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section 8 Infectious diseases 1278 is not promptly recognized and treated, the case fatality can reach around 88%. Alterations of consciousness (excitement, stupor, and coma) and progressive or focal neurological features, biochemical evidence of hepatic dysfunction (increased transaminases and alka- line phosphatase), pulmonary complications (noncardiogenic pul- monary oedema), severe neurological involvement, anasarca (severe hypoalbuminaemia), pregnancy, and not being indigenous are all associated with a higher mortality. Treatment Chloramphenicol, penicillin, erythromycin, co-trimoxazole, and ciprofloxacin are effective, usually eliminating the fever in around 48 h. Because of the common association with salmonellosis, ciprofloxacin is the treatment of choice in a dose of 500 mg orally twice a day for 14 days. However, there are recent reports of increased resistance of bartonellas to quinolones. The alternative is amoxicillin plus clavulanic acid 1 g orally twice a day for 14 days, which is the treatment of choice in pregnant women and children under 14 years of age. In severe acute disease, the drugs indicated are ceftriaxone 2 g intravenously daily plus ciprofloxacin 400 mg intravenously twice a day for 14 days. Supportive treatment includes transfusion of packed red cells and empirical dexamethasone if there is severe neurological involvement. Azithromycin 500 mg orally once a day for 7 days is the drug of choice for the verrucous form. The dose in children is 10 mg/ kg daily orally for 7 days. The alternative is rifampicin (300 mg twice a day in adults or 10 mg/kg daily in children orally for 21–28 days). The antibiotic treatment in the acute phase of the disease does not elim- inate the chance of developing eruptive lesions weeks or months later, suggesting persistence of bacteraemia in an unknown percentage. Prevention There is no satisfactory prevention for people who live in endemic areas. Sandflies can be eliminated temporarily by spraying inside and outside with dichlorodiphenyltrichloroethane or pyrethroids, and this strategy is recommended during outbreaks. Spraying in- secticides inside the house and mass use of long-lasting insecticide-impregnated bed nets are measures that reduce both incidence and secondary attack rate of the disease. Tourists can protect themselves with insect repellents, clothes impregnated with pyrethroids, and sleeping with nets impregnated with insecticides, or by avoiding sleeping in highly endemic areas. There is no vaccine. FURTHER READING Birtles RJ, et al. (2002). Identification of Bartonella bacilliformis genotypes and their relevance to epidemiological investigations of human

Bartonellosis. J Clin Microbiol, 40, 3606–12. Chaloner GL, et al. (2011). Multi-locus sequence analysis reveals profound genetic diversity among isolates of the human pathogen Bartonella bacilliformis. PLoS Negl Trop Dis, 5, e1248. Chamberlin J, et al. (2002). Epidemiology of endemic Bartonella bacil liformis: a prospective cohort study in a Peruvian mountain valley community. J Infect Dis, 186, 983–90. Maguiña C (1998). Bartonellosis o Enfermedad de Carrión. A.F.A. Editores Importadores S.A. Lima, Peru. Ministry of Health of Peru (2011). Atención de la Bartonelosis o Enfermedad de Carrión en el Perú. Norma técnica No. 048-MINSA/ DGSP-C.01. Sanchez Clemente N, et al. (2012). Bartonella bacilliformis: a system- atic review of the literature to guide the research agenda for elimin- ation. PLoS Negl Trop Dis. http://www.scopus.com/inward/record.url?eid=2-s2.0-84869061206&partnerID=40&md5=be4ccb039bf6 20fbe67e6b37468c2684 8.6.45 Chlamydial infections Patrick Horner, David Mabey, David Taylor-Robinson, and Magnus Unemo ESSENTIALS Chlamydiae are pathogenic bacteria that likely evolved from host- independent, Gram-negative ancestors. The Chlamydiae have a unique biphasic developmental cycle and obligate intracellular lifestyle. Chlamydiae depend on a eukaryotic host cell for their replication which takes place in an inclusion inside the host cell, and for their dispersal, cell lysis, or extrusion subsequently occurs. Although the phylum Chlamydiae (order Chlamydiales) was ori- ginally thought to only contain one family, the Chlamydiaceae, a total of nine families are now recognized. The genus Chlamydia re- mains the most widely studied. The species Chlamydia trachomatis was proposed some decades ago on the basis of 16S rRNA and 23S rRNA sequences, to belong to the genus Chlamydia together with C. muridarum and C. suis. The other human pathogenic Chlamydiae were classified as species of a separate genus, that is, Chlamydophila pneumoniae and Chlamydophila psittaci. However, this subdivision of the family Chlamydiaceae into the two genera, Chlamydia and Chlamydophila has been controversial. Based on genomic data and the biological properties of these bacteria, it was proposed recently to classify all the 11 currently described Chlamydiaceae species within a single Chlamydia genus. This is the classification used in the present chapter. In the Chlamydia genus, C. trachomatis and C. pneumoniae are primarily human pathogens, and C. psittaci, C. abortus, and C. felis are species transmitted occa- sionally from animals. The other families, the so-called Chlamydia- like organisms are also emerging pathogens, as many, such as Parachlamydia sp., Simkania sp. and Waddlia sp., have been as- sociated with human disease, and others, such as Piscichlamydia sp. and Parilichlamydia sp., have been documented in association with diseases in animals. This chapter primarily focuses on the species C. trachomatis, which causes the disease of ocular trachoma (serovars A–C), oculo- anogenital tract infection (serovars D–K) and lymphogranuloma venereum (serovars L1–L3). However, infections caused by C. pneumoniae and C. psittaci are also discussed.

8.6.45 Chlamydial infections 1279 Oculo-anogenital tract infections These are caused by C. trachomatis serovars D–K, which exist world- wide. In men they cause up to 50% of symptomatic nongonococcal urethritis and a similar proportion of acute epididymitis. In women they cause up to 50% of (often asymptomatic) urethritis and of (mostly asymptomatic) cervicitis; further spread leads to endo- metritis, salpingitis and (occasionally) perihepatitis. Women with untreated infection have about a 17% risk of pelvic inflammatory disease, a 7% risk of salpingitis, a 0.5% risk of tubal factor infertility and 0.2% risk of ectopic pregnancy. Other diseases—(1) Rectal and pharyngeal infections. (2) Adult paratrachoma and otitis media. (3) Reactive arthritis—at least one- third of sexually acquired reactive arthritis is initiated by genital C. trachomatis infection (see Chapter 19.6). (4) Neonatal infection— babies exposed to serovars D–K at birth often develop conjunctivitis, and some develop pneumonia. Lymphogranuloma venereum The invasive ulcerative

lymphogranuloma venereum is caused by C. trachomatis serovars L1, L2 (including subvariants such as L2b) or L3. Lymphogranuloma venereum has been endemic in parts of Africa, Asia, South America, and the Caribbean. The traditional clinical course comprises three stages: (a) primary—a small painless papule occurs at the site of inoculation; followed some weeks later by (b) secondary—inguinal and/or femoral lymphadenopathy with systemic features; anorectal involvement is usually seen in men who have sex with men; sometimes progressing to (c) tertiary—severe fibrosis, which is rarely seen because of earlier broad-spectrum antibiotic therapy. Lymphogranuloma venereum has been rare in Western Europe and North America for many years. However, since a lymphogranuloma venereum (serovar L2b) outbreak in men who have sex with men was detected in 2003 in Rotterdam, out- breaks similar to the Netherlands outbreak have been seen in sev- eral other West European countries, North America, and Australia. Lymphogranuloma venereum has now become endemic among, mostly HIV-positive, men who have sex with men in several of those European countries. The lymphogranuloma venereum L2b strain is also found in the heterosexual population. Most of these patients have presented with proctitis or tenesmus, anorectal discharge, and discomfort, diarrhoea, or altered bowel habits. It has now also been shown that about 25% of lymphogranuloma venereum infections can be asymptomatic in some settings. Diagnosis depends on iden- tification of C. trachomatis lymphogranuloma venereum serovars in appropriate clinical specimens using nucleic acid amplification testing and, if that is not available, serology. Recommended first-line treatment is doxycycline (three weeks), with erythromycin as second- line (three weeks). Trachoma Trachoma is caused by C. trachomatis serovars A, B, Ba, and C. It is a disease of poor rural communities, mainly in Africa and Asia, where the reservoir of infection is the eye (and possibly nasopharynx) of children with active disease, with transmission from the eye of one individual to that of another via fingers, fomites, coughing and sneezing, and by eye-seeking flies. Clinical features and diagnosis—the active (inflammatory) stage is a follicular conjunctivitis with characteristic subconjunctival follicles that are usually seen in children in endemic areas. Repeated infec- tions lead to conjunctival scarring, with turned-in eyelashes rub- bing against the cornea (trichiasis) which eventually causing severe damage (1.4% of global blindness, or 0.5 million cases, and 1.8 mil- lion cases of visual impairment). In endemic areas diagnosis is made on clinical grounds. Treatment and prevention—inflammatory trachoma responds to ei- ther an appropriate course of 1% topical tetracycline ointment or a single oral dose of azithromycin up to 1 g. Community-based mass treatment is recommended when there is high prevalence of dis- ease in children aged 1 to 9 years. Trichiasis requires surgical cor- rection. A World Health Organization initiative to eliminate blinding trachoma as a public health problem by 2020 is based on the acronym ‘SAFE’: Surgery for trichiasis; Antibiotics for treatment; Face washing; Environmental improvement to reduce fly populations that transmit the organisms. Other Chlamydiae C. pneumoniae—transmitted directly from person to person by droplet spread and causes respiratory tract disease (pharyngitis, bronchitis, pneumonia); it is a possible trigger for reactive arthritis and for some cases of juvenile chronic arthritis, and C. pneumoniae DNA has been detected in atheromatous arteries, but without definite evidence that it contributes to heart disease. C. psittaci— transmitted from psittacine birds and causes psittacosis, which can range from a mild influenza-like illness to a fulminating toxic state with multiorgan involvement. Ornithosis refers to infection trans- ferred from nonpsittacine birds. C. abortus—causes abortion in sheep and may do so in pregnant women exposed to infected animals during the lambing season. Diagnosis and treatment Diagnosis—depends on (1) the use of nucleic acid amplification tests—the ‘gold standard’ for routine diagnosis, screening, and for research into chronic or persistent disease; and—to a much

