly fills in and grows in size as the RBs grow. The RB offspring re-condense back into infectious EBs that is metabolically dormant after a period of 24-48 hours. When the host cell ruptures or exocytosis occurs 48 to 72 hours after infection, the EB are kept in the inclusion lumen until they are freed and can then invade other cells. The range of the developmental cycle diverges depending on the species (Moulder 1991).

Classification

Human-infecting Chlamydiae are classified to 3 species, *C. trachomatis*, *C. pneumoniae*, and *C. psittaci*, based on their antigenic content, susceptibility to sulfadiazine, intracellular inclusions and ability to cause disease (Carroll et al. 2016). The 3 *Chlamydia* species infecting human and their characteristic features have been enlisted in Table 1.

Chlamydia trachomatis

General Characteristics

Humans are virtually entirely infected with *C. trachomatis*, which causes a number of clinical symptoms. 18 distinct serovars of *C. trachomatis* have been identified, each of which is linked with a different primary clinical symptom based on MOMP antigenic differences. The main way that *C. trachomatis* infections spread from person to person is through dealings with infected secretions. Some diseases, including neonatal pneumonia or inclusion conjunctivitis, are passed from mother to the child after birth (Batteiger and Tan 2015; Witkin et al. 2017).

Pathogenesis

Humans are the primary host for *C. trachomatis'*. Whereas the processes causing the tissue damage and inflammation produced on by *C. trachomatis* are not well known. The chlamydial species may infect a widespread domain of cells,

Table 1: *Chlamydia* with various features that cause human disease.

Property	*Chlamydia trachomatis*	*Chlamydia pneumoniae*	*Chlamydia psittaci*
Inclusion morphology	Circular and vacuolar	Circular and dense	Large, erratic in shape and dense
Glycogen in inclusions	Yes	No	No
Elementary body morphology	Circular	Circular and pears-shaped	Circular
Susceptible to sulfonamide	Yes	No	No
Plasmid	Yes	No	Yes
Serovars	15	1	≥4
Natural host	Humans	Humans and animals	Birds
Mode of transmission	Mother to child, person to person	Airborne, person to person	Airborne, bird excreta to humans
Major diseases	Trachoma, LGV ,STDs, infant and pneumonia	Pneumonia, pharyngitis, bronchitis and sinusitis	Psittacosis, pneumonia

including smooth muscle cells, monocytes and epithelial cells of the mucosa and blood vessels. The chlamydial EB enters the host cell by phagocytosis and is stored in a vacuole that does not combine with a lysosome, allowing the organism to survive inside the cell and avoid the host immune response (Darville and Hiltke 2010).

Apoptosis (organized cell death pathways) can be activated or deactivated by chlamydiae in infected host cells. In the acute infection process, the organism negatively regulates inflammation by causing surrounding host damaged cells, whereas in the event of chronic infection, the organism maintains the host cell's existence by blocking apoptosis, enabling it to persist (Wyrick 2010).

The Aspects of Disease

A- Trachoma

The Ebers Papyrus, which was written in Egypt 3800 years ago, provides a detailed description of the ancient eye disease "trachoma". The chronic keratoconjunctivitis causes blindness and scarring after starting as a severe inflammatory alteration in the conjunctiva and cornea (Tille 2017). The infection spread through the contact with infectious fluids on hands, towels, or flies. Clinical trachoma is related to the *C. trachomatis* serovars A, B, Ba, and C (Batteiger and Tan 2015).

Clinical Findings

Chlamydial conjunctival incubation lasts for 3 to 10 days. The contact of organisms with contaminated secretions, which may be found on clothing, fingers, or those carried by flies resulting in the infection (Satterwhite and Douglas 2013).

Lacrimation, mucopurulent discharge, conjunctival hyperemia, and follicular enlargement are the early signs of trachoma. Epithelial keratitis, sub epithelial infiltrates, and the expansion of limbal capillaries into the cornea are all visible when the cornea is examined under a microscope (pannus). As the pannus extends downward across the cornea, there are scarring of the conjunctiva, eyelid deformities (entropion, trichiasis) and an added insult caused by eyelashes sweeping across the cornea (trichiasis). With secondary bacterial infection, loss of vision progresses over a period of years. There are, however, no systemic symptoms or signs of infection (Carroll et al. 2016).

B- Lymphogranuloma Venereum

A sexually transmitted infection known as lymphogranuloma venereum (LGV), which is uncommon in North America but it's quite common in Africa, Asia, and South America. In Europe, the infection is resurfacing primarily among male homosexuals. Unlike *C. trachomatis* serovars A through K, which allow the mucosa to extend to the localized lymph nodes, *C. trachomatis* serovars L1, L2, L2b and L3 are invasive and produce LGV (DeVries et al. 2010; Lefebvre 2014).

