Chapter

Treatment of Chlamydial Infections

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Abstract

Sexually transmitted infections (STIs) are a major health problem with an estimated burden of disease transmission as high as one million new cases per day globally. *Chlamydia trachomatis,* a member of the genus *Chlamydia*, is one of the most common and curable causative agents of STIs. *C. trochomatis* infections usually affect sexually active young adults and adolescents; and are composed of a broad spectrum of diseases varying from asymptomatic infection to severe genito-urinary infection leading to infertility and acute or chronic ocular infection (trachoma), which may result in blindness and pneumonia. Among the members of the genus *Chlamydia,* there are also two pathogenic species, *Chlamydia pneumoniae* and C*hlamydia psittaci* which are responsible for acute respiratory tract infections and febrile illness in humans. The incidence, pathophysiology, and diagnostic methods are discussed in detail in the previous chapters. The purpose of this chapter is to elucidate the management of infections due to *C. trachomatis, C. pneumoniae,* and *C. psittaci* including antibiotic susceptibility and resistance mechanisms, treatment recommendations for ocular infections, genito-urinary and respiratory tract infections, and management of sex partners, pregnant women, neonates, and children according to the latest data.

Keywords: *Chlamydia trachomatis*, *C. pneumoniae*, *C. psittaci*, chlamydial infection, antibiotic treatment

1. Introduction

Chlamydia spp. (order *Chlamydiales*; family *Chlamydiaceae*; genus *Chlamydia*) are obligatory intracellular gram-negative bacteria that cause acute and chronic infections in humans and animals. Genus *Chlamydia* is the sole member of the family *Chlamydiaceae* and includes nine different species. Among them, *C. trachomatis* and *C. pneumoniae* are primarily human pathogens, whereas *C. psitacii*, *Chlamydia abortus,* and *Chlamydia felis* mainly infect animals but occasionally cause zoonotic diseases [1, 2].

Sexually transmitted infections (STIs) are a major health problem with an estimated burden of disease transmission as high as one million new cases per day globally. *C. trachomatis* is one of the most common curable causative agents of STIs and usually affects sexually active young adults and adolescents. The pathogen is the causative agent of a disease called chlamydia, which constitutes a broad spectrum of illnesses varying from asymptomatic infection to severe genital infection leading

to infertility, especially in women. Apart from the spread by sexual activity, direct personal contact with shared contaminated items may also cause a chronic ocular infection called trachoma and result in blindness if left untreated. Finally, perinatal transmission of the agent is another undesired entity with adverse clinical outcomes. *C. pneumoniae* and *C. psittaci* are two other pathogens in the genus *Chlamydia* and are responsible for acute respiratory tract infections and febrile illness in humans. However, *C. trachomatis* draws much attention as chlamydial infections account for significant morbidity worldwide. The global control of chlamydia faces some difficulties such as diagnostic challenges, social stigma, and the necessity of routine screening programs due to the asymptomatic course of the disease also concerns about treatment adherence and antibiotic efficacy in extra-genital involvements. The incidence, pathophysiology, and diagnostic methods of chlamydial infections are discussed in detail in the previous chapters. The purpose of this chapter is to elucidate the management of human chlamydial infections in every aspect including antibiotic susceptibility and resistance mechanisms, treatment recommendations for ocular infections, genito-urinary and respiratory tract infections, and also the management of sex partners, pregnant women, neonates, and children according to the latest data.

2. Antibiotic susceptibility and resistance mechanisms in human chlamydial infections

Chlamydiae are obligate intracellular bacteria that have a distinctive bi-phasic life cycle that typically lasts 40–72 hours [3]. The extracellular infectious form is called the elementary body (EB); however, EB does not have metabolic activity and is resistant to antibiotics. On the other hand, the intracellular form, the reticulate body (RB), is the replicative element that synchronously duplicates every 2 to 3 hours and is the target for antibacterial agents [2, 3]. To achieve optimal bacterial clearance, antibiotics with good intracellular penetration and preservation of antibiotic concentration throughout the life-cycle of the organism are needed.

Chlamydiae are sensitive to a wide range of antibiotics such as tetracyclines, macrolides, fluoroquinolones, rifamycins, and clindamycin, which prevent deoxyribonucleic acid (DNA) and protein synthesis and have good activity against intracellular bacteria. Beta-lactam antibiotics and especially penicillins may exhibit *in vitro* efficacy but are linked to the persistence of chlamydial infection and therefore are not recommended for treatment. However, studies revealed that amoxicillin may exhibit higher efficacy than erythromycin in pregnant women with chlamydia disease and due to the paucity of antibiotic options in this period amoxicillin might be offered as an alternative therapy during pregnancy [4–6]. Among other antibacterial classes, aminoglycosides and glycopeptides are ineffective against chlamydial infections since *Chlamydiae* are constitutively resistant. Also, trimethoprim is not effective against *Chlamydia* spp. but *C. trachomatis* is susceptible to sulfonamides [7].

Despite having a severely condensed genome of only about 1 megabase, *Chlamydia* spp. have a highly reserved genomic structure and evidence of horizontally acquired foreign DNA is scarce. Antibiotic resistance is not common in human chlamydial infections but significant resistance phenotypes such as heterotypic resistance, which is characterized by few organisms (less than 1%) that are resistant to antibiotics at concentrations higher than their minimal inhibitory concentrations (MIC), might be expressed [8]. Currently, *in vitro* susceptibility testing of *Chlamydia* spp. is not

methodized because resistant clinical isolates are rare; without host cells, the organism cannot be recovered; the identification and interpretation of antibiotic resistance are not standard; and the impact of heterotypic resistance is uncertain [3].

In vitro studies have shown that antibiotic exposure can lead to the accumulation of point mutations, which result in antibiotic resistance in *Chlamydiae.* Stable genetic resistance and transmission of resistance genes across strains have not been reported for human chlamydial infections; however, genetically stable tetracycline resistance has been detected in *Chlamydia suis* (which causes disease in pigs) isolates and acquired tetracycline resistance (Tet^R) has been shown *via* horizontal gene transfer and homologous recombination mechanisms [3, 6, 9, 10].