lesser extent—(2) serology. Treatment—Chlamydiae are particularly sensitive to tetracyc- lines (e.g. doxycycline) and macrolides (e.g. erythromycin and azithromycin). Azithromycin has gained popularity because it can be effective as a single dose: however, there is a debate as to whether it is sufficiently effective compared to doxycycline. Introduction Trachoma is recognizable from historical descriptions of blind- ness in ancient Chinese and Egyptian writings, but it was not until 1907 that L. Halberstaedter and S. von Prowazek first described intracytoplasmic inclusions in stained conjunctival scrapings from orangutans that had been inoculated with human trachomatous material and recognized the involvement of an infectious agent. In 1930, a chlamydial agent (Chlamydia psittaci) was first isolated from psittacosis; 27 years later the species associated with trachoma, C. trachomatis, was isolated in the yolk sac of fertile hens' eggs. The advent of the cell-culture technique paved the way for the isolation of oculo-anogenital C. trachomatis by this means in 1959. C. pneumo niae was initially isolated in 1965 from the eye of a child participating

section 8 Infectious diseases 1280 in a trachoma vaccine study and reclassified as C. pneumoniae in 1989. Advances in immunology, molecular diagnostics, molecular biology, and more recently genomics have made it possible to ex- plore the nature, range, prevalence, and pathogenesis of clinical conditions associated with chlamydial infection. Classification The phylum Chlamydiae refers to ubiquitous pathogens infecting many eukaryotes including many species of animals, birds, insects, and amoeba. The family Chlamydiaceae contains a single genus that, based on recent genomic data and the biological properties of these bacteria, contains 11 different species. The Chlamydiaceae and Chlamydia, are the most widely studied family and genus, re- spectively, of the Chlamydiae, and until the 1990s these were the only family and genus of the order Chlamydiales. The 11 Chlamydia species include C. trachomatis causing human ocular and anogenital infections; C. pneumoniae causing mainly human respiratory tract disease, but with some strains infecting a range of animals including horses and amphibians; C. psittaci infecting birds and other animals, with occasional transmission to humans; and C. abortus, which is endemic in ruminants causing abortion in sheep and rarely in pregnant women. Over the last 20 years research has revealed that the family Chlamydiaceae represents only the tip of the iceberg in terms of di- versity within the phylum Chlamydiae. Eight additional families of genetically obligate intracellular bacteria have since been identified. These new families are often referred to as 'Chlamydia-like organ- isms' as the developmental cycle is remarkably conserved across the phylum Chlamydiae. There is evidence that several of these species may cause disease in both humans and animals. For ex- ample, Waddlia chondrophila has been linked with miscarriage and Parachlamydia acanthamoebae and Simkaniaceae negevensis with respiratory tract disease. Growth cycle, genomics, and serovars Chlamydiae likely evolved from host-independent Gram-negative ancestors with traditional peptidoglycan structures in their cell walls. They are bacteria specialized to exist intracellularly. The chlamydial envelope possesses bacteria-like inner and outer mem- branes. The infectious elementary body is environmentally re- sistant, metabolically inactive, electron dense, DNA rich, and approximately 200–400 nm in diameter. It binds to the host cell and enters by endocytosis. Fusion of the chlamydia-containing endocytic vesicle with lysosomes is inhibited and the elementary body begins its unique bi-phasic developmental cycle within the eukaryotic cell. After about 6–10 h it differentiates into the larger (500–1000 nm) noninfectious, metabolically active, more perme- able, pleomorphic reticulate body. This replicates by binary fission and by 20–30 h has begun to reorganize into a new generation of elementary bodies (Fig. 8.6.45.1). These rapidly accumulate within the endocytic vacuole to be released from the cell (and/or cell is lysed) between

30 and 72 h for C. trachomatis after the start of the cycle (exact time can differ dependent on species, strains, and cell type). The developmental cycle of C. pneumoniae is longer c.72 h. Chlamydiae have the ability to enter a persistent state intracellu- larly within the inclusion in response to various conditions. They can then remain dormant as abnormal reticulate bodies for consid- erable lengths of time but are able to be re-activated. This has been widely studied in vitro. Although the evidence in vivo is limited, its occurrence has been demonstrated during cervical infection and presumptively in patients with reactive arthritis and tubal factor in- fertility. In this persistent state, chlamydial organisms have shown to be refractory to antimicrobial therapy in vitro. The genome sequences of species within the Chlamydia genus are small relative to most other bacterial genomes, and have a high level of conservation (interspecies and intraspecies), overall gene con- tent and gene synteny (order). In one study, a total of 736 protein- coding sequences was shown to be shared among the species of C. psittaci, C. abortus, C. pneumoniae and C. trachomatis, with the total protein-coding sequence count of these species ranging from 874 to 1097. The minor differences are obviously sufficient to de- fine host range, tissue tropisms, and disease presentation. There was also considerable amino acid identity (average 62%) between proteins encoded by the common protein-coding sequences from C. trachomatis and C. pneumoniae and, thus, the potential that these proteins may contain cross reactive epitopes is high. This has impli- cations for the development and interpretation of species-specific antibody tests. The major outer membrane protein (MOMP) is immunodominant in the elementary body and contains epitopes exhibiting genus, spe- cies, and serovar specificity. The serovar-specific epitope is the basis of the microimmunofluorescence (MIF) test by which C. trachoma tis has been separated into 15 serovars: A, B, Ba, and C are respon- sible mainly for endemic trachoma; D to K for oculo-anogenital infections; and L1, L2, and L3 for the more invasive genital disease lymphogranuloma venereum (LGV). Using sequencing of the ompA gene (encoding MOMP), the corresponding genovars including intraserovar sequence variants, are nowadays usually assigned. Recent whole genome sequence analysis indicates that C. trachoma tis undergoes recombination (intra- and interserovar) in vitro and in vivo. Replacement and chimerism of large segments of the genome including ompA and accordingly encoded MOMP is most likely one of many strategies used by C. trachomatis to evolve in general and also counteract the effect of the immune system protecting the host Fig. 8.6.45.1 Elementary bodies (E) and reticulate bodies (R) of C. trachomatis, forming an inclusion in an oviduct cell; shown by transmission electron microscopy.

 against immediate reinfection. Thus, serovar and genovar typing systems for C. trachomatis can be poor indicators of genetic related- ness within the species. Only one C. pneumoniae serovar has been identified, although minor geographical serovar variations have been described. C. psittaci was originally divided into nine serovars. Amino acid sequences of the MOMPs of all C. trachomatis sero- vars and epitope maps of different antigenic domains have been elucidated. The MOMP amino acid sequences consist of five highly conserved regions punctuated by four short extracellularly-exposed variable sequences. Serovar-specific epitopes have been demon- strated in variable sequence I and II, while species-specific epitopes have been found in variable sequence IV. This understanding has formed the theoretical basis for development of C. trachomatis spe- cific MOMP peptide antibody assays. All species of Chlamydia add- itionally contain a common heat-stable lipopolysaccharide (LPS) antigen, which is exposed on the surface of the reticulate body, but not on the elementary body. Antibodies to LPS are considered genus specific. The plasmid encoded protein Pgp3 of C. trachomatis is not present in the human pathogenic C. pneumoniae strains, as they do not contain a plasmid. Pgp3 is highly

immunogenic, with most women producing serum IgG antibody following infection. Men are less likely to develop antibodies to Pgp3 following infection, the reason for which is unclear. Immune response and pathogenesis The immune response to chlamydial infections may be protective or damaging. Active trachoma is uncommon in adults in endemic areas, suggesting that protective immunity follows natural infec- tion. Similarly, genital C. trachomatis infection is most prevalent in the youngest sexually active age groups, and the chlamydial isola- tion rate for men with nongonococcal urethritis is lower in those who have had previous episodes. The duration of ocular infection is shorter in adults than in children. It is unclear how long pro- tective immunity lasts but with genital tract infections this is be- lieved to be short lived. Several trachoma vaccine trials in the 1960s used killed whole organism vaccines, which provided some degree of protection. Primate studies suggested that vaccination could provoke more severe disease on subsequent challenge, indicating immunopathological damage by C. trachomatis. Evidence from human studies suggests women with reinfection, which is not un- common, may be at greater risk of developing reproductive sequelae. The average duration of asymptomatic genital infection in women has been estimated to be about 16 months with about 20% and 5% still positive at two years and four years, respectively, following in- fection. The duration of infection is believed to be similar in men, but additional evidence would be valuable. Approximately 20–25% of women and men become detection-negative after a few weeks. This could be a consequence of ‘passive’ carriage clearing after one week, in which infection has not been established. The data in women are also compatible with a three-rate model which in- cludes fast clearing infection as a result of a protective immune re- sponse, in addition to passive carriage and slow clearing infection. How often and how long Chlamydiae can persist in a nonreplicating state in vivo (see earlier) is unknown as an answer would require invasive sampling of the upper genital tract by biopsy, in apparently healthy individuals. While recent evidence indicates that long term persistence is probably uncommon, there remains the possibility that some women with tubal factor infertility who are nucleic acid amplification test (NAAT)-negative but chlamydia-antibody posi- tive may harbour viable organisms which could ‘reactivate’ after uterine instrumentation. Many women with urogenital tract infection, who do not prac- tice anal sex, may be coinfected in the rectum. Auto-inoculation has been proposed as the most likely mechanism, although it is diffi- cult to exclude contamination of the swab during rectal sampling as a result of passive perineal contamination from vaginal secretions. Animal and human studies suggest that gastrointestinal C. tracho matis infection may occur in humans and may be less susceptible to treatment with azithromycin. Several groups have identified the DNA of C. trachomatis uro- genital serotypes in joints of patients with reactive arthritis. A recent report of C. trachomatis trachoma serotypes A–C and not urogenital serotypes D–K in joints is mystifying and needs substantiation given the association of reactive arthritis with urogenital infection and not trachoma. C. pneumoniae has been identified in atheromatous plaques of pa- tients with cardiovascular disease and associated serologically with disease. Experimental studies in atheroma models in mice and rab- bits have demonstrated biological plausibility, with infection accel- erating progression. Thus, it is possible that inflammation secondary to persistent infection might contribute to disease progression in hu- mans. However, placebo-controlled antibiotic treatment trials have failed to establish any therapeutic benefit to patients with established atheromatous disease. There are several potential explanations for this including the possibility that persistent C. pneumoniae infection may be resistant to antimicrobial therapy. Chlamydial infection is associated with a T-helper cell type 1 (Th1) or cytotoxic profile of immune response, with the production of IFN-γ, IL-8, IL-1, and IL-6 cytokines. Studies in trachoma-endemic communities suggest that Th1 type cell-mediated