Clinical Findings

Through few days to several weeks a small evanescent papule or vesicle may appear anywhere on the external genital organs, rectum and anus (Witkin et al. 2017). A primary vaginal lesion that manifests itself briefly at the location of the original infection identifies the disease. Particularly in individuals who are female, this lesion is usually tiny and impossible to see. The inguinal lymph nodes are commonly detected by the second stage of acute lymphadenitis, which causes them to swell and mat together, creating a significant region of groin swelling referred as the bubo (Dewart et al. 2018). During this stage, an infection may spread locally and result in granulomatous proctitis or it may spread systemically and produce fever. A small percentage of patients (more women than men) develop a chronic third stage of the disease, which results in the production of vaginal hyperplasia, rectal fistulas, rectal strictures, draining sinuses, and other symptoms (Chan et al. 2016).

C- Oculogenital Infections

Particularly in industrial countries, *C. trachomatis* serovars D-K cause a sexually transmitted disease and may also lead to an eye infection (inclusion conjunctivitis). Both adults and infants could get acute inclusion conjunctivitis from *C.*

trachomatis. Infection is transmitted, when infected vaginal discharges are touched into the eyes, or when a newborn is delivered through the birth canal (Workowski et al. 2021).
Auto-infection may happen but infrequent cases have been reported. Additionally, the organism can be obtained through hot tubs that lack proper chlorination, swimming pools, or by exchanging eye makeup. The symptoms of inclusion conjunctivitis include dilated eyes and a purulent secretion. It does not cause adult blindness, unlike trachoma (or newborns) (Carroll et al. 2016).
C. trachomatis can occasionally lead in epididymitis and nongonococcal urethritis in high sexually energized males. *C. trachomatis* also causes urethral inflammation, cervicitis, and pelvic inflammation in females, which can induce infertility and raise the probability of an ectopic pregnancy (Falasinnu et al. 2016).
Asymptomatic carriage in both sexes may remain, frequently for months. Many genital chlamydial infections in both sexes were silent or difficult to identify by clinical standards. Up to 50% of men and 70% to 80% of women with chlamydial genital tract infections are observed to be asymptomatic (Tille 2017).

D- Perinatal Infections

Inclusion conjunctivitis affects between one-fourth and one-half of infants born by the women who have *C. trachomatis* infection. The incubation phase typically lasts between 5 to 12 days after birth, although it can extend up to 6 weeks. Even though inclusion conjunctivitis affects the majority of babies, 10% to 20% of them progress to pneumonia. *C. trachomatis* infection acquired during pregnancy may last longer than two years in the nasopharynx, urogenital tract, or rectum (Chan et al. 2016).

E- Infant Pneumonia

10-20% of infants who contracted the mother's infection might suffer respiratory problems 2–12 weeks after birth, leading to pneumonia. Infants with the condition experience nasal blockage or discharge, severe tachypnea, a recognizable paroxysmal staccato cough, no temperature and eosinophilia. On radiographs, interstitial infiltrates and hyperinflation can be visible. An immunoglobulin M (IgM) antibody titer to *C. trachomatis* of 1:32 or greater was regarded as diagnostic in such newborn pneumonia. Systemic erythromycin is a good therapy for severe patients but oral erythromycin for 14 days is generally advised (Batteiger and Tan 2015).

Laboratory Diagnosis

Cytology, culture, direct detection of antigen or nucleic acid amplification test (NAAT), and serologic testing can all be used to detect *C. trachomatis* (Gaydos and Quinn 2005; Lefebvre 2014).

Treatment

Azithromycin, doxycycline, erythromycin, tetracycline, fluoroquinolones and other macrolide antibiotics are common drugs used to treat diseases that are caused by *C. trachomatis* (Kong et al. 2014).

Chlamydia pneumoniae

In 1965, a Taiwanese child's conjunctiva was the source of the initial isolation of the TWAR strain of *C. pneumoniae*. Because the inclusions formed in cell culture like those of *C. psittaci*, it was previously thought to represent a strain of psittacosis. The newly found strain was given the name "TWAR," an abbreviation for TW and AR, because the Taiwan isolate (TW-183) is serologically close to a pharyngeal isolate (AR-39) identified from a student in college from the United States **of** America (acute respiratory). There is just one recognized serotype of *C. pneumonia* (Pospisil and Canderle 2004).

General Characteristics

Due to the uniformity of the MOMP, all of the studied isolates of *C. pneumoniae* are immunologically identical, making it more homogeneity than both *C. trachomatis* and *C. psittaci*. The pear-shaped form of *C. pneumonia's* EB is one major variation between it and other *chlamydia* species (Carroll et al. 2016).

Pathogenesis

C. pneumoniae seems exclusively to be a human pathogen and did not determine in animals or birds as a carrier for disease. It is spread from individual to individual by nasal discharges via respiratory path. Of interest, *C. pneumoniae* infections are both endemic and epidemic. Regrettably, a few information were registered about the infection and the pathogen of *C. pneumoniae*, however it is analogues to *C. trachomatis* regarding for stimulation of inflammation that contributes to tissue damage (Hammerschlag et al. 2015).