As mentioned above, the mechanisms that might be related to antibiotic resistance in human chlamydial infections are the persistence of the microorganism, heterotypic resistance, and antibiotic point mutations, which will be detailed as follows:

2.1 Chlamydial persistence

When exposed to stressful circumstances such as beta-lactam antibiotics, interferon-gamma (IFN-γ), a lack of iron supplements, or amino acids, *Chlamydia* spp. exhibit characteristics of chlamydial persistence [3, 11]. Among them, beta-lactam antibiotics constitute a major problem since they are among the groups of antibiotics that are most frequently used for the treatment of various infections [12]. Similar to gram-negative bacteria, *Chlamydia* spp. have an outer membrane but they lack peptidoglycan while having genes that code for proteins necessary for its formation [13]. Studies have shown that *C. pneumoniae* and *C. trachomatis* can synthesize an unusual truncated type of peptidoglycan, which may serve as a target for beta-lactam antibiotics. However, following antibiotic exposure, the pathogen enters a stage known as persistence in which the stressed *Chlamydiae* remain viable but non-culturable. Moreover, it was shown that the persistence of *Chlamydiae* may remain in culture for months and result in clinical treatment failure because of phenotypic resistance to antibiotics, which are often quite efficient [3, 14]. As an example azithromycin, phenotypic resistance emerged in *C. trachomatis* isolates after pre-exposure to penicillin in experimentally infected endometrial epithelial cells *in vitro*, rendering the pathogen refractory to the given medication [15]. Azithromycin and ofloxacin resistance in *C. pneumoniae* and doxycycline resistance in *C. trachomatis* have both been demonstrated to increase in response to environmental changes [16, 17]. More importantly other than phenotypic resistance, recent data indicate that chlamydial persistence may potentially be associated with chronic diseases such as reactive arthritis, chronic prostatitis, asthma, and atherosclerosis [3, 7].

2.2 Heterotypic resistance

Although many antibiotics are effective against chlamydial infections, antibiotic failure rates that vary between 5 and 23% of cases have been reported in chlamydia disease. However, chlamydial resistance is not frequent in humans. Much of these failures have been connected to re-infection and antibiotic compliance issues [6]. In the literature, antibiotic-resistant, *C. trachomatis* clinical isolates are scarce and displayed characteristics of heterotypic resistance as previously explained [3]. It was hypothesized that heterotypic resistance may be due to the slow growth of the organism in certain environments or the exhibition of an adaptive response that makes the

pathogen resistant to antibiotics [9]. On the other hand, resistant isolates exhibited reduced fitness, which impaired long-term survival or led to the loss of resistance pattern upon serial passaging. It is considered that this phenotypic alteration seems to impair the transmission and therefore prevents the emergence of non-susceptible clones [3, 18, 19].

2.3 Genes and mutations associated with human chlamydial infections

For the treatment of chlamydial infections, tetracyclines and macrolides are quite effective. It is commonly acknowledged that antibiotic misuse or overuse increases the chance of microorganisms' developing antibiotic resistance, which poses a critical and dangerous public health issue globally [20, 21]. However, human chlamydial infections have not been associated with persistent and heritable genetic resistance. *In vivo* studies have shown that *Chlamydiae* may acquire resistance through several mutations to antimicrobials [3]. Additionally, it has been demonstrated that the serial passage of *Chlamydia* spp. leads to the selection of resistant isolates if exposed to sub-inhibitory antibiotic doses [21].

Tetracyclines are bacteriostatic antibiotics that prevent aminoacyl tRNAs from binding with ribosomal 30S subunit, hence inhibiting bacterial protein production [3]. Doxycycline is a semisynthetic tetracycline and is recommended as the primary therapeutic option against *C. trachomatis* infections. Apart from human infections tetracyclines are widely used in veterinary medicine. The emergence of genetically stable TetR resistance is first described in the 1990s and observed in *C. suis* isolates recovered from pigs both healthy and sick. Since then, the threat of transmission of TetR resistance to other members of *Chlamydiae* is of great concern [10]. Although *in vitro* tests have shown that TetR may be horizontally transmitted from *C. suis* to clinical isolates of *C. trachomatis* during co-culture; to date, antibiotic failure due to stable TetR has not been reported in human chlamydial infections. In a study by O'Neill et al., a porB gene mutation was discovered in two clinically resistant isolates but the isolates were reported to be phenotypically sensitive to tetracyclines *in vitro* and stable genetic resistance was not evident [22].

Macrolides are a group of antimicrobials that bind to bacterial 50S ribosomal subunit and impair bacterial growth due to the inhibition of protein synthesis. They are also effective front-line classes of antibiotics used for the treatment of chlamydia infections. The size of the macrocyclic lactone ring determines whether the group is classified as having a 12-, 14-, 15-, or 16-membered ring. Among macrolides, erythromycin (14-membered first generation), clarithromycin (14-membered second generation), and azithromycin (15-membered) are widely used for chlamydial infections [23]. The 23S rRNA gene alterations that make antibiotics less able to bind to the 50S ribosomal subunit, which is necessary for bacteriostatic action, usually cause macrolide resistance. It has been demonstrated that mutations to the 23S rRNA gene can cause *C. trachomatis* and *C. psittaci* to become resistant to macrolides. In addition by means of alterations in the rplD and rplV genes, *C. trachomatis* may also exhibit macrolide resistance [21].

Fluoroquinolones are broad-spectrum widely used bactericidal antibiotics that function by blocking the DNA gyrase and DNA topoisomerase IV enzymes needed for bacterial DNA synthesis [24]. The first-generation fluorinated quinolones include norfloxacin, ciprofloxacin, and ofloxacin. The usage of norfloxacin is restricted to the treatment of STIs and urinary tract infections because of its relatively low serum levels and inadequate tissue penetration. On the other hand, ciprofloxacin is

an effective antibiotic that is still being widely used for the treatment of a number of gram-negative systemic infections. The more recent fluoroquinolones, such as levofloxacin (an isomer of ofloxacin) and moxifloxacin, have improved efficacy against gram-positive respiratory tract infections [25]. Fluoroquinolones generally have good activity against chlamydial infections; however, *in vitro* experiments have shown that sub-inhibitory antibiotic concentrations may lead to resistance in various *Chlamydia* spp. including *C. trachomatis*. It was discovered that mutations in the gyrA, parC, and ygeD genes may cause *C. trachomatis* to become resistant to fluoroquinolones, while changes in the gyrA gene may cause *C. pneumoniae* to become resistant [21].

Bactericidal drugs known as rifamycins selectively bind to the β-subunit of RNA polymerase, which result in the inhibition of the transcription process. Although they have strong *in vitro* activity, these medicines are not the first-line treatments for chlamydial infections. *In vitro* studies have demonstrated that *Chlamydia* spp., such as *C. pneumonia*, *C. trachomatis*, and *C. psittaci*, rapidly establish a resistance to rifamycins following exposure to sub-inhibitory antibiotic concentrations [3, 26]. In most research, rifampin (RIF) serves as a representative of rifamycins and rifampin resistance mostly results from rpoB gene nucleotide mutation [21].

Resistance to lincomycin, a bacteriostatic protein synthesis inhibitor, is noted in *in vitro*-generated *C. trachomatis* strains exposed to sub-inhibitory antibiotic concentrations. It was revealed that resistant strains exhibit mutations in 23S rRNA genes [3, 27].