responses are important in the clearance of ocular C. trachomatis infection and are believed to also be important in resolution of genital tract in- fection. However, the specific immune responses and cytokine levels that lead to resolution of infection rather than promotion of tissue damage remain undefined. An adaptive immune memory re- sponse, as a result of previous infections, probably also exacerbates the risk of pathological outcomes in the form of fibrosis and scar- ring. Persistent chlamydial infected epithelium which results in the production of pro-inflammatory chemokines and cytokines can also cause cell damage and fibrosis. Delayed hypersensitivity and/ or molecular mimicry in response to specifiic chlamydial antigens, notably the chlamydial heat shock protein (hsp 60), homologous with the GroEL protein of Escherichia coli and human hsp 60, has also been proposed. However, inconsistencies in the published find- ings have made this potential mechanism increasingly controversial. It is likely that disease caused by Chlamydiae is a combination of the effects of the immunological (adaptive immunity) and the cellular (innate epithelial cell responses) systems. Recent evidence from studying trachoma suggests that other mechanisms might also be involved. A longitudinal study of patients with trachoma indicated that progression of scarring as a result of immune activity occurred in the absence of detectable reinfection. Scarring trachoma is as- sociated with nonchlamydial bacterial infection. It is possible that bacteria could continue to drive on-going innate pro-inflammatory

section 8 Infectious diseases 1282 responses in the conjunctiva. Another possibility is that prior re- current C. trachomatis infection modifies the conjunctival tissue, increasing susceptibility to bacteria, perhaps as a result of imprinted epigenetic changes. Whether other bacteria might also play a role in the development of tubal factor infertility or ectopic pregnancy following chlamydial pelvic inflammatory disease (PID), similar to trachoma, is unknown. Persistent chlamydial infection is only rarely detected in women with tubal factor infertility, and bacterial vagin- osis, which can colonize the endometrium, is associated with tubal factor infertility. Chlamydia genotype and disease Chlamydia trachomatis is split into two biovars: the trachoma biovar (serovars A-K) which contains ocular and anogenital strains that are characterized by localized infections of the epithelial surface of the conjunctiva or anogenital mucosa; and the LGV biovar (serovars L1- L3) that contains more invasive strains which are distinguished by their ability to spread systemically through the lymphatic system, causing genital ulceration and bubonic disease. The biovars are genomically very closely related and it is unclear which genotypic differences determine variation in clinical disease. The best-known genotype that mediates tissue tropism is poly- morphism in the trpAB operon, which enables the synthesis of tryp- tophan from indole in C. trachomatis. This is disabled in ocular but not in anogenital strains of the trachoma biovar. IFNγ, an important Th1 mediator, acts against C. trachomatis via tryptophan nutrient deprivation. Environmental tryptophan levels are therefore likely to influence whether C. trachomatis either enters into a persistent state of growth, or can be eradicated. It was recently demonstrated that in the presence of bacterial vaginosis in women, a source of indole, C. trachomatis can persist as abnormal reticulate bodies in the pres- ence of high IFNγ levels, consistent with a robust Th1 type immune response. Presumably the ocular strains lost the functional trpAB operon because of an absence of indole producing bacteria in the healthy conjunctival space. The reasons why strains of the LGV biovar are more invasive, pre- dominantly infect monocytes and macrophages and disseminate to the lymph nodes and consequently cause systemic disease remain to be clearly elucidated. The LGV strains are genomically extremely closely related (gene order and sequence) to strains of the trachoma biovar. However, the LGV strains have a slightly smaller genome which is mainly due to differences in the plasticity zone of the re- spective genomes and to the differential deletion of the

chlamydial cytotoxin gene(s), which have been almost entirely removed from many LGV strains. In general, small-scale gene variation such as single amino acid alterations, a few pseudogenes, and alterations in timing and level of gene transcription and translation might provide the lymphotropic properties. Human genotype and risk of disease Several human genetic polymorphisms have been associated with the development of disease following infection with C. trachoma tis. These include polymorphisms in Toll-like receptors (TLRs) 1, 2, and 4 that are expressed in the female genital tract. Also in NLRP3 that results in altered secretion of IL-1β, mannose-binding lectin, human leukocyte antigen class 1 molecules (A2 and B/C– trachoma) and class II molecules (DR, DQ, and DP—tubal factor infertility), and in a range of cytokines including IL-10 and TNFα. A recent large genome-wide association study of polymorphisms and pathways associated with pathological sequelae of ocular C. tra chomatis infection identified 27 single nucleotide polymorphisms (SNPs) with strong association with scarring. Pathway analysis of genome-wide association study data was significantly enriched for mitotic cell cycle processes, the immune response, and for multiple cell surface receptor signalling pathways. Interestingly, it failed to confirm previously identified associations of scarring with SNPs in cytokine genes such as IL-10 and matrix metalloproteinase 9. Oculo-anogenital tract infections Oculo-anogenital tract infections due to C. trachomatis serovars D-K (Table 8.6.45.1) occur worldwide and are associated with a significant health and economic burden. The World Health Organization (WHO) estimated, globally, that there were 131 mil- lion new genital infections among adults in 2012. Women with untreated infection have about a 17% risk of pelvic inflammatory disease, a 7% risk of salpingitis, a 0.5% risk of tubal factor infertility and 0.2% risk of ectopic pregnancy. Infection is usually asymp- tomatic in men and women, with undetected infection sustaining transmission in the community. The prevalence of C. trachomatis infection in population-based studies has ranged between 0.1% and 12.1% in men, and 1.1% and 10.6% in women. The highest prevalence is in women of 15 to 24 years of age and in men of 20 to 24 years of age. In England, it has been estimated that the an- nual incidence in women aged 16–24 years was 5.2%. In the United States of America in 2013 it is estimated that in women there were 1.3 million new cases of genital chlamydial infection. Infection is associated with young age, increasing number of sexual partners, failure to use barrier protection consistently and correctly, and lower socioeconomic status. It is likely that higher prevalence in specific sexual networks, which is related to lower socioeconomic status and social disadvantage, might result in a higher incidence. Nongonococcal urethritis The incubation period is usually 7 to 14 days compared to 2 to 8 days for gonococcal urethritis. C. trachomatis is detectable in the ur- ethra of up to 50% of men with symptomatic nongonococcal ur- ethritis and in as many as 7% of those who are asymptomatic (see Chapter 9.5 on urethritis). Doxycycline 100 mg twice daily for 7 days, recommended first-line treatment for nongonococcal ureth- ritis, has a failure rate of 3% and azithromycin 1 g a failure rate of 10%. It is therefore likely that C. trachomatis is a cause of some cases of chronic (persistent/recurrent) nongonococcal urethritis. In women, chlamydial urethral infection may cause urethritis but, in contrast to men, infection and inflammation are mostly asymptomatic. The ‘urethral syndrome’ (dysuria and frequency with <105 organisms/ml urine) is rarely of chlamydial origin. Prostatitis and epididymitis There is no evidence that C. trachomatis causes acute symptom- atic prostatitis. Transperineal biopsies from patients with chronic nonprostatitis show chronic inflammation, but C. trachomatis has not been detected by culture or direct immunofluorescence tech- niques, although NAATs are positive in about 10%. These results,

 combined with the failure to detect chlamydial antibody, suggest that C. trachomatis is not often implicated directly in chronic pros- tatitis. However, the observation

that, in vitro, C. trachomatis can infect immortalized prostatic epithelium which results in the production of pro-inflammatory cytokines suggests that some cases of chronic disease might be of chlamydial origin. C. trachomatis is responsible for up to 50% of cases of acute epididymitis or epididymo-orchitis occurring primarily in young men (≤35 years of age) in developed countries, and has been de- tected in at least one-third of epididymal aspirates. There is usually a strong correlation between IgM and/or IgG chlamydial anti- bodies, measured by MIF, and chlamydia-positive epididymitis/ epididymo-orchitis. In developing countries, although C. tracho matis is important, N. gonorrhoeae is the major cause of acute epididymitis. Historically, the assumption has been that in pa- tients older than 35 years, urinary tract pathogens are the primary cause of epididymitis/epididymo-orchitis. However a significant but small group of men remain at risk of sexually transmitted infections. The most recent National Survey of Sexual Attitudes and Lifestyles (NATSAL) in the United Kingdom showed that Table 8.6.45.1 Assessment of the extent to which C. trachomatis is involved in various oculo-anogenital and associated diseases Disease Evidence that C. trachomatis is a causea Proportion of disease due to C. trachomatisb In men Acute NGU ++++ Up to 50% Persistent and recurrent NGU +++ 10–20% (dependent on initial therapy and effectiveness of partner notification) Acute epididymo-orchitis ++++ Up to 50% Acute and chronic prostatitis + ? Infertility + ? (only during active infection) In women Cervicitis ++++ <30% Urethritis +++ ? Vaginitis (prepuberty only) +++ ? Endometritis +++ ? Salpingitis ++++ 20–40% Perihepatitis +++ ? Tubal factor infertility +++ 30–45% (secondary to tubal scarring from previous infection) Ectopic pregnancy +++ ? Periappendicitis ++ ? Bartholinitis + ? Early miscarriage + ? Cervical dysplasia + ? Bacterial vaginosis – In men or women Conjunctivitis ++++ ? Proctitis +++ ? Arthritis (SARA) +++ About 40% Otitis media ++ ? Endocarditis ++ ? Pharyngitis + Lymphogranuloma venereum ++++ 100% (by definition) In infants Conjunctivitis ++++ ? Pneumonia ++++ ? Chronic lung disease ++ ? Gastroenteritis – NGU, nongonococcal urethritis; SARA, sexually acquired reactive arthritis. a ++++, overwhelming; +++, good; ++, moderate; +, weak; –, none. b Can vary by study population, geographic setting, and diagnostics used in studies.

