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8.6.46 Mycoplasmas 1295 specimens. Examination of serum samples, preferably paired, is advocated for diagnosing C. pneumoniae and C. psittaci infections. Using a complement-fixation test is an out-of-date practice and im- munofluorescence assays have been the mainstay in C. pneumoniae diagnosis but may be less reliable for C. psittaci. However, measure- ment of MOMP-specific antibody titres in a rELISA is a reliable and more practical approach to diagnosis. Treatment The treatment of C. pneumoniae and C. psittaci infections is the same as for C. trachomatis, except that a longer duration of treatment is advisable (Table 8.6.45.2). FURTHER READING Burton MJ, et al. (2004). Cytokine and fibrogenic gene expression in the conjunctivas of subjects from a Gambian community where trachoma is endemic. Infection and Immunity, 72, 7352–6. Campbell LA, et al. (2014). Persistent C. pneumoniae infection in ath- erosclerotic lesions: rethinking the clinical trials. Front Cell Infect Microbiol, 4, 34. de Vries HJ, et al. (2015). 2013 European guideline on the management of lymphogranuloma venereum. J Eur Acad Dermatol Venereol, 29, 1–6. de Vrieze NH, de Vries HJ (2014). Lymphogranuloma venereum among men who have sex with men: an epidemiological and clinical review. Expert Rev Anti Infect Ther, 12, 697–704. Gottlieb SD, et al. (2010). Summary: the natural history and immuno biology of Chlamydia trachomatis genital infection and implications for chlamydia control. J Infect Dis, 201(S2), 190–204. Grayston JT, et al. (1990). A new respiratory tract pathogen: Chlamydia pneumoniae strain TWAR. J Infect Dis, 161, 618–25. Habtamu E, et al. (2016). Posterior versus bilamellar tarsal rotation surgery for trachomatous trichiasis in Ethiopia: a randomised con- trolled trial. Lancet Glob Health, 4, e175–84. Hadfield J, et al. (2017). Comprehensive global genome dynamics of Chlamydia trachomatis show ancient diversification followed by contemporary mixing and recent lineage expansion. Genome Res, 27, 1220–9. Harris SR, et al. (2012). Whole-genome analysis of diverse Chlamydia trachomatis strains identifies phylogenetic relationships masked by current clinical typing. Nat Genet, 44, 413–9. Horner PJ (2012). Azithromycin antimicrobial resistance and genital Chlamydia trachomatis infection: duration of therapy may be the key to improving efficacy. Sex Transm Infect, 88, 154–6. Hu V, et al. (2010). Epidemiology and control of trachoma. Trop Med Int Health, 15, 673–91. Knittler MR, Sachse K (2015). Chlamydia psittaci: update on an under- estimated zoonotic agent. Pathog Dis, 73, 1–15. Kong FYS, et al. (2014). Azithromycin versus doxycycline for the treat- ment of genital chlamydia infection—a meta-analysis of random- ised controlled trials. Clin Infect Dis, 59, 193–205. Kong FYS, et al. (2015). The efficacy of azithromycin and doxycycline for the treatment of rectal chlamydia infection: a systematic review and meta-analysis. J Antimicrob Chemother, 70, 1290–7. Lanjouw ES, et al. (2015). 2015 European guideline on the manage- ment of Chlamydia trachomatis infections. Int J STD AIDS, 27, 333–48. Lanjouw E, et al. (2015). Background review for the ‘2015 European