3. Management of human chlamydial infections

Management of human Chlamydial infections will be discussed as separate sections and will include the most common etiological agents: *C. trochomatis, C. pneumoniae*, and *C. psittaci*, respectively.

3.1 Management of *C. trochomatis* infections

Infections due to *C. trochomatis* are caused by 19 serovars, which affect the ocular, genito-urinary tract, and pulmonary systems. Ocular infections mainly result from serovars A-C, which led to trachoma and to a lesser extent serovars D-K which led to inclusion conjunctivitis and sometimes infant pneumonia [28]. On the other hand, genito-urinary tract infections include chlamydia and lymphogranuloma venereum (LGV), which are caused by serovars D-K and serovars L1-L3, respectively [2, 18, 29].

In most men and women, chlamydia maintains an asymptomatic course and becomes a silent reservoir for infection [5, 30]. Spontaneous clearance of the pathogen may occur gradually over years but if chlamydia is not treated effectively, major medical conditions with both immediate and long-term complications could arise [3, 31, 32]. These health problems include clinical or subclinical pelvic inflammatory disease (PID) leading to chronic pelvic pain, infertility, ectopic pregnancy and Fitzhugh-Curtis syndrome in women; pre-term delivery, inclusion conjunctivitis, and pneumonia in the newborn; and reactive arthritis in both sexes [5, 33, 34]. It was also shown that untreated chlamydia may promote the spread of other STIs, such as human immunodeficiency virus (HIV) [35]. Therefore to prevent chlamydia-associated diseases and to decrease the degree of transmission to susceptible populations, presumptive or guided therapy should be started in all suspected or confirmed chlamydia infections including asymptomatic diseases.

3.1.1 Treatment of ocular infections due to C. trachomatis

The most prevalent infectious etiology of blindness all over the world is *C. trachomatis*, which leads to ocular illnesses known as trachoma and adult/neonatal inclusion conjunctivitis. Trachoma is transmitted through direct or indirect contact with objects such as hands, fomites, bed sheets, eye-seeking insects, and polluted towels in unsanitary settings [28]. On the other hand, inclusion conjunctivitis is spread by perinatal transmission in neonates or by hand-to-eye inoculation of infected genital secretions in adults.

3.1.1.1 Treatment of trachoma

Trachoma specifically targets the world's poorest regions. According to data from June 2022 provided by the World Health Organization (WHO), 125 million people reside in areas where trachoma is an endemic disease [36]. Trachoma is initiated in early childhood and recurrent ocular infection leads to conjunctival scarring and eventually blindness. Trachoma incidents decreased as a result of general improvements in living conditions, but recent predictions show that 1.9 million individuals worldwide are blind or have significant vision problems as a result of trachoma. The WHO is implementing the SAFE strategy as part of a global initiative to eradicate blinding trachoma. The SAFE strategy includes early surgical intervention for trichiasis (contact between the eyelids and the eye that results in blindness), widespread use of antibiotics like azithromycin to manage infections, regular facial hygiene, and advancements in living conditions to minimize bacterial spread.

The World Health Organization divides trachoma into five stages, with Stages 1 and 2 characterized by trachomatous inflammation that is follicular (TF) or intense (TI), respectively; Stage 3 by trachomatous scarring (TS); Stage 4 by trachomatous trichiasis (TT); and Stage 5 by corneal opacity (CO), which results in visual impairment and blindness.

Antibacterial treatment is advised in the first two stages of trachoma's inflammatory phase (stages 1 and 2) and before scarring sets in, which is Stage 3 [37, 38]. The antibacterial drug of choice is oral azithromycin because it can be taken as a single dose, has a relatively long half-life, and is more concentrated in tissue than in plasma [39]. Adults and children are given a single oral dose of azithromycin at doses of 1 g and 20 mg/kg, respectively. In case of antibiotic failure, topical 1% tetracycline eye ointment, twice a day, for 6 weeks or erythromycin, 20 mg/kg (maximum 1 gr), orally, twice a day, for 14 days can be given. In stages 3 and 5, no treatment option exists but in Stage 4 surgical treatment is advocated for the protection of the cornea from abrasion.

Because trachoma is a major public health issue, the WHO recommends widespread administration of antibiotics in places with populations of 100,000–250,000 people and when the prevalence of the active trachoma, Stage 1 (TF), is greater than 5% in children aged 1–9 years. According to the most recent estimate of TF prevalence and until the percentage falls below 5%, it is advised that all inhabitants receive antibiotic therapy on an annual basis. It is also recommended that all inhabitants receive antibiotic medication annually up until the most current estimate of the prevalence of TF drops below 5% [40].

3.1.1.2 Treatment of neonatal inclusion conjunctivitis

Neonatal inclusion conjunctivitis is a preventable yet an undesired complication of active maternal chlamydial infection that affects newborns. Perinatal transmission of

C. trachomatis to neonates during vaginal delivery occurs as high as 60% of the cases [41]. Though neonatal infection may retain an asymptomatic course, the infection is usually progressive and mostly affects the conjunctiva, nasopharynx, and lungs. Among infants presenting with conjunctivitis, the likelihood of neonatal-acquired inclusion conjunctivitis varies between 20 and 64% [41, 42]. Conjunctivitis that is left untreated can last for months and cause corneal and conjunctival scarring. Also, the disease may spread to the lungs and cause infantile pneumonia [41]. To prevent the systemic spread of the agent, all infants infected with *C. trachomatis* should receive treatment even if they are asymptomatic.

The neonatal inclusion conjunctivitis incubation period is generally 5–12 days after birth. Conjunctivitis in newborns younger than 30 days should be investigated for chlamydial infection, particularly if the mother has a past history of illness. Infection with ophthalmia neonatorum should also be considered and ocular samples should be examined for *Neisseria gonorrhoeae* [43].

Neonatal inclusion conjunctivitis is treated with oral erythromycin base or ethyl succinate, 50 mg/kg/day in four divided doses for 14 days. The alternative treatment is oral azithromycin 20 mg/kg/day for 3 days [44]. Both antimicrobials have been associated with infantile hypertrophic pyloric stenosis (IHPS) in infants less than 6 weeks of age; consequently, newborns medicated with any of these antimicrobials should be monitored for IHPS [45]. Compared to oral therapy, topical medication has been demonstrated to be ineffective in eliminating nasopharyngeal colonization and linked to persistent infection [46].

There is currently no effective prophylaxis for the prevention of newborn inclusion conjunctivitis, and neonatal gonococcal ophthalmia neonatorum prophylaxis does not offer protection against chlamydial conjunctivitis. Implementing health policies for routine antenatal testing and treatment of pregnant women at risk for chlamydia is advocated as a substitute, however, due to the financial burden of the strategy the screening programs cannot be utilized globally [47].