 10–13% of men aged 35–64 years had at least one new sexual partner in the previous year. Thus, age alone should not be used to exclude the possibility of C. trachomatis causing epididymitis/ epididymo-orchitis. There is insufficient evidence that chlamydial epididymitis or chlamydial urethral infection lead to male infertility. Cervicitis, vaginitis, and bartholinitis In prepubertal children, the vaginal epithelium is columnar and susceptible to chlamydial infection. In adults, the squamous epi- thelium of the vagina is not susceptible, and the cervix is the pri- mary target for C. trachomatis, where it is an established cause of mucopurulent/follicular cervicitis (Figs. 8.6.45.2a and b) and often asymptomatic. Women who have signs of cervicitis are at increased risk of C. trachomatis, Mycoplasma genitalium, Trichomonas vagi nalis, and N. gonorrhoeae infection if the latter two infections are not uncommon in the population under study. Most women with cervicitis do not have a specific pathogen detected. A significant association between cervical chlamydial infection and cervical squamous cell carcinoma, but not adenocarcinoma, has been established and it has been suggested that C. trachomatis infection may enhance the oncogenic effect of papillomaviruses. C. trachomatis has been weakly associated with bartholinitis and should be considered in the absence of other known pathogens. C. trachomatis is often detected more frequently in women with bacterial vaginosis than in those without. There is emerging evi- dence that indoles produced by bacterial vaginosis may facilitate persistence of chlamydial infection (see section ‘Chlamydia geno- type and disease’). Pelvic inflammatory disease PID comprises a spectrum of upper genital tract inflammatory dis-

orders among women, which includes any combination of endo- metritis, salpingitis, tubo-ovarian abscess and pelvic peritonitis. Chlamydial infection could be as much as 5–6 times more likely to be the cause of PID in women aged 16–19 years than in women aged 35–44 years. Chlamydial infection causes around one-third of PID cases in 16- to 24-year-old women, and about one-fifth of cases in 16- to 44-year-olds overall. Canalicular spread of C. trachomatis to the upper genital tract leads to endometritis, which is often plasma cell-associated and sometimes intensely lymphoid; it occurs in about 17% of women if left untreated. Further spread causes overt salpingitis (Fig. 8.6.45.3), which occurs in about 7% of women. It is women with visible evidence of salpingitis at laparosocopy who are at increased risk of reproductive sequelae. Spread to the peritoneum results in perihepatitis (the Fitz-Hugh– Curtis syndrome) (Fig. 8.6.45.4), sometimes confused with acute cholecystitis in young women, in addition to peri-appendicitis and other abdominal symptoms. This is uncommon. Surgical termination of pregnancy or insertion or removal of an intrauterine contraceptive device might predispose to dissemination of infection. PID is not easy to diagnose. Recent onset of lower abdominal pain in association with local tenderness on bimanual examination is now considered sufficient to believe that PID is possible and that early treatment is required. This is because it is now recognized that many women with salpingitis have subtle or mild symptoms and early treatment reduces the risk of developing chronic sequelae. (a) (b)
Fig. 8.6.45.2 (a) Mucopurulent cervicitis; (b) follicular cervicitis. Fig. 8.6.45.3 Laparoscopic view of inflamed fallopian tube due to C. trachomatis. Courtesy of P. Greenhouse.

8.6.45 Chlamydial infections 1285 A recent multiparameter evidence synthesis study of the natural history of C. trachomatis infection estimated that about 15% of in- cident infections progress to symptomatic PID, which may remain undiagnosed, with a further 2% developing asymptomatic disease. Of the c.7% of women who develop acute salpingitis, about 5–8% will develop tubal factor infertility and have a 2–3% risk of ectopic pregnancy. Other consequences of PID include chronic pelvic pain lasting more than 6 months, the risk of which is difficult to estimate and may occur in about a third of women with mild or moderate PID following treatment. There is conflicting evidence of the effect of C. trachomatis on pregnancy. Some studies have shown C. trachomatis infection to be associated with low birth weight and preterm delivery, but others have failed to confirm this. However, a recent observational study from the Netherlands showed a strong association between the de- tection of C. trachomatis and preterm labour. Rectal and pharyngeal infection Rectal infections are usually asymptomatic, but anal symptoms including discharge and discomfort occur occasionally. Rectal in- fection in men is associated with unprotected receptive anal inter- course. If men are symptomatic, LGV is the most likely cause. There is increasing evidence that rectal infection in women is associated with urogenital tract infection (see earlier) in addition to receptive anal intercourse. Pharyngeal infection is usually asymptomatic. While both men and women can be infected in the throat without ano-genital infection, this appears to be relatively uncommon. Other diseases associated with C. trachomatis Adult paratrachoma (inclusion conjunctivitis)
and otitis media Adult chlamydial ophthalmia is distinguished from trachoma by its causative C. trachomatis serovars D-K. It commonly results from the accidental transfer of infected genital discharge to the eye. In contrast to ‘reactive’ conjunctivitis observed in multisystem disease of sexu- ally acquired reactive arthritis (see next), C. trachomatis can usually be detected in conjunctival specimens. It usually presents as a uni- lateral follicular conjunctivitis, acute or subacute in onset, with an incubation period of up to 21 days. The features are swollen eyelids, mucopurulent discharge, papillary hyperplasia, and, later, follicular hypertrophy and occasionally

punctate keratitis. Up to one-third of patients have otitis media and complain of blocked ears and hearing loss. The disease is generally benign and self-limited. Pannus forma- tion and corneal scarring are rare and not seen if systemic treatment is given. Patients and their sexual contacts should be investigated for genital chlamydial infection and managed appropriately. Arthritis Arthritis occurring with, or soon after, nongonococcal ureth- ritis is sexually acquired reactive arthritis. A multisystem disease including a combination of urethritis, conjunctivitis, and arthritis is seen in about one-third of patients. Laboratory evidence of chla- mydial infection is found in at least one-third of patients. C. tracho matis has also been associated in the same way with 'seronegative' arthritis in women. Viable C. trachomatis has not been detected in the joints of patients with sexually acquired reactive arthritis, which is probably the result of immunopathology. The role of antimicro- bial therapy is uncertain. One recent treatment trial of chronic disease using combination therapy demonstrated benefit, whereas numerous previous treatment studies using appropriate therapy provided disappointing results. Immunocompromised patients C. trachomatis has been isolated from the lower respiratory tract of a few immunocompromised adults with pneumonia, some after renal transplantation. However, other pathogens have often also been present. C. pneumoniae is not an especially important re- spiratory tract pathogen in AIDS patients. Genital C. trachomatis infection is likely to increase viral shedding from HIV-positive people, and enhance the susceptibility to HIV in the uninfected. Hypogammaglobulinaemic patients do not appear to be especially prone to infection with any of the chlamydial species. Neonatal infections Although intrauterine chlamydial infection can occur, the major risk of infection to the infant is from passing through an infected cervix. The proportion of neonates exposed to infection de- pends, of course, on the prevalence of maternal cervical infection, which varies widely. Conjunctivitis appears in 20–50% of infants Fig. 8.6.45.4 Adhesions in perihepatitis (Fitz-Hugh–Curtis syndrome). Courtesy of P. Greenhouse

 exposed to C. trachomatis (serovars D–K) infecting the cervix at birth. A mucopurulent discharge (Fig. 8.6.45.5) and occasionally pseudomembrane formation occur 1 to 3 weeks later. It usually re- solves without visual impairment. Complications tend to be in un-treated infants. Approximately one-half of the infants who have conjunctivitis also develop pneumonia, although a history of recent conjunctiv- itis and bulging eardrums is found in only one-half of infants with pneumonia. Chlamydial pneumonia usually begins between the 4th and 11th week of life, preceded by upper respiratory tract symp- toms. There is tachypnoea, a prominent staccato cough, but no fever, and the illness is protracted. Radiographs show hyperinflation of the lungs with bilateral diffuse symmetrical interstitial infiltration and scattered areas of atelectasis. Finding serum IgM antibody to C. trachomatis in infants with pneumonia confirms the diagnosis. Children infected during infancy are more likely to develop ob- structive lung disease and asthma than are those who have had pneumonia due to other causes. The vagina and rectum of infants also may be colonized by C. tra chomatis at birth in about 25% of those infected, but this has not been associated with clinical disease. The majority remained posi- tive in the rectum up to one year after birth, suggesting colonization of the gastrointestinal tract, but there is no evidence of infant chla- mydial gastroenteritis. Diagnosis The laboratory diagnosis of current C. trachomatis infection is re- commended to be performed using validated and quality assured nucleic acid amplification tests (NAATs), identifying chlamydial- specific nucleic acid (DNA or RNA) in clinical specimens. If chlamydial NAATs are not available or affordable, isolation of C. tra chomatis in cell culture or detection of chlamydial cells or antigens by direct fluorescence assays or enzyme-linked immunosorbent as- says (ELISA) can be used for diagnosis of acute chlamydial infection. However,