Clinical Findings

Pneumonia, bronchitis, pharyngitis, sinusitis, and a flu-like disease have all been related to *C. pneumoniae*. It causes 5% to 10% of cases of community-acquired pneumonia. Young adults often have mild to moderate infections; the main characteristics of the clinical and laboratory differential diagnosis are infection with *Mycoplasma pneumonia* (Watson and Alp 2008).
There are multiple diseases of the upper and lower airways caused by *C. pneumoniae*. Pharyngitis is the most frequent disease to occur. Lower airway disease can develop together

with sinusitis and middle ear infection. Elderly or people with impaired respiratory systems could get severe pneumonia. It should be noted that *C. pneumoniae* frequently causes asymptomatic infection which is undiagnosed, or the slightly symptomatic infections. Furthermore, there is a link between *C. pneumoniae* infection and the formation of asthmatic signs (Wolff et al. 2018).

Laboratory Diagnosis

The most sensitive test for diagnosing *C. pneumoniae* infections is the MIF test, which is used in laboratories to detect *C. pneumoniae* infections by cytology, serologic testing, and other means. By utilizing the proper reagents, the test is species-specific and may identify IgG or IgM antibodies. Assays known as NAATs are also used to identify *C. pneumoniae* nucleic acid sequences in clinical specimens. Additionally, pharyngeal swab samples should be placed in a *chlamydia* transport medium and kept at 4°C for cell culture. *C. pneumoniae* develops better in HL and HEp-2 cells than in HeLa 229 or McCoy cells (Conklin et al. 2013).

Treatment

Tetracycline, certain fluoroquinolones, and the macrolides all could destroy *C. pneumoniae*. The treatment of *C. pneumoniae* infectious diseases with doxycycline, azithromycin, clarithromycin, levofloxacin, or moxifloxacin appears to be highly beneficial for patients (Hammerschlag et al.2015).

Chlamydia psittaci

General Characteristics

The elementary and inclusion bodies of *C. psittaci*, as well as its sulfonamide resistance, distinguishes it apart from *C. trachomatis*. Although birds and domestic animals frequently get this chlamydial species, human infections are very rare (Zhang et al. 2022).

Pathogenesis

All bird species have an endemic pathogen called *C. psittaci*. Psittacine birds, such cockatiels, parrots, and parakeets, are a significant source of disease in humans. Employees at chicken slaughter and working facilities, veterinarians, veterinary technicians, laboratory staff, avian quarantine station staff, taxidermists, farmers, animal rehabilitators, and zoo staff are among the professions thought to be at the highest risk for psittacosis (Kalmar et al. 2014; Vorimore et al. 2015).

The birds might be asymptomatic or suffer diarrhea. The disease is spread among people by aerosol inhalation. The organisms are released into the alveoli, where some of them are later taken up by alveolar macrophages and transmitted to nearby lymph nodes. From there, they spread all over the body while developing inside the cells of reticuloendothelial system. Because human-to-human transmission is uncommon, hospital patients are not required to be isolated (Balsamo et al. 2017).

Clinical Findings

Typically, a 5 to 15-day incubation period precedes the onset of a disease (Schlossberg 2015). The initial phase might be sneaky or sudden. The infection can appear clinically in people in a variety of ways, from silent infection or a moderate flu-like disease to a systemic illness with extreme unusual pneumonia. The usual symptoms of symptomatic infection comprises of an unexpected beginning of headache, fever, chills, malaise and myalgia. Additional symptoms include non-productive coughing, trouble breathing, chest tightness, changes in mental state, and hepatosplenomegaly (Chaber et al. 2021).

Laboratory Diagnosis

Psittacosis is usually diagnosed using serologic techniques. Only laboratories with biosafety third stage biohazard containment facilities may safely cultivate *C. psittaci* due to the risks involved in working with the agents. State health agencies actively engage in physician consultations concerning potential instances (Van Lent et al. 2012; Wolff et al. 2018).

In individuals with suspected psittacosis infections, complement fixation and indirect micro-immuno-fluorescence have been employed to identify anti-*C. psittaci* antibodies. It is possible to attempt the isolation in cell cultures, but it's necessary to keep in mind that *C. psittaci* can infect lab animals. NAATs are not yet available for purchase. There have been tests using wide spectrum, multi-species pan-*Chlamydia* probes (Read et al. 2013; Balsamo et al. 2017).

Treatment

The preferred treatment for psittacosis is tetracycline. When it is not treated, it has a 20% mortality rate (Schlossberg 2015).

Conclusion

Chlamydia is microscopic organisms that proliferate in the cytoplasm of their host cells and also has distinctive biphasic developmental cycles. *Chlamydia* species that can cause human disease include *C. trachomatis*, *C. pneumoniae*, and *C. psittaci*. *C. trachomatis* is the cause of sexually transmitted diseases. A range of upper and lower respiratory infections are produced by the *C. pneumoniae*. Just contact with birds

can transmit *C. psittaci*. Psittacosis might be moderate or obvious, but it has also been shown to cause severe pneumonia and sepsis, both of which have a significant fatality rate.

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