3.1.1.3 Treatment of adult inclusion conjunctivitis

Adult inclusion conjunctivitis, a self-limiting condition, is brought on by the inoculation of the eye with infected vaginal fluids. Without treatment, the infection might resolve spontaneously in 6–18 months but more frequently the disease progresses to complicated/uncomplicated chlamydia or impair reproductive health. Also, ocular complications such as conjunctival scarring, punctate keratitis, and iritis may take place. To prevent morbidity and related complications, treatment should be given to all patients. Topical antibiotics alone are not sufficient due to the possible concomitant urogenital infection; therefore, combined therapy with systemic antibiotics is necessary. Systemic oral antibiotic therapy options include azithromycin 1 g, single-dose; doxycycline 100 mg, twice a day for 7 days; tetracycline 100 mg, four times a day for 7–10 days; or erythromycin 500 mg, four times a day for 7 days. Of note, the usage of tetracycline and doxycycline during pregnancy is contraindicated and should be avoided. Adjunctive topical treatment of adult inclusion conjunctivitis includes antibacterial drugs such as erythromycin, gentamicin, tetracycline, and fluoroquinolones [48].

3.1.2 Treatment of urogenital and extra-genital infections due to C. trachomatis

In this section, the management of chlamydia and LGV will be discussed in detail.

3.1.2.1 General approach to chlamydia disease and treatment options

The key to the management of chlamydia starts with clinical suspicion. Patients who have chlamydia disease may present with urinary symptoms and might be misdiagnosed as urinary tract infections. Also, patients who experienced sexual assault or sexually active adolescents may be reluctant to give the right information or may be unaware of the situation. Therefore in case of doubt about chlamydia, clinicians should immediately initiate diagnostic methods and send appropriate clinical specimens to the laboratory for testing. Moreover, co-infection with other STIs including gonorrhea, HIV, and syphilis must be investigated [49]. Early appropriate antibiotic therapy is important and the patient's age, pregnancy status, access to medication, and treatment compliance should all be taken into account. In case of severe PID, consultation with obstetrics/gynecology and in case of ocular involvement consultation with ophthalmology should be performed. In order to prevent reinfection, patients should be informed about safe sex practices and the necessity of partner management. Finally, a patient-based follow-up test strategy should be determined after the completion of treatment [45].

For treatment purposes, chlamydia is mainly categorized into two forms according to the anatomical site involved. Oropharyngeal and lower genital tract involvement (cervicitis/urethritis/epididymitis/anorectal infection) are defined as uncomplicated disease, whereas upper genital tract involvement [salpingitis/endometritis/pelvic inflammatory disease (PID), Fitzhugh-Curtis syndrome] is defined as a complicated disease.

The laboratory diagnosis of chlamydia has significantly improved as a result of the switch from culture-based to molecular-based testing procedures [50]. Because of its high sensitivity, high specificity, and convenience to be utilized on a variety of clinical specimen types, nucleic acid amplification testing (NAAT) is the most efficient method [45, 51, 52]. Unfortunately, NAAT may not always be available in every facility and patients who are at risk for STIs may sometimes be unlikely to return for test results; therefore, WHO recommends consideration of a syndromic approach (to detect and treat patients with STIs based on particular symptoms and signs, which are indicators of infection) in these situations [43, 53]. Also when administering single-dose or multidose regimens to patients, medicine should be given with the first dosage being closely monitored on-site and in the clinic [43].

Doxycycline 100 mg, orally, twice a day for 7 days (or delayed release 200 mg tablet, once a day for 7 days) is the recommended regimen for non-pregnant adults and adolescents with uncomplicated chlamydia involving cervical, urethral, rectal, and oropharyngeal sites. Oral azithromycin 1 g single-dose is the alternative treatment regimen for uncomplicated chlamydia. Previously, single-dose azithromycin had been another preferred option due to its high efficacy against *C. trachomatis,* better adherence due to once-daily usage, and similar adverse effect profiles. However, mounting evidence suggests that azithromycin has a lesser rate of microbiologic cure than doxycycline especially in treating rectal and oropharyngeal infections, and currently, it is accepted as the alternative treatment option [45].

According to a meta-analysis and a Cochrane systematic review that included men with urogenital chlamydia, a 7-day course of doxycycline achieved higher success rates than single-dose azithromycin regimens [54, 55]. Furthermore, as shown by two randomized, double-blind clinical trials and several nonrandomized studies doxycycline regimen may be 20% more effective than azithromycin in managing rectal *C. trachomatis* infection in both women and men who have sex with men (MSM) [54, 56–59].

Similar findings have been published from prospective, open-label research involving individuals with oropharyngeal chlamydia and a 7-day doxycycline regimen showed less treatment failure when compared with azithromycin single-dose treatment [60]. Urogenital *C. trachomatis* infections may be accompanied by concomitant anorectal and oropharyngeal chlamydia, which might remain asymptomatic for that reason doxycycline regimen should be chosen as the primary treatment regimen in adults and adolescents with chlamydia except in patients who are unlikely to be able to complete the 7-day doxycycline course and pregnant women. In such cases, azithromycin regimen should be considered [45, 61, 62].

Among other therapeutic options erythromycin base 500 mg, orally, four times a day for 7 days, is also an effective alternative regimen but gastrointestinal side effects are frequent and nonadherence might be observed. Fluoroquinolones are highly active against *C. trachomatis* infections and levofloxacin 500 mg, orally, once a day for 7 days or ofloxacin 200–400 mg, orally, twice a day for 7 days are other alternative medications yet the regimens are more expensive and cannot be offered during pregnancy and breastfeeding periods [43].

3.1.2.2 Treatment of cervicitis due to C. trachomatis

Chlamydia majorly presents as cervicitis in women. The majority of patients who have chlamydia cervicitis are asymptomatic or present with mild nonspecific symptoms such as irregular vaginal discharge, intermenstrual or post-coital bleeding, and dyspareunia. Patients should be evaluated for PID since cervicitis may be a marker of upper genital tract involvement [43]. In order to prevent the complications that impair reproductive health and to avoid sexual and perinatal transmission to susceptible people, all women with chlamydia cervicitis should receive treatment for chlamydia. However, under the following circumstances, presumptive antibiotic treatment for *C. trachomatis* should be administered:

- The patient is prone to contracting *C. trachomatis* infection (e.g., women under 25 years old, women who have a new sex partner, a sex partner with multiple partners, or a sex partner with an STI) and testing with NAAT/quality-assured rapid test with a minimum sensitivity of 80% and specificity of 90% are not possible.

- The patient is prone to contracting *C. trachomatis* infection as above and NAAT/quality-assured rapid tests are accessible in the facility but the results are not obtainable at the same appointment, and patient follow-up cannot be assured [43, 53].