the modern NAATs, with their clearly superior sensitivity and other performance characteristics (e.g. high specificity, range of specimen types, automation, and independence from maintain ing organism viability), have made these other diagnostic methods obsolete in high-income countries. For urogenital chlamydial detec- tion, NAATs can be used to examine noninvasively collected speci- mens such as a first catch urine samples in men, or a vulvo-vaginal swab in women, which are the first-choice clinical samples. Specimen type A vulvo-vaginal swab is the preferred specimen type in women for detection using a NAAT. It is important that manufacturers' in- structions are followed strictly with the swab being gently rotated for 10–30 seconds inside the vagina. It can be self-collected or clinician-obtained. It is more sensitive than either a urine specimen or an endocervical swab and more acceptable to women than the other specimen types. Endocervical specimens require a speculum examination and it is important to ensure the columnar epithelial cells are adequately sampled. Inadequate vulvo-vaginal swab and endocervical specimens will reduce the sensitivity of the test. First catch urine specimens from women have a good sensitivity, despite not being ideal, and can be used when a vulvo-vaginal swab spe- cimen is not possible. A first catch urine specimen is easy to collect in men and has similar if not better sensitivity to a urethral swab (which is painful) for detection using a NAAT. A first catch urine specimen is there- fore the specimen of choice in men. Men should be instructed to not void urine at least one hour prior to producing a first catch urine specimen. There is some evidence that a self-taken meatal swab may also be an adequate specimen type in men. A swab should be used for collecting rectal and pharyngeal spe- cimens for analysis using NAATs. These can be clinician or patient collected. Care needs to be taken when pharyngeal specimens are collected as it is important that the pharynx and not the mouth is sampled. While current NAATs are not commercially licensed for rectal and pharyngeal specimens, the published evidence suggests that test performance is also high for these specimens. When specimens are required for culture they must contain col- umnar epithelial cells. Endocervical swabs in women and urethral swabs in men are therefore the required specimen type. Nucleic acid amplification tests (NAATs) The enormous amplification of specific nucleic acid sequences with the polymerase chain reaction (PCR) assay, the strand displacement assay (SDA), and the transcription-mediated amplification (TMA) technique has overcome the lack of specificity and relatively low sensitivity of all other C. trachomatis diagnostic tests. Furthermore, additional advantages are that many NAATs detect C. trachomatis and N. gonorrhoeae simultaneously and that NAATs can be used to test noninvasive specimens such as first catch urine samples in men or vulvo-vaginal swabs in women (first catch urine samples in women result in a suboptimal sensitivity). The NAATs are also ideal for automation, which increases the standardization and quality as- surance, and high throughput. The currently available commercial TMA-based C. trachomatis NAATs target 23S rRNA or 16S rRNA, which are present in many copies in each bacterial cell. Several of the commercially available C. trachomatis PCR assays, as well as the SDA-based NAAT, detect genetic sequences in the cryptic plasmid, also present in multiple copies in each C. trachomatis cell. Plasmid- free C. trachomatis strains have been exceedingly rare and are most likely less virulent. Using a multiple copy target significantly in- creases the sensitivity of the NAATs. A new variant of C. trachomatis Fig. 8.6.45.5 Mucopurulent neonatal conjunctival discharge due to C. trachomatis.

 (nvCT; serovar E) that had escaped detection by two internationally commonly used PCR-based NAATs was found in Sweden in 2006. The nvCT has a 377 bp deletion in the cryptic plasmid, which in- cluded the genetic target sequence for both these NAATs. The nvCT caused thousands of false-negative C. trachomatis tests in Sweden, fewer tests in

other Scandinavian countries, and very few in other countries. All the main commercial NAATs used in Europe can now detect nvCT; that is, the affected NAATs have been redesigned (in- cluded a second genetic target sequence) to ensure detection of the nvCT. This underlines the importance of taking into account the structure and function of genomes when selecting appropriate target sequences for NAATs and also that dual-target NAATs might have to be considered for many infectious diseases. The nvCT story also emphasizes the importance of detailed analysis of incidence, locally, nationally, and internationally, and timely attention to unexplained significant declines, as well as participation in appropriate external quality assurance schemes. Currently commercially available and properly validated C. tra chomatis NAATs are sufficiently specific to not require confirmation by another NAAT, targeting another genetic sequence, when used in high prevalence populations. However, no test is 100% sensitive or specific, and in medico-legal cases a reactive NAAT should be con- firmed using a different NAAT target. NAAT technology is rapidly advancing with the emergence of rapid point-of-care NAATs and multiplex NAATs. In general, the performance characteristics of dif- ferent NAATs differ. Accordingly, care should be taken to use only those assays which have been appropriately validated using properly designed studies of sufficient size. Culture and staining of Chlamydiae The growth of Chlamydiae more than 50 years ago in cultured cells, rather than in embryonated eggs, revolutionized their detection and chlamydial research. C. pneumoniae is particularly difficult to iso- late, but will grow in selected cell lines including Hep-2. The iso- lation of C. trachomatis involves centrifugation of specimens onto cycloheximide-treated McCoy cell monolayers, followed by incu- bation and then staining with a fluorescent monoclonal antibody or with a vital dye, usually Giemsa, to detect inclusions. One blind passage may increase sensitivity, but cell-culture techniques need to maintain organism viability and are slow, labour intensive, and no more than 70% sensitive compared to appropriate NAATs in many settings. Staining of epithelial cells in ocular and genital smears with vital dyes to detect chlamydial inclusions in microscopy is insensitive and often nonspecific. In contrast, microscopic detection of elem- entary bodies using species-specific fluorescent monoclonal anti- bodies is rapid, relatively sensitive, and specific for C. trachomatis oculo-anogenital infections, in the hands of skilled observers. When NAATs are not available or affordable, this test can be suitable for testing lower number of specimens. Due to the superior sensitivity and most other performance char- acteristics of the modern C. trachomatis NAATs, almost all these earlier diagnostic methods are obsolete in high-income countries. Point-of-care tests The currently available, mostly immunochromatographic, rapid point-of-care (POC) tests for C. trachomatis have insufficient sen- sitivity, compared to NAATs, to be used in clinical practice. Rapid POC tests using nucleic acid amplification technologies with in- creased sensitivity and high specificity have been developed. The number of such tests approved for clinical use is likely to increase over time. While modelling suggests POC NAAT tests could im- prove outcomes and reduce costs this has yet to be demonstrated in clinical practice. Serological tests NAATs detect current infection, but not past exposure. Serological tests, on the other hand, detect both current and previous exposure with varying degrees of sensitivity and specificity. Mucosal infection produces a weak antibody response in many patients, particularly in men, while invasive and/or upper genital tract infections usually result in high antibody titres. Antibody titres, in general, decline with time since infection, but can remain detectable for many years. Serology should, therefore, not be used to detect current uncom- plicated infection. Nevertheless, when NAATs are not available, de- tection of specific antibodies to C. trachomatis might support the diagnosis of invasive disease, such as invasive LGV and neonatal pneumonia Detection of C. trachomatis antibodies in patients is compli- cated by cross-reaction with other chlamydial species, particularly C. pneumoniae. More recent serological

assays have overcome this by using C. trachomatis specific MOMP peptides or Pgp3 antigen which is not present in C. pneumoniae. The traditional complement-fixation test cannot distinguish between the chlamydial species as it detects the genus-specific LPS antigen. Historically most of the pertinent diagnostic information originates from use of the MIF test which measures class-specific antibodies (IgM, IgG, IgA, or secretory) to the purified elementary bodies. A significant increase in IgM and/or IgG titre is so unusual in uncomplicated infection that the test is of little value. In PID, espe- cially in the Fitz-Hugh–Curtis syndrome, antibody titres tend to be higher than in uncomplicated cervical infections. A high IgG anti- body titre (1:256 or greater), suggests causation in pelvic disease, but high titres do not always correlate with detection of Chlamydiae and are associated more with chronic or recurrent disease. Specific C. trachomatis IgM antibody in babies with pneumonia is pathog- nomonic of chlamydia-induced disease. Furthermore, patients with rectal LGV infections develop high antibody titres and, if NAATs are not available, high antibody titres can be used as a diagnostic tool. Treatment of C. trachomatis infections Chlamydiae are intracellular and hence insensitive to aminoglycosides and other antibiotics that do not penetrate cells efficiently. They are however sensitive to many antibiotics and particularly sensitive to tetracyclines and macrolides, and also to a variety of other drugs. The rifamycins are probably more active than the tetracyclines in vitro, but the activity has been lower in vivo. Rifamycins have only rarely been used to treat refractory chlamydial infections, and they are reserved for mycobacterial infections. Antimicrobial resistance Induced resistance to antimicrobials in C. trachomatis due to muta- tions in drug target or other bacterial genes has been demonstrated in vitro. However, there is no evidence of any classical antimicrobial

 resistance (stable, homotypic genetic resulting in phenotypic resistance in bacteria) to any antimicrobials in clinical C. trachomatis strains that affects the in vivo treatment in humans. Nevertheless, vigilance is needed to detect resistant strains if and when they do emerge, which would not be possible with the routine diagnostic procedures using commercial NAATs (see earlier). There is evidence to suggest that phenotypic switching of at least part of the cell population of a C. trachomatis strain can occur. The bacterium exhibits the phenomenon of heterotypic resistance at high infectious loads in vitro and there is circumstantial evidence this may occur in vivo. That is, replication, at high loads, generates a heterogeneous population of resistant and susceptible bacteria. Subsequent subculture of a single resistant organism derived fol- lowing propagation on antimicrobial-containing medium, results in a fully susceptible organism (i.e. the antimicrobial resistance is not genetically inherited, or the decreased biological fitness of the resistant cells results in them getting outcompeted by susceptible cells). The resistant cells might replicate more slowly, which also might make them less susceptible to antimicrobial therapy. High infectious loads are associated with disease (e.g. nongonococcal ur- ethritis in men). It has been proposed that this might explain the reduced efficacy of azithromycin in men with nongonococcal ur- ethritis compared to asymptomatic individuals, with a higher dose likely to increase efficacy. Antimicrobial therapy Doxycycline 100 mg twice a day for 7 days in uncomplicated ano- genital non-LGV C. trachomatis infection including nongonococcal urethritis is more than 97% effective. In LGV, a 21-day treatment is recommended (see the ‘Lymphogranuloma venereum’ section). A single dose of azithromycin 1 g enhances compliance and has a similar efficacy, although efficacy is reduced in chlamydial urethritis and rectal infection. There is a danger of inducing resistance in other bacteria, for example Mycoplasma genitalium (see Chapter 8.6.46 on Mycoplasmas). It has been proposed that a longer duration of therapy and increased dose might improve efficacy of azithromycin. The macrolide erythromycin can be used to treat chlamydial