guideline on the management of Chlamydia trachomatis infections’. Int J STD AIDS, pii: 0956462415618838. Lewis ME, et al. (2014). Morphologic and molecular evaluation of Chlamydia trachomatis growth in human endocervix reveals dis- tinct growth patterns. Front Cell Infect Microbiol, 4, 71. Mabey DCW, et al. (2014). Towards a safe and effective chlamydial vac- cine: lessons from the eye. Vaccine, 32, 1572–8. Menon, S., P. et al. (2015). Human and pathogen factors associated with chlamydia trachomatis-related infertility in women. Clin Microbiol Rev, 28, 969–85. Nwokolo NC, et al. (2016). 2015 UK national guideline for the management of infection with Chlamydia trachomatis. Int J STD AIDS, 27, 251–67. Price MAE, et al. (2016). The natural history of Chlamydia trachomatis infection in women: a multi-parameter evidence synthesis. Health Technol Assess (Winchester, England), 20, 1–250. Roberts CH, et al. (2015). Conjunctival fibrosis and the innate barriers to Chlamydia trachomatis intracellular infection: a genome wide as- sociation study. Sci Rep, 5, 17447. Roulis EA, et al. (2013). Chlamydia pneumoniae: modern insights into an ancient pathogen. Trends Microbiol, 21, 120–8. Sachse K, et al. (2015). Emendation of the family Chlamydiaceae: pro- posal of a single genus, Chlamydia, to include all currently recog- nized species. Syst Appl Microbiol, 38, 99–103. Taylor-Brown A, et al. (2015). Twenty years of research into Chlamydia-like organisms: a revolution in our understanding of the biology and patho- genicity of members of the phylum Chlamydiae. Pathog Dis, 73, 1–15. Unemo M, Clarke IN (2011). The Swedish new variant of Chlamydia trachomatis. Curr Opin Infect Dis, 24, 62–9. Wang SP, et al. (1967). Trachoma vaccine studies in monkeys. Am J Ophthalmol, 63, 1615–20. White JA. (2009). Manifestations and management of lympho granuloma venereum. Curr Opin Infect Dis, 22, 57–66. 8.6.46 Mycoplasmas Jørgen Skov Jensen and David Taylor-Robinson ESSENTIALS Mycoplasmas are the smallest self-replicating prokaryotes. They are devoid of cell walls, with the plasticity of their outer membrane favouring pleomorphism, although some have a characteristic flask- shaped appearance. Mycoplasmas recovered from humans belong to the genera Mycoplasma (14 species and one candidatus species) and Ureaplasma (2 species). They are predominantly found in the re- spiratory and genital tracts, but sometimes invade the bloodstream and thus gain access to joints and other organs. Respiratory infection Clinical features—Mycoplasma pneumoniae is the most important mycoplasmal respiratory pathogen, with presentations ranging from inapparent infection and mild, afebrile, upper respiratory tract dis- ease to severe pneumonia. It is responsible for 15–20% of all pneu- monias in the United States of America, and is particularly common in older children and younger adults. Extrapulmonary manifestations include Stevens–Johnson syndrome and haemolytic anaemia.

 Diagnosis and treatment—diagnosis is made by nucleic acid amp- lification tests and/or serology. Culture is slow and of limited value in clinical diagnosis. Apart from supportive care, treatment is usually with tetracyclines or macrolides, although an increasing prevalence of macrolide resistance is seen, primarily in Asia. There is no com- mercially available effective vaccine. Genitourinary and related infections Clinical features—(1) Men—M. genitalium causes nongonococcal ur- ethritis in men, and Ureaplasma urealyticum but not U. parvum may play a role in some cases. (2) Women—M. genitalium causes ureth- ritis, cervicitis, endometritis, and possibly salpingitis; M. hominis and (to a lesser extent) ureaplasmas are associated with bacterial vagin- osis, but are not a cause of the condition; M. hominis may contribute to salpingitis. (3) Pregnancy—ureaplasma infection of amniotic fluid is associated with preterm labour; ureaplasmas may be involved in the chronic lung disease of very low birthweight babies. Diagnosis and treatment—diagnosis of infection by ureaplasmas and M. hominis is usually by culture of swabs from the urethra or cervix/vagina but this will not distinguish between the two urea- plasma