- The suggested treatment for chlamydia cervicitis in non-pregnant adults and adolescents is a 7-day course of doxycycline. Alternative treatment plans include a single dosage of azithromycin or a 7-day course of either erythromycin or ofloxacin [53]. Patients should also be assessed for concomitant gonococcal infection and other STIs.

3.1.2.3 Treatment of urethritis due to C. trachomatis

It was shown that nearly all women who have chlamydia cervicitis also have concomitant urethritis [63]. In men, chlamydia disease generally involves the male

urethra. *C. trachomatis* is a frequent cause of acute urethritis in young, sexually active individuals and is responsible for more than half of all instances of non-gonococcal urethritis [43, 64, 65]. Most cases of chlamydia urethritis in both men and women go unnoticed. In women, urinary symptoms such as frequent urination and dysuria are common, whereas in male patients additional complaints of urethral discharge and discomfort are prevalent [66]. Ideally, treatment should be given after pathogen detection but quick access to diagnostic data might not always be possible; therefore, presumptive treatment should begin for non-gonococcal urethritis (NGU) for those who have symptoms of urethral discharge from the penis, and patient follow-up cannot be assured or test results are not accessible on the same day. Evaluation and treatment of NGU should also include gonococci. For gonococci, a single intramuscular dose of ceftriaxone (500 mg [or 1 gr for individuals ≥150 kg]) might be considered but the choice of appropriate treatment regimen should be guided according to the local antibiotic resistance patterns [43, 53]. The recommended and alternative treatment options for urethritis due to *C. trachomatis* are the same as other uncomplicated chlamydia infections mentioned above.

3.1.2.4 Treatment of rectal infections due to C. trachomatis

Acute proctitis and proctocolitis are two distinct manifestations of chlamydia in individuals who have anal exposure to *C. trachomatis* by oral, genital, or digital interaction. Proctitis is the inflammation of the distal part of the rectum and presents with anorectal discomfort, tenesmus, or rectal discharge, whereas proctocolitis is the extension of proctitis to the colonic mucosa above the anus and additional symptoms such as diarrhea or abdominal cramps may be seen [43]. Rectal *C. trachomatis* infection rates in MSM and women are similar and range from 1 to 18%. It was shown that in women, the rectal disease may accompany urogenital infection in up to 83% of cases and can occur regardless of receptive anal sexual behavior [61]. In MSM, the incidence of asymptomatic rectal infection is high and reaches above 80% [62].

Either asymptomatic or not, microbial eradication at the rectal site is crucial for treating urogenital chlamydia. Due to its higher microbiologic cure rates and asymptomatic nature of rectal chlamydia disease, doxycycline is the recommended antibiotic choice for anal infections caused by *C. trachomatis* [54, 59].

A 7-day course of doxycycline 100 mg orally, twice a day is the suggested regimen for proctitis and proctocolitis due to chlamydia. Doxycycline treatment should be extended to 21 days if symptoms indicating lymphogranuloma venereum such as anal bloody discharge, tenesmus, perianal or mucosal ulcers are present. Erythromycin 500 mg, orally, 4 times a day for 14 days is the alternative regimen. Treatment of patients with sexually acquired proctitis should also include treatment for gonococci. For gonococci, a single intramuscular dose of ceftriaxone (500 mg [or 1 gr for individuals ≥150 kg]) should be added. WHO advises a syndromic approach in cases with anorectal discharge and a reported history of receptive anal sex to allow treatment on the day of the visit in regions that have little to no molecular testing or laboratory capacity [53].

3.1.2.5 Treatment of oropharyngeal infections due to C. trachomatis

C. trachomatis can lead to oropharyngeal infection in those having receptive oral intercourse, same as gonorrhea [43]. The prevalence of oropharyngeal chlamydia infection approximately ranges from 1 to 3% in MSM and women [61]. Without

therapy, oropharyngeal chlamydia can spread to other genital locations *via* sexual contact [67, 68]. The optimal antibiotic regimen for oropharyngeal chlamydia has not been thoroughly investigated. It was revealed that doxycycline is more efficient in treating oropharyngeal chlamydia than azithromycin similar to rectal chlamydia infections. The recommended treatment is a 7-day course of oral, twice a daily 100 mg doxycycline [45].

3.1.2.6 Treatment of epididymitis due to C. trachomatis

An uncomfortable, swollen, and inflamed epididymis is symptom of the clinical illness known as epididymitis. Unilateral testicular pain and palpable swelling are common in patients with acute epididymitis. The disease sometimes involves the testicles and is called epididymo-orchitis. Testicular torsion is a complication of epididymitis that requires emergency surgery. Acute epididymitis caused by STIs is a typical complication of young, sexually active men, and the condition frequently coexists with urethritis. Gonococci and *C. trachomatis* testing should be performed on all suspected instances of acute epididymitis. If patients are unable to follow the prescribed antibiotic regimen or if significant pain or fever points to complications such as testicular torsion, abscess, or necrotizing fasciitis, patient evaluation for hospitalization should be considered. All sexually active men who have acute epididymitis should get presumptive therapy Doxycycline 100 mg orally, twice a day for 10 days, is the recommended treatment for acute epididymitis caused by *C. trachomatis*. The therapy should include treatment for gonococci and a single intramuscular dose of ceftriaxone (500 mg [or 1 g for individuals ≥150 kg]) should be added [43]. In patients who report insertive anal sex, enteric organisms might be involved in epididymitis. In such cases, fluoroquinolones are effective against both gram-negative enteric bacteria and chlamydia therefore ofloxacin 300 mg orally, twice a day for 10 days or levofloxacin 500 mg orally, once a day for 10 days (plus ceftriaxone for gonococci) can be offered [43, 69].

3.1.2.7 Treatment of PID due to C. trachomatis

PID is an inflammatory disease affecting female upper genital tract organs including endometritis, salpingitis, tubo-ovarian abscess, and pelvic peritonitis. PID is often caused by STIs, with *N. gonorrhoeae* or *C. trachomatis* as the etiological agent in up to half of the cases [43]. Women with PID frequently exhibit mild and vague symptoms such as abnormal vaginal discharge, spotting, and dyspareunia but may also be asymptomatic. Untreated PID might impair reproductive health and lead to complications such as tubal infertility and ectopic pregnancy [53]. Moreover, PID can also extend to abdominal organs and cause Fitzhugh-Curtis syndrome, which requires in-patient treatment and is characterized by peritonitis and inflammation of the liver capsule [32]. Since PID is related to severe morbidity, presumptive therapy should begin for sexually active women at risk for STIs who complain of pelvic or lower abdominal discomfort and there is tenderness on pelvic examination [43].