infec- tions in infants and young children. The newer fluoroquinolones are among other active drugs, but they have not been appropriately evaluated in vivo and are not used regularly. Table 8.6.45.2 shows details of the doses and duration of anti- biotic treatment. Systemic treatment is given as well as, or in pref- erence to, topical treatment to eradicate nasopharyngeal carriage in trachoma, for paratrachoma and for neonatal chlamydial conjunc- tivitis, since topical treatment provides no additional benefit. Oral erythromycin should be used to treat conjunctivitis and to prevent the development of pneumonia in infants and young children due to the limited data on efficacy and optimal dose of azithromycin in this patient group. Table 8.6.45.2 Recommended first-line treatment schedules for chlamydial infections and associated diseases (readers should refer to respective chapters for syndromic management of specific diseases and online guidelines published by BASHH, IUSTI, and CDC) Disease/infection Antibiotic Dose schedulea Duration (days) Trachoma Azithromycin alone 20 mg/kg (up to 1 g) Single dose Topical tetracycline 1% ointment daily 42 Oculo-anogenital tract infectionb Doxycycline 100 mg twice daily 7 or azithromycin 1 g Single dose Rectal infection (serovars D–K) Doxycycline 100 mg twice daily 7 Adult inclusion conjunctivitis Doxycycline 100 mg twice daily 7 or azithromycin 1 g Single dose Epididymo-orchitis secondary to C. trachomatis Doxycycline 100 mg twice daily 14 Include ceftriaxone if N. gonorrhoeae coinfection not excluded 500 mg intramuscularly Single dose Pelvic inflammatory disease secondary to C. trachomatis (see Chapter 9.8) Ceftriaxone 500 mg intramuscularly Single dose then doxycycline 100 mg twice daily 14 and metronidazole 400 mg twice daily 14 Pelvic inflammatory disease secondary to C. trachomatis (see Chapter 9.8) and N. gonorrhoeae excluded Ofloxacin 400 mg twice daily 14 and metronidazole 400 mg twice daily 14 Neonatal infections Erythromycin syrup 50 mg/kg daily in four divided doses 14 Lymphogranuloma venereum Doxycycline 100 mg twice daily 21 C. pneumoniae infections Doxycycline 100 mg twice daily 14–21c C. psittaci infections Doxycycline 100 mg twice daily 14–21c BASHH, British association for Sexual Health and HIV (www.bashh.org/BASHH/Guidelines/Guidelines/BASHH/Guidelines/Guidelines.aspx); IUSTI, International Union against Sexually Transmitted infections (www.iusti.org/regions/Europe/euroguidelines.htm); CDC, Centers for Disease Control and Prevention (www.cdc.gov/std/tg2015/) a All antibiotics orally unless otherwise indicated. b Doxycycline is preferred if urethritis is present in men. c. Relapse more often with short course.

8.6.45 Chlamydial infections 1289 Complicated infections In general, a longer duration of therapy is administered in com- plicated disease such as epididymo-orchitis and PID. Treatment is usually started before a microbiological diagnosis can be established and gonorrhoea excluded. If gonorrhoea is suspected treatment regimens include cover for this infection as well. As PID is often polymicrobial, additional broad-spectrum antibiotic cover particu- larly for anaerobes is required (see Chapter 9.8 on PID). Compliance and partner notification Compliance is improved if a brief discussion about C. trachomatis is undertaken, supplemented by a leaflet, about how it is transmitted and what can happen if it is not treated. Patients should be advised about the importance of completing the course of antimicrobial pre- scribed and to avoid sexual intercourse (including oral sex) until they and their partner(s) have completed treatment (or wait 7 days if treated with azithromycin 1 g) and their symptoms, if present, have resolved. Identification and treatment of partners is essential to re- duce the risk of reinfection and on-going transmission from infected partner(s). This is best undertaken by a person with specific training in partner notification. In general, for symptomatic individuals the look-back period is 4 weeks and 6 months if asymptomatic. Test of cure and repeated testing A test of cure (TOC) is not advocated to be

performed in patients treated with recommended first-line treatment. However, it is recommended in pregnancy, in complicated infections, if symptoms persist, if second-line or third-line treatments have been used, and if noncompliance to therapy or re-exposure of infection is suspected. It could also be considered in rectal infections, that is, when azithromycin 1 g stat has been administered for treatment of rectal infections. In these situations, TOC using NAATs should be performed 4–5 weeks after completion of therapy. Accordingly, NAATs may remain positive for at least 3 weeks after treatment (and in some patients possibly up to 8 weeks due to intermittent shedding of nu- cleic acid). However, a positive test does not necessarily mean active infection as it may represent the presence of nonviable organisms. C. trachomatis-positive individuals are at increased risk of re- testing positive within the next year. There are several potential ex- planations and it is likely that more than one applies. These include reinfection, repeat infection from an untreated partner and anti- microbial failure. Accordingly, repeat testing in 3–6 months should ideally be offered to at least young women and men (<25 years of age) who test positive for C. trachomatis. Prevention Health promotion The risk of chlamydial infection and sexually transmitted infections (STIs) in general can be reduced by consistently and correctly using condoms until all partners have had a sexual health screen, and re- ducing the number of sexual partners and avoiding overlapping sexual relationships. As the incidence of C. trachomatis infection is highest in women aged 16–17 years, this advice needs to be pro- vided not only to sexually active adults and reinforced when and if they acquire a STI but also before individuals become sexually ac- tive. The most appropriate way to deliver this advice is through high quality sex education in schools which focuses as much on healthy relationships and self-esteem as the negative consequences of sexual intercourse. Chlamydia screening Due to the disease burden associated with chlamydial infection, testing has been promoted and increased worldwide. Detection rates of C. trachomatis infections have increased since around 2000 in most developed countries, which is largely attributable to increased testing made possible by the introduction of highly sensitive NAATs enabling noninvasive testing. Moreover, chlamydia screening has been demonstrated in randomized controlled trials to reduce the rates of PID in women, but not prevalence. England and the United States have introduced screening programmes. England fully im- plemented the National Chlamydia Screening Programme (NCSP) in 2008 for men and women less than 25 years of age. Screening is recommended annually and on change of sexual partner. Annual screening is also recommended in the United States for sexually ac- tive women aged less than 25 years, as is screening of older women at increased risk for infection. This has resulted in a substantial in- crease in testing in both countries. Mathematical models in general have estimated that screening will reduce prevalence, that is, if the screening coverage is suffi- ciently high. In England 1.6 million tests in 16–24 years old indi- viduals were undertaken in 2014 with an estimated 35% of young females and 14% of young males being tested. Routine surveillance data is not representative of the general population. This means that current infection in those tested is not an adequate indicator of population prevalence and exposure over time and cannot be used to evaluate effectiveness. It is, as yet, not known whether the NCSP has reduced prevalence or is cost effective. A sensitive and specific sero- logical marker of cumulative lifetime exposure would contribute to evaluation of the screening programmes. The use of Pgp3 antibody for this purpose is currently being evaluated. A recent ecological association study from the United States suggests that widespread chlamydia screening may have resulted in a decline in incidence of chlamydia infection, PID, and ectopic pregnancy. Lymphogranuloma venereum LGV is a systemic, ulcerative sexually transmitted infection caused by serovars L1, L2 (including subvariants such as L2b), and L3 of C. trachomatis. These serovars are more virulent in animal models than serovars A-K, and

more invasive in humans. Serovars A-K are largely confined to mucosal columnar epithelial surfaces of the uro- genital tract and eye, but the LGV serovars predominantly infect monocytes and macrophages, which pass through the epithelial sur- face to regional lymph nodes and may cause ulceration and bubonic disseminated infection. Clinical features The incubation period is from less than 1 to 4 weeks. The traditional clinical course of LGV can be divided into three stages. The primary stage at the site of inoculation, the secondary stage in the regional lymph nodes and/or the anorectum, and the tertiary stage of late sequelae affecting the genitalia and/or rectum. The primary stage begins with a small, painless papule which might ulcerate. It occurs at the site of inoculation, usually the

section 8 Infectious diseases 1290 prepuce or glans in men; anorectal and rectosigmoid colon sites in men who have sex with men (MSM); or the vulva, vaginal wall, or occasionally the cervix in women. Extragenital primary lesions on fingers or tongue are rare. The primary lesion is self-healing and may pass unnoticed by the patient, especially if it is in the alimentary tract of MSM. Patients with LGV presenting with buboes might not be aware of having had an ulcer. The secondary stage occurs some weeks after the primary lesion, which has usually healed.
C. trachomatis-infected cells are carried to regional or rectal lymph nodes. The inguinal form is more common in men than women, since the lymphatic drainage of the upper va- gina and cervix is to the retroperitoneal rather than the inguinal lymph nodes. LGV proctitis occurs in those who practise receptive anal intercourse, probably due to direct inoculation. The cardinal feature of the inguinal form of LGV is painful, usu- ally unilateral, inguinal, and/or femoral lymphadenopathy (bubo) (Fig. 8.6.45.6). Adenopathy above and below the inguinal ligament gives rise to the ‘groove sign’ in 10 to 20% of patients, once believed to be pathognomonic. Enlarged lymph nodes are usually firm and often accompanied by systemic signs of fever, chills, arthralgia, and headache. Biopsy reveals small discrete areas of necrosis surrounded by proliferating epithelioid and endothelial cells. These areas of ne- crosis may enlarge to form stellate abscesses, which may coalesce and break down to form discharging sinuses, although this phe- nomenon occurs in less than one-third of patients with inguinal dis- ease. In women, signs include a hypertrophic suppurative cervicitis, backache, and adnexal tenderness. Anorectal involvement is seen predominantly in MSM. Clinical features include a haemopurulent anal discharge, anorectal pain, and bleeding due to an acute haem- orrhagic proctitis or proctocolitis, and there may be pronounced systemic signs of fever, chills, and weight loss. In contrast to pre- vious reports from the United Kingdom, studies in the Netherlands have now shown that about 25% of LGV infections among MSM can be asymptomatic. These cases might also include early detection of LGV at a ‘presymptomatic’ stage of disease, found among people who are regularly screened for rectal C. trachomatis. Proctoscopy re- veals a granular or ulcerative proctitis from which large numbers of polymorphonuclear leucocytes are seen in rectal smears. Computer tomography or magnetic resonance imaging scans may show pro- nounced thickening of the rectal wall, with enlargement of iliac lymph nodes. Enlarged inguinal nodes may also be palpable. Extragenital infection can cause lymphadenopathy outside the inguinal region. For example, cervical adenopathy due to LGV has been reported after oral sex, and laboratory workers who de- veloped pneumonitis after accidental inhalation of LGV strains of C. trachomatis were found to have mediastinal and supraclavicular adenopathy. A follicular conjunctivitis has also been described fol- lowing direct inoculation of the eye, which may be accompanied by preauricular lymphadenopathy. Other rare manifestations of the secondary stage include acute meningoencephalitis, synovitis, and cardiac involvement. The tertiary stage appears after a latent period of several years, but all late complications are rare

today because of the use of broad- spectrum antibiotics. Chronic untreated LGV leads to fibrosis, which may cause lymphatic obstruction and elephantiasis of the genitalia in either sex, or rectal strictures and fistulae. Rarely, it can give rise to the syndrome of esthiomene (Greek: ‘eating away’), with widespread destruction of the external genitalia (Fig. 8.6.45.7). Epidemiology LGV has been endemic in parts of Africa, Asia, South America, and the Caribbean, but before 2003 very rarely detected in Western Europe, North America, and other high-income countries for many
Fig. 8.6.45.6 Ulcer on penis and lymphadenopathy with ‘the groove sign’ due to lymphogranuloma venereum. Courtesy of C. O’Mahony. Fig. 8.6.45.7 Esthiomene: destruction of the female genitalia by lymphogranuloma venereum in a Nigerian patient. Copyright D. A. Warrell

 years. The reported sex ratio is greater than 5:1 in favour of men, which is probably due to the easier recognition of disease in men. The global epidemiology of infection is poorly defined because LGV is often indistinguishable clinically from chancroid and other causes of genital ulceration with bubo formation, and it has been difficult to obtain laboratory confirmation in many settings world- wide. In 2003, an outbreak of LGV proctitis and proctocolitis due to a clonal expansion of a serovar L2b strain was reported among MSM in Rotterdam, the Netherlands, and since then many thousands of cases have been reported in MSM across Western Europe (including the United Kingdom), North America, and Australia. The LGV L2b strain is also found in the heterosexual population. Genomic ana- lysis of the LGV L2b strain has now shown that this is unlikely a newly emerged epidemic strain, but instead an old strain. A LGV L2b sample was originally identified in San Francisco, United States in the 1980s. Furthermore, rectal LGV has probably been present for years, remaining undetected because of the poor sensitivity of diagnostic tests prior to the introduction of NAATs and/or lack of sampling for C. trachomatis diagnostics in many of these patients. Most infected MSM have been HIV-positive. Many of these patients have attended healthcare departments with atypical presentations (that is without any genital ulceration or the typical inguinal buboes) including proctitis or tenesmus, anorectal discharge, and discom- fort, diarrhoea, or altered bowel habits. Due to this symptomology, LGV should be considered as a differential diagnosis in patients with proctitis or inflammatory bowel disease (IBD)-related symptoms, especially among HIV-positive men. Diagnosis LGV can present as a genital ulcer, inguinal lymphadenopathy (usu- ally painful) without evidence of genital ulceration, or proctitis/ proctocolitis. The differential diagnosis of sexually acquired genital ulceration also includes chancroid, herpes, syphilis, and the exceed- ingly rare donovanosis (granuloma inguinale). Less common causes of ulceration include trauma, nonvenereal infections such as cuta- neous leishmaniasis or amoebiasis, and fixed drug eruption. The differential diagnosis of inguinal adenopathy includes chancroid, herpes, and syphilis, although there is usually a genital ulcer or at least a history of an ulcer in these conditions. Chronic sinus for- mation in the inguinal region might be due to tuberculosis of the lumbar spine, and bubonic plague should be considered in endemic areas where a patient with inguinal lymphadenopathy is acutely ill. LGV proctitis should be considered as a differential diagnosis in pa- tients with inflammatory bowel disease due to ulcerative colitis or Crohn’s disease, particularly among HIV-positive men, because clin- ical and histopathological features may be identical. Since anorectal LGV needs management different to that for non-LGV chlamydial infections, in some European settings all MSM, irrespective of ano- rectal symptoms, who report receptive anal sex in the previous six months are tested for anorectal C. trachomatis infection with a com- mercially available NAAT. MSM who are anorectal C. trachomatis- positive are then recommended to be tested for LGV using a genovar L-specific NAAT. Highly sensitive and specific laboratory diagnosis of LGV depends on identification of

C. trachomatis LGV serovars (L1-L3) in appro- priate clinical specimens using NAATs. All commercially available validated C. trachomatis NAATs detect LGV strains. However, an LGV-specific in-house PCR or ompA-sequencing is required to distinguish the LGV serovars (L1-L3) from the trachoma serovars (A-K). If a NAAT is unavailable, serology can be used. Accordingly, due to its invasive nature LGV infections induce higher serum anti- body titres than do uncomplicated genital infections with C. tra chomatis serovars D-K. The MIF test can distinguish between infections with different chlamydial species. A MIF titre exceeding 1:128 strongly suggests LGV, particularly in a patient with typical signs and symptoms, although invasive genital infection with C. tra chomatis serovars D-K, as in PID, can also give rise to high anti- body titres. However, a low antibody titre does not exclude LGV. C. trachomatis can also be identified in a smear of bubo material by direct fluorescence microscopy using commercially available con- jugated monoclonal antibody, although bacterial contamination impedes detection and the sensitivity of this diagnostic method is suboptimal. C. trachomatis can be isolated in cell culture from ulcer material, bubo aspirate, or endourethral or endocervical scrapings, but the success rate is poor. Treatment Despite a paucity of strong evidence regarding the efficacy of therapy for LGV, 21 days of oral doxycycline 100 mg twice daily is the first- line recommendation. However, doxycycline is contraindicated in pregnancy and breastfeeding. Second-line is erythromycin 500 mg four times daily for 21 days. Fever and bubo pain subside rapidly after antimicrobial treatment is started, but buboes may take several weeks to resolve. Azithromycin in single- or multiple-dose regimens has been suggested and also successfully used in some cases, but suf- ficient evidence is lacking to currently recommend this antibiotic. Adjunctive therapy might also be needed. This includes prompt as- piration of fluctuant buboes through healthy adjacent skin and sur- gical repair, including reconstructive genital surgery, for patients with residual fibrotic lesions, strictures, fistulae, or esthiomene. Trachoma Trachoma is a chronic keratoconjunctivitis caused by the ‘ocular’ serovars A, B, Ba, and C of C. trachomatis. In the 19th century it was an important and common cause of blindness in Europe and North America, but it disappeared from more affluent parts of the world as living standards improved in the 20th century. In poor commu- nities where hygiene standards are low, there is direct transfer of chlamydial organisms from eye to eye and trachoma is endemic. As standards of hygiene improve, this mode of transmission is no longer possible, and trachoma tends to disappear. It is now a disease of poor rural communities, mainly in Africa and Asia, but it remains the leading infectious cause of blindness worldwide. A recent review by the WHO estimated that trachoma was responsible for 1.4% of global blindness, causing visual impairment in 1.8 million people and irreversible blindness in 0.5 million. Clinical features The active (inflammatory) stage of trachoma is a follicular con- junctivitis, affecting chiefly the subtarsal conjunctiva, but follicles can be seen elsewhere on the conjunctiva and at the limbus. Such subconjunctival follicles are the characteristic sign of active disease (Fig. 8.6.45.8) and are usually seen in children in endemic areas. Limbal follicles resolve leaving characteristic shallow depressions

 known as Herbert’s pits. New vessels (pannus) might be seen at this stage in the cornea (Fig. 8.6.45.9), usually at the superior margin, and punctate keratitis might also be a feature. Since symptoms are mild or absent at this stage, the disease might not be suspected un- less the upper eyelid is everted. C. trachomatis can often be found in active cases, although follicles can persist for some time after infec- tion has been cleared. Intense inflammation is seen in the subtarsal conjunctiva in some cases (Fig. 8.6.45.10) in which the C. tracho matis bacterial loads are higher. The disease can progress over many years and, with repeated infection, result in conjunctival scarring (Fig. 8.6.45.11). As the scars contract, the lid margin turns inwards

(entropion), and the eyelashes rub against the cornea, a condition known as trichiasis (Fig. 8.6.45.12). This damages the cornea, even- tually rendering it opaque and causing blindness. The WHO criteria for the clinical diagnosis of active trachoma and its potentially blinding sequelae, and for grading their severity is as follows: 1 Trachomatous inflammation, follicular (TF)—five or more follicles, each at least 0.5 mm in diameter, in the upper tarsal conjunctiva (Fig. 8.6.45.8) 2 Trachomatous inflammation, intense (TI)—pronounced in- flammatory thickening of the tarsal conjunctiva that obscures more than one-half of the normal deep tarsal blood vessels (Fig. 8.6.45.10) 3 Trachomatous conjunctival scarring (TS)—easily visible scar- ring in the tarsal conjunctiva (Fig. 8.6.45.11) 4 Trachomatous trichiasis (TT)—at least one eyelash rubbing on the eyeball, or evidence of recent removal of inturned eyelashes (Fig. 8.6.45.12) 5 Corneal opacity (CO)—easily visible corneal opacity over the pupil, so dense that at least part of the pupil margin is blurred when viewed through the opacity Epidemiology Trachoma is a disease of poverty, which disappears as living stand- ards improve. In the past, it has been endemic in urban commu- nities such as in the East End of London, but it is now a disease of rural communities that lack access to water and sanitation, espe- cially affecting marginalized groups. The reservoir of infection in endemic areas is the eye, and possibly the nasopharynx, of children with active disease.
C. trachomatis can be transferred from the eye of one individual to that of another via fingers, fomites, coughing and sneezing, and by eye-seeking flies. Active cases tend to cluster in households with prolonged intimate contact within the family. Fig. 8.6.45.8 Everted upper eyelid showing follicular trachoma. Fig. 8.6.45.9 Extensive neovascularization of the cornea (pannus) due to trachoma. Fig. 8.6.45.10 Everted upper eyelid showing intense inflammatory trachoma.
Fig. 8.6.45.11 Everted upper eyelid showing trachomatous scarring.