The women who present with PID should also be evaluated for the need for hospitalization when there is suspicion of surgical emergency, presence of tubo-ovarian abscess, pregnancy status, severe illness [nausea, vomiting, and fever >38.5°C (101°F)], or no clinical benefit from oral antibiotic treatment. Broad-spectrum antibiotics against probable agents should be initiated as soon as possible. Antibiotics should cover *C. trachomatis* and *N. gonorrhoeae* even if endocervical testing is negative as

upper genital tract infection cannot be fully ruled out [43]. The recommended regimen for *C. trachomatis*-related PID is doxycycline 100 mg, orally, twice a day for 14 days combined with antibiotics active against gonococci. Facultative anaerobic bacteria and enteric gram-negative rods are among other etiologic agents that should be considered for the treatment of PID [43].

3.1.2.8 Treatment of LGV

C. trachomatis serovars L1, L2, or L3 are the culprits behind LGV and are responsible for a more invasive form of the chlamydial disease called LGV characterized by genital ulcer disease, lymphadenopathy, and proctocolitis. Among them, proctocolitis is a frequent finding in LGV and is especially seen in MSM. Inflammatory bowel disease-like symptoms, such as mucoid or hemorrhagic rectal discharge, anal pain, constipation, fever, or tenesmus, might be clinical indicators of proctocolitis. Until recently, LGV was exclusively a problem in tropical and subtropical regions of the globe with little resources. Since 2003, endemic LGV cases have been observed in MSM across Europe [70, 71]. If untreated, rectal LGV may be invasive and cause chronic colorectal fistulas and strictures. LGV can also cause inguinal or femoral lymphadenopathy with suppurated bubo formation and the condition may lead to genital elephantiasis. Consequently, presumptive treatment should be started if a patient with proctocolitis exhibits symptoms or signs such as bloody discharge, tenesmus, or ulceration at the rectal site; if a patient with a recent history of genital ulcer displays severe inguinal lymphadenopathy with bubo formation; or if the patient has genital ulcer disease and other causes have been ruled out [43, 72].

The most effective antibiotic for the treatment of LGV is doxycycline but unlike uncomplicated chlamydia caused by serovars D-K, treatment of LGV needs a prolonged course of therapy. Doxycycline 100 mg twice a day for 21 days is the standard course of treatment for LGV. Azithromycin 1 g orally once a week for 3 weeks and erythromycin base 500 mg orally four times a day for 21 days are two alternate regimens. Unfortunately, the LGV-specific azithromycin regimen has not been confirmed, and a follow-up test with *C. trachomatis* NAAT is advised about 4 weeks after the end of therapy [43]. Patients who have LGV should be observed until all symptoms and signs have disappeared [43].

3.1.2.9 Treatment of chlamydia and LGV during pregnancy and breastfeeding

The tetracycline group of antibiotics including doxycycline which is the primary antibiotic option for chlamydia and LGV is contraindicated during pregnancy and breastfeeding due to the possibility of tooth discoloration [43]. In pregnant and breastfeeding women suffering from chlamydia disease, azithromycin, erythromycin, and amoxicillin are the safer antibiotic options [73]. The recommended antibiotic regimen for pregnant and breastfeeding adults and adolescents with cervical, urethral, rectal, and oropharyngeal chlamydia is azithromycin 1 g orally given as a single-dose. As a secondary option amoxicillin 500 mg orally, three times a day for 7 days can be used. Beta-lactam antibiotics are associated with the persistence of chlamydia; therefore, caution must be given for re-emergence of viable pathogen after discontinuation of amoxicillin therapy [43]. Erythromycins 500 mg orally, four times a day for 7 days, or erythromycin 500 mg orally, twice a day for 14 days, are two alternative possibilities for pregnant and nursing women with uncomplicated chlamydia. Of note, estolate formulation of erythromycin is contraindicated in pregnancy due to the

risk for drug-related hepatotoxicity, and erythromycin base or erythromycin ethyl succinate should be prescribed instead [53, 74, 75].

For many years, macrolides including azithromycin and erythromycin have been frequently utilized as safe antibiotic options during pregnancy; however, in a recent population-based cohort study it was found that first-trimester usage of macrolides (mainly erythromycin given over several days) was associated with a higher incidence of congenital abnormalities than penicillins [76]. It was also shown that erythromycin medication during 7 weeks of delivery or while breastfeeding has been linked to a higher incidence of IHPS [7]. The impact of azithromycin single-dose regimen on a fetus is unknown but it is considered that the advantages of azithromycin therapy outweigh any potential risks. Finally, although fluoroquinolones can be used in non-pregnant patients, its usage is restricted during pregnancy and breastfeeding due to fetal and neonatal adverse effects [43].

For pregnant women with LGV, the optimum dose and duration of antibiotic therapy are not known. Azithromycin 1 g orally, once a week for 3 weeks, can be used. Erythromycin 500 mg orally, four times a day for 21 days is another option for use in pregnancy and nursing women but gastrointestinal adverse effects are frequent [43, 74].

All pregnant women should get a NAAT retest around 4 weeks following the end of their therapy since the infection can remain and cause serious side effects in both mothers and neonates [45]. Also to detect re-infection, retesting should be repeated in pregnant women 3 months after completing therapy [45].

To prevent maternal complications and infant chlamydial infections, it is advised that pregnant women under 25 years old, pregnant women who have a new sex partner, a sex partner with multiple partners, or a sex partner with an STI, should be checked at the first antenatal control and retested in the third trimester. However, routine antenatal screening of pregnant women at risk for chlamydia disease cannot be utilized in all countries [31, 77].

3.1.2.10 Treatment of chlamydia disease among infants and children

C. trachomatis acquired in the perinatal period can persist for up to 3 years. Any prepubertal youngster with chlamydia disease should be evaluated for the possibility of sexual abuse. In case of a suspect of sexual abuse, local authorities should be notified. The recommended regimens for chlamydia disease among infants and children are as follows:

- For infants and children weighing less than 45 kg: erythromycin base or ethyl succinate 50 mg/kg/day orally divided into four doses daily for 14 days;
- For children weighing more than 45 kg but aged under 8 years old: azithromycin 1 g orally, in a single dose; and
- For children aged above 8 years: azithromycin 1 g orally in a single dose or doxycycline 100 mg orally, two times a day for 7 days.

3.1.2.11 Follow-up recommendations for chlamydia and LGV

Sexual activity should be avoided by people with *C. trachomatis* (LVG or non-LGV serotypes) and their partners until treatment is complete (7 days after single-dose therapy or after completion of a multiple-dose regimen) and all current partners have recovered [43, 74].

A test of cure to detect therapeutic failure (repeated testing 4 weeks after finishing therapy) is not advocated for non-pregnant patients with uncomplicated chlamydia disease. But if therapeutic adherence is not assured, the patient has persistent symptoms, regimens with low efficacy (such as erythromycin or amoxicillin) have been implemented, or re-infection is suspected, clinician can offer a follow-up visit and retest the patient. Nonviable organisms may persist up to 4 weeks after completion of therapy and may cause false positive test results therefore testing with chlamydial NAATs at less than 4 weeks following the conclusion of medication is not advised [45].

In order to detect re-infection, all patients should be retested for chlamydia in 3 months (or retesting at 3 months is not feasible, within 12-months) after completion of therapy. It is suggested to schedule the follow-up appointment at the time of treatment [43].

If the patient has complaints of chronic or recurring symptoms, non-adherence to the given medication, re-infection, completion of sex partner treatment, and coinfection with other STIs should be questioned and evaluated. Assuming that *C. trachomatis* is found on repeat testing, treating with the same regimen (preferably doxycycline regimen) is advised since drug resistance to doxycycline (or azithromycin) has not yet been proven in *C. trachomatis* as explained previously in the Subsection 2.

3.1.2.12 Management of sex partners of patients who have chlamydia and LGV

If a patient with chlamydia or LGV had intercourse with a partner within 60 days of the onset of their symptoms or chlamydia diagnosis, the partner should be referred for screening for *C. trachomatis*. A 7-day doxycycline regimen should be presumptively given to asymptomatic partners. In addition, co-infection with other STIs such as gonorrhea, HIV, and syphilis should be investigated in individuals and their sex partners who had a diagnosis of chlamydia or LGV [43]. However, if the clinician is worried that sex partners are unable to access evaluation and treatment services, a strategy termed "expedited partner therapy" (EPT) can be applied as permitted by law. In this strategy, treatment is delivered to the sex partner without examination by either giving an antibiotic/prescription to the index patient (so they can give it to their partners) or by calling in a prescription directly for the partner. Partners who will receive EPT should be informed about the significance of treatment, potential side effects of the medications, and complications of the disease [43].

3.1.3 Treatment of infantile chlamydial pneumonia

Chlamydial pneumoniae is subacute pneumonia that mainly affects newborns between the ages of 1–3 months. *C. trachomatis* testing should be performed in all newborns aged 1–3 months who are suspected of having pneumonia especially if there is a risk for chlamydia infection in the mother such as pregnant women under 25 years old and pregnant women who have a new sex partner, more than one sex partner, a sex partner with multiple partners, or a sex partner with an STI [43].

Erythromycin base or ethyl succinate 50 mg/kg/day orally divided into four doses every day for 14 days is the recommended regimen for infantile chlamydial pneumonia. Azithromycin suspension 20 mg/kg/day orally, once a day for 3 days is the alternative regimen that can be given presumptively when there is a strong suspicion of chlamydia infection and there are limited laboratory resources or infant follow-up is not possible [43]. It is advised to monitor infants for resolution of pneumonia

symptoms as the efficacy of erythromycin against *C. trachomatis* pneumonia is approximately 80% [43, 78]. Additionally, mothers of babies with infantile chlamydial pneumonia should be assessed, screened, and treated for chlamydia disease [43].

3.1.4 Reactive arthritis due to C. trachomatis *infection*

Reactive arthritis is a type of arthritides known as the spondyloarthritides that usually develops following an enteric or venereal infection. Both men and women can develop reactive arthritis after infection due to *C. trachomatis* whether they are symptomatic or not. Moreover, reactive arthritis can occasionally be one of the three symptoms that used to be known as Reiter's syndrome, which also includes urethritis and conjunctivitis [34]. Although randomized studies for long-term anti-chlamydial antibiotic treatment for reactive arthritis showed varied results, the majority of studies showed no benefit. Therefore, antibacterial medication is not recommended in reactive arthritis related to *C. trachomatis* [79, 80].

3.2 Treatment of infections due to *C. pneumoniae*

C. pneumoniae is another important human pathogen in the family *Chlamydiaceae* that mainly infects the respiratory tract. The agent causes upper or lower respiratory tract infections including pharyngitis, laryngitis, and community-acquired pneumoniae (CAP). Most *C. pneumoniae*-related respiratory infections are asymptomatic or mild; however, severe complications such as exacerbation of asthma, encephalitis, and myocarditis can occur, which may require hospitalization [81]. *C. pneumoniae* prevalence rates in individuals with CAP range from 1 to 20% of cases [82, 83]. Therefore, empiric treatment of CAP frequently includes the usage of antibiotics effective against *C. pneumoniae* [84].

Among antibacterial medications, beta-lactam antibiotics, aminoglycosides, glycopeptides (such as vancomycin), and sulfonamides are not effective against *C. pneumoniae*, whereas macrolides, doxycycline, and fluoroquinolones are effective options [72, 85]. Acquired and heritable antibacterial resistance have not been revealed in *C. pneumoniae* and laboratory tests for the detection of *C. pneumoniae* are not routinely recommended in CAP management. Decisions for testing can be individualized on a case-by-case basis and the availability of microbiological tests [3, 84]. In the literature, clinical trials that show the efficacy of antibacterial medications on outcomes of pneumonia due to *C. pneumoniae* are limited [86]. However, the performance of antibacterial agents in eradicating nasopharyngeal *C. pneumonia* has been evaluated in several studies. The efficiency of eradicating microorganisms was shown as around 80% in those trials using a 5-day course of azithromycin and between 70% and 100% when using 7 to 10-day courses of clarithromycin, erythromycin, moxifloxacin, or levofloxacin. The authors revealed that the majority of patients improved despite the organism's persistence in the nasopharynx; therefore, the significance of bacterial eradication for treatment success is still controversial [86–90]. Studies have shown that in patients who remained culture positive after treatment, antibiotic failure is the result of the persistent state of the organism and not due to drug resistance [72, 91].

Numerous researchers have questioned the ideal length of antibiotic treatment in CAP. Historically at least 7 days of treatment was recommended for CAP; however, in the last decades there is a tendency toward shorter courses of therapy in both adults and children due to the abundant evidence showing non-inferior efficacy compared

to longer courses [84, 92–95]. In recent years, guidelines have changed their recommendations to the usage of shorter duration of antibiotic regimens for CAP. But not all patients respond to a standard duration of therapy; therefore, it is advised that clinicians should use clinical stability indicators such as the return of normal vital sign patterns, the capacity to eat, and mental function to determine the length of antibiotic therapy. The recommendation is that the treatment is administered for a minimum of 5 days overall and until the patient reaches stability [84, 95, 96].

In adult patients where *C. pneumonia* is the confirmed etiological agent for pneumonia the following therapy regimens can be given as a 5-day course of antibiotic therapy and according to the patients' clinical stability [84, 95]. The necessity of eradication of *C. pneumoniae* from clinical isolates for treatment success is not known but treatment might be extended up to 10 days in selected cases due to the previously mentioned studies about post-treatment bacterial eradication rates.