 The higher prevalence of active disease and scarring in women than in men is probably due to their closer contact with children. Severe conjunctival scarring is associated with repeated exposure to reinfection. Diagnosis In trachoma-endemic areas, the diagnosis is made on clinical grounds, following the simplified WHO grading scheme (Figs. 8.6.45.8, 8.6.45.10–8.6.45.12). Trachomatous follicles (TF) might be con- fused with the giant papillae of vernal conjunctivitis, in which pannus may also be seen. Several viruses, notably adenoviruses, can cause a short-lived follicular conjunctivitis. Intense cases of trachoma inflammatory (TI), in which follicles might not be visible, should be distinguished from bacterial conjunctivitis. The diagnosis of trachomatous scarring (TS) is usually obvious, as few other condi- tions cause conjunctival scarring affecting the upper lid. Laboratory diagnosis of ocular C. trachomatis infection can help to direct treat- ment to communities with the greatest need, since clinical signs can persist for years after infection has been cleared. C. trachomatis can be found by PCR or another NAAT in a high proportion of cases of active inflammation (TF or TI), but in only a minority of those with scarring disease (TS). Treatment Inflammatory trachoma (TF and TI) responds to antimicrobial treatment (Table 8.6.45.2). The WHO recommends a single oral dose of azithromycin (20 mg/kg, to a maximum of 1 g) or, in pregnant women and children under 6 months of age, 1% top- ical tetracycline ointment, to be applied to both eyes twice daily for 6 weeks. Community-based mass treatment is recommended where the prevalence of TF exceeds 10% in children aged 1 to 9 years. Reinfection is rapid if individual cases are treated sep- arately, and the WHO also recommends that interventions to reduce transmission, such as face washing and environmental im- provement, should be implemented where trachoma is endemic. Trichiasis requires surgical correction. Several eyelid operations have been described, but a recent randomized controlled trial showed clearly that posterior lamellar tarsal rotation is the oper- ation of choice. Prevention The WHO has

launched a strategy for the global elimination of blinding trachoma as a public health problem by the year 2020, based on the acronym ‘SAFE’: Surgery for trichiasis, Antibiotics for the treatment of inflammatory disease and the elimination of the res- ervoir of infection, promotion of Face washing, and Environmental improvement to reduce fly populations and hence transmission. There is evidence that the prevalence of active trachoma has fallen in several countries in Africa and Asia in recent years following the implementation of the SAFE strategy. C. pneumoniae infections The prototype strains of C. pneumoniae were isolated in the 1960s from conjunctival samples collected from a child in Taiwan (strain TW-183) and another in Iran (strain IOL-207). In 1983, a third C. pneumoniae strain was isolated, this time from the throat of a pa- tient with acute respiratory (AR) disease, such as pharyngitis (strain AR-39). This prompted the name TWAR (TW + AR) being coined for the isolates. The two original isolates (TW-183 and IOL-207) were serologically identical and distinct from C. trachomatis and C. psittaci. In 1989, C. pneumoniae was defined as the third species of the genus Chlamydia. Only one serovar of C. pneumoniae has been identified, although minor geographical serovar variations are described. Clinical features Respiratory tract disease After an incubation period of approximately 3 weeks, acute dis- ease often begins with pharyngitis. More than 80% of patients with lower respiratory tract disease have a sore throat. A cough may de- velop later but fever is uncommon. Bronchitis sometimes appears and in young adults about 5% of primary sinusitis is associated with C. pneumoniae. Mild respiratory tract infections are probably frequent, but pneumonia is most common. Radiographs usually reveal a unilateral pneumonia, but more severe infection causes bilateral signs. This is often difficult to distinguish clinically from Mycoplasma pneumoniae and other pneumonias. Up to one-fifth of exacerbations of chronic obstructive pulmonary disease are associ- ated with C. pneumoniae and it has been implicated in exacerbations of both adult and childhood asthma. Arthritis An exaggerated synovial lymphocyte response to C. pneumoniae has been found in some adults with reactive arthritis and C. pneumoniae DNA and high titres of specific antibody have been detected in syn- ovial fluid from the joints of a few children with juvenile chronic arthritis, suggesting the possibility of a causal role. Atherosclerosis Finnish investigators in the 1980s observed an association between chronic coronary heart disease or acute myocardial infarction and antibody to C. pneumoniae. The idea of chronic infection was en- hanced by the detection of Chlamydiae or their DNA in at least 40% of atheromatous plaques in coronaries and other major and occasionally minor arteries, but not in normal tissue, of people as young as 15 years of age. Specific DNA was also found in peripheral

Fig. 8.6.45.12 Trachomatous trichiasis.

 blood mononuclear cells, suggesting the possibility that they might transmit the organisms from the respiratory tract to the arterial wall. Furthermore, studies in animal models provided some support for the atheroma-C. pneumoniae association. However, euphoria about these findings was dealt a blow by the results of three major anti- biotic trials in the United States. Subjects who received long courses of azithromycin in two trials and gatifloxacin in the other, subse- quently experienced untoward coronary events as often as those given a placebo. Admittedly this outcome was not completely unex- pected in patients with well-established, long-standing disease. Other diseases The existence of C. pneumoniae in peripheral monocytes means that the organisms might engage with any tissue/organ. In hindsight, this provides some credibility for claims for a role in conditions as di- verse as Alzheimer’s disease, stroke, and multiple sclerosis, as well as chronic secretory otitis media, cystic fibrosis, sarcoidosis, and primary biliary cirrhosis. However, there is absolutely no credible evidence to suggest a causal association with any of the conditions mentioned. Epidemiology Molecular typing studies suggest that animal strains of C. pneumo niae are ancestral to human strains and that C. pneumoniae crossed from animals to

humans as a result of at least one relatively re- cent zoonotic event. C. pneumoniae genotypes have been detected in horses, koalas, bandicoots, amphibians, and reptiles but, apart from the event mentioned earlier, there is otherwise no evidence of transfer to humans, even when there might be close contact, for ex- ample with koalas. It is thought that human strains of C. pneumoniae are transmitted directly from person to person and serological evi- dence indicates that infection is widespread and endemic in many areas. However, localized respiratory epidemics have been recorded in both military and civilian groups in Scandinavia, the United States, the United Kingdom, and elsewhere. C. pneumoniae probably causes many mild respiratory tract infections that were previously thought to be viral in origin and it is also likely that many infections labelled 'human psittacosis' or 'ornithosis' in the past were due to C. pneumoniae and not C. psittaci. C. psittaci infections The C. psittaci species forms a diverse group isolated from a variety of mammals, reptiles, and many avian species. There is a relatively low degree of homology between six serovars exhibited in DNA– DNA hybridization analyses, with the possibility of further differen- tiation between organisms assigned to the species. The spectrum of diseases in animals, cattle, sheep, goats, and more than 400 species of birds caused by C. psittaci includes conjunctivitis, pneumonia, enteritis, abortion, sterility, arthritis, and encephalitis, all of which result in economic loss. Organisms of all serovars, but particularly those of A, C and D, are capable of being transmitted occasionally through inhalation to humans, being a potential hazard to those who keep pet birds and those employed in the poultry industry or in slaughter houses. Infectious forms of the organisms are shed in nasal discharges or occur in faeces or feather dust from symp- tomatic as well as apparently healthy birds and may remain viable for several months. The term 'psittacosis' refers to both avian and human infection by C. psittaci found in psittacine birds, and ornith- osis to infection by strains from other birds. 'Psittacosis' is often used indiscriminately when referring to infection from psittacine and nonpsittacine birds. Outbreaks and sporadic cases of psittacosis are now a rare occurrence due to quarantine of imported birds and im- proved veterinary-hygiene measures. Clinical features After an incubation period of 1 to 2 weeks, the presentation of human infection (psittacosis) varies from a mild influenza-like illness to a fulminating toxic state with multiple organ involvement. The disease may begin insidiously over a few days, or start abruptly with high fever, rigors, and anorexia. A headache is common, a cough, often dry, occurs in over two-thirds of patients, and arthralgia and myalgia in over one-third of patients. Inspiratory crepitations are more usual than classic signs of consolidation. Chest radiographs show patchy shadowing, often in the lower lobes. Homogeneous lobar shadowing is less frequent, miliary and nodular patterns even less so, and sig- nificant pleural effusions are rare. Extrapulmonary complications, mostly rare, include endocarditis, myocarditis, pericarditis, a toxic confusional state, encephalitis, meningitis, tender hepatomegaly, splenomegaly, pancreatitis, haemolysis, and disseminated intravas- cular coagulation. Fatal cases have been rare in the postantibiotic era. Improved diagnostic tests should not allow C. psittaci infections to be confused with those caused by C. pneumoniae. Other chlamydial infections C. abortus is endemic among ruminants and colonizes the placenta, causing abortion in sheep and rarely in pregnant women. They are often farmers' wives exposed to sheep with enzootic abortion during the lambing season. C. felis is endemic among domestic cats world- wide causing feline keratoconjunctivitis, rhinitis, and pneumonitis, and it can be isolated from the genital tract of female cats. In humans it has caused follicular conjunctivitis similar to that caused by C. tra chomatis serovars D–K. The so-called Chlamydia-like organisms are also emerging patho- gens, as many, such as Parachlamydia sp., Simkania sp., and Waddlia sp., have been associated with human disease, and others, such as Piscichlamydia sp. and Parilichlamydia sp., have been documented in association with diseases in animals. Diagnosis C. psittaci is more robust than other chlamydial species but, never- theless,

clinical specimens should be placed in a transport medium prior to examination. Attempted isolation is a health risk and should be undertaken only by experienced workers in specially equipped laboratories. Hence, isolation in cell culture is often not done but the procedure would be along the same lines as for C. trachomatis and C. pneumoniae where cell cultures after incubation are examined, by means of a specific fluorescent monoclonal antibody for identifi- cation. Not surprisingly NAATs are far superior in performance to any other procedure for detecting C. pneumoniae and C. psittaci. In the case of the latter, some PCR-based assays have been developed, but due to the rarity of psittacosis the performance characteristics of these assays have been rather poorly evaluated for testing clinical

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