- Azithromycin 500 mg orally once a day on the first day then 250 mg daily on the following days for up to 5 days,
- Clarithromycin 500 mg orally two times a day (or clarithromycin extended-release tablet 1 g once a day),
- Erythromycin 500 mg four times a day (for pregnant women),
- Doxycycline 100 mg orally two times a day,
- Levofloxacin 500 or 750 mg orally once a day,
- Moxifloxacin 400 mg orally once a day and
- Gemifloxacin 320 mg orally once a day.

Intravenous (IV) formulations of levofloxacin and moxifloxacin can be given in the same oral dosages to severe patients who are hospitalized and unable to take oral medication [84, 95]. All patients should be reassessed within 3 days for improvement of symptoms and the possibility of transition to oral medication [95].

For children, the recommendations for assessing the duration of antibiotics for pneumonia are the same as the adult patients [95, 97]. The treatment options for confirmed *C. pneumonia* in pediatric patients are:

- Azithromycin 10 mg/kg orally or IV once a day on the first day then 5 mg/kg once daily for up to 5 days,
- Erythromycin 40 mg/kg/day orally divided into four doses or erythromycin lactobionate 20 mg/kg/day IV four times a day,
- Clarithromycin 15 mg/kg/day orally divided into two doses,
- Levofloxacin 16–20 mg/kg/day IV divided into two doses for children 6 months to 5 years old and 8–10 mg/kg/day once a day for children 5 to 16 years old and levofloxacin 500 mg/day orally once a day for adolescents with skeletal maturity (the pediatric dosage of levofloxacin should not exceed 750 mg/day),

- Moxifloxacin 400 mg/day once a day for adolescents with skeletal maturity, and

- Doxycycline 2–4 mg/kg/day orally divided into two doses for children>7 years old (the pediatric dosage of doxycycline should not exceed 200 mg/day).

Similar to adult patients response to therapy and decision to transition to oral therapy should be assessed within 3 days of treatment [97]. Due to the paucity of clinical trials directly evaluating the efficacy of antibiotics on clinical outcomes in children with *C. pneumoniae* pneumonia, the medications might be lengthened to 10 days according to the physician's decision [97].

3.2.1 C. Pneumonia-*related chronic diseases*

The connection between chronic persistent *C. pneumoniae* infection and chronic inflammatory disorders is still up for debate. In addition to contributing to respiratory tract infections, a growing body of research suggests that *C. pneumoniae* may also be involved in the pathogenesis of several inflammatory diseases, including atherosclerosis, arthritis, asthma, chronic obstructive pulmonary disease (COPD), lung cancer, and some neurological conditions such as Alzheimer's disease, multiple sclerosis, and schizophrenia [98]. Among them, patients who have asthma/COPD and present with symptoms of confirmed *C. pneumonia* airway infection should be treated according to the treatment recommendations for acute respiratory infections mentioned above. Due to a paucity of data, there are presently no recommendations for treating any other chronic diseases associated with *C. pneumoniae* infection, other than asthma and COPD [3, 72, 98].

3.3 Treatment of infections due to *C. psittaci*

C. psittaci causes a zoonotic disease called psittacosis, also known as ornithosis. Psittacosis is frequently transmitted to humans predominantly from birds *via* inhalation of dried droppings, feather dust, or respiratory secretions [99, 100]. The disease can manifest clinically in a variety of ways, ranging from asymptomatic disease or non-specific flu-like illness to severe systemic illness with pneumonia [100, 101]. Other complications that may require hospitalization are cardiac infections (such as endocarditis and myocarditis), hepatitis, arthritis, encephalitis, and sepsis [102]. The most typical illness manifestation is an upper respiratory infection. It is assumed that about 1–8% of CAP is caused by psittacosis [101, 103]. The laboratory diagnosis of psittacosis is usually difficult. Clinical application of traditional pathogen culture is uncommon since it takes a long time and requires high-standard laboratory conditions to culture *C. psittaci* in cells. Serological testing is primarily utilized in retrospective research and is not very useful for the earlier detection of severe patients. *C. psittaci* is easily identified by NAAT and metagenomic next-generation sequencing; however, these procedures are not routinely utilized in most hospitals [104]. Therefore, a patient with a history of bird contact who exhibits atypical pneumonia symptoms or unexplained fever without localizing signs, clinicians should consider a diagnosis of psittacosis, and treatment should not await a definitive diagnosis.

Beta-lactam antibiotics are not effective in psittacosis, whereas tetracyclines and macrolides are both effective against *C. psittaci*. Tetracyclines and especially doxycycline is the preferred medication for the treatment of *C. psittaci* pneumoniae [104, 105].

As an alternative or in situations where tetracyclines are prohibited, such as in pregnant women or young children under the age of eight, macrolides such as erythromycin and azithromycin may be utilized [106]. Doxycycline 100 mg orally two times a day for 7 to 10 days is the suggested regimen for psittacosis. Also, a 5 to 7-day regimen of azithromycin (if a clinical response is observed) can be used alternatively. The third-line antibiotics for *C. psittaci* are fluoroquinolones, which have less potency than tetracyclines and macrolides [95, 104, 107]. With proper and early treatment overall prognosis is good and death occurs in less than 1% of patients [102, 104].

4. Conclusions

Chlamydial infections are one of the most prevalent infectious diseases reported worldwide. The spectrum of diseases varies from asymptomatic silent infection to severe disease affecting ocular, genito-urinary, and pulmonary systems. Without proper management, the infections might progress and result in blindness, infertility, sepsis, or death. Antibacterial medications such as tetracyclines, macrolides, and quinolones, which have been used for many years to treat a variety of infections that are also effective for human infections caused by *C. pneumoniae*, *C. trachomatis*, and *C. psittaci*. Although persistent and heritable antibacterial resistance is common in some *Chlamydia* spp. such as *C. suis*, genotypic stable resistance has not been reported in human chlamydial infections. Phenotypic antibacterial resistance might result from the persistence of microorganisms or heterotypic resistance, whereas antibiotic failure might result from non-adherence to medication, re-infection, or choice of regimens with lower success. The laboratory diagnosis of chlamydial infections might be challenging in many centers and patient follow-up cannot be assured on some occasions; therefore, in case of doubt of chlamydial infection early presumptive treatment with recommended regimens, proper follow-up of the patients, prevention of re-infection via patient and partner counseling and protection of susceptible populations by the implementation of screening programs in high-risk patients should be established.

Conflict of interest

The author declares no conflict of interest.

Treatment of Chlamydial Infections
DOI: http://dx.doi.org/10.5772/intechopen.109648

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