species as do nucleic acid amplification tests; nucleic acid amplification tests are used to detect M. genitalium. Patients with nongonococcal urethritis should ideally receive an antibiotic with activity against C. trachomatis, ureaplasmas, and M. genitalium. However, with an increasing prevalence of macrolide resistance in M. genitalium, doxycycline should be first-line treatment with moxifloxacin used for macrolide-resistant M. genitalium. Rheumatological manifestations (1) Sexually acquired reactive arthritis is not uncommon after M. genitalium-positive nongonococcal urethritis, but no causal
link has been established. (2) Arthritis in patients with hypo gammaglobulinaemia is often caused by mycoplasmas (particu- larly ureaplasmas). Introduction Mycoplasmas, the trivial name for members of the class Mollicutes, are the smallest free-living microorganisms (0.3 µm diameter). They lack the rigid cell wall of other bacteria, making them resistant to penicillins and related antimicrobials. Instead, they have a pliable trilaminar unit membrane (Fig. 8.6.46.1) enclosing the cytoplasm, DNA, RNA, and other components necessary for propagation in cell-free media. The small size of the mycoplasma genome (as little as 580 kbp) restricts metabolic capabilities, making culture of some mycoplasmas difficult or impossible. Despite their general simi- larity, mycoplasmas are a heterogeneous group with differing host specificities, nutritional requirements, metabolic reactions, and DNA and antigenic composition. Mycoplasmas are divided into four orders: Mycoplasmatales, Entomoplasmatales comprising those from insects and plants, Acholeplasmatales, and the strictly anaerobic Anaeroplasmatales. The last two do not need sterol for growth. The mycoplasmas isolated commonly from humans belong to the family Mycoplasmataceae within the order Mycoplasmatales. This family includes the genus Mycoplasma, the organisms of which metabolize glucose or arginine or both, and the genus Ureaplasma, the organisms (ureaplasmas) of which uniquely hydrolyse urea. Ureaplasmas were originally termed T-strains or T-mycoplasmas because of the tiny (T) colonies they form on agar medium (15–60 µm diameter), in con- trast to the larger characteristic fried-egg-like colonies produced by most other mycoplasmas (≥90 µm diameter) (Fig. 8.6.46.2). Historical perspective The first mycoplasma to be recognized, Mycoplasma mycoides subsp. mycoides, was isolated in 1898 from cattle with pleuropneumonia. As other pathogenic and saprophytic isolates accu- mulated from veterinary and human sources, they became known as pleuropneumonia-like organisms (PPLO), a term later super- seded by mycoplasmas. The first mycoplasma of human origin, M. hominis, was recovered from a Bartholin’s gland abscess in 1937 and the first of undoubted pathogenicity, M. pneumoniae, from the respiratory tract in 1962. Ureaplasmas were first detected in the urethras of men with nongonococcal urethritis in 1954 and M. genitalium was isolated from this site in 1981. Subsequently, in 1995, a mycoplasma of human origin named M. amphoriforme was isolated from patients with agammaglobulinaemia. Most re- cently, an uncultivated mycoplasma has been detected by mo- lecular methods in specimens from the urogenital tract of women infected with Trichomonas vaginalis. This new species is tentatively named Canditatus M. girerdii. Numerous other mycoplasmas have been isolated from various animals and have been shown to be of economic importance be- cause of the pneumonia, arthritis, keratoconjunctivitis, and mastitis they cause among livestock and poultry. This is apart from the plant diseases recognized as being due to mycoplasmas in recent years. In Fig. 8.6.46.1 Electron micrograph of M. pulmonis (murine origin), illustrating that the organism does not have a bacterial cell wall but has a trilaminar unit membrane (arrow); also note what appears to be a terminal structure (T). Magnification ×66 000.

 humans, as in other animal species, mycoplasmas cause respiratory and genital tract diseases and escape from these sites to cause disease elsewhere (e.g. in joints or

wounds). Mycoplasmas are also notorious for infecting cell cultures, par- ticularly continuous cell lines. Various mycoplasma species are responsible (e.g. M. hyorhinis of porcine origin and M. orale or M. fermentans of human origin). The contamination may affect al- most any property under investigation in a totally unpredictable way and may lead to misinterpretation of any result based on studies in cultured cells. Occurrence of mycoplasmas in humans Fourteen species of mycoplasmas as well as one with candidatus status, and two ureaplasma species, have been isolated from humans and are constituents of the normal flora or behave as pathogens (Tables 8.6.46.1, 8.6.46.2); in addition, several case reports have de- scribed infection with species of animal origin. Most mycoplasmas of human origin are found in the oropharynx. There is little infor- mation about the distribution or significance of M. amphoriforme, M. penetrans, M. pirum, and M. spermatophilum. Respiratory infections Relationship between mycoplasmas and respiratory disease M. pneumoniae is the most important mycoplasma found in the re- spiratory tract (see next); most of the others behave as commensals (Table 8.6.46.1). M. fermentans has been detected in the throat more often since the use of polymerase chain reaction (PCR) (see next) and has been recovered from adults with an acute influenza-like illness, with rare development of a fatal respiratory distress syn- drome. M. hominis is occasionally recovered from the respiratory tract. However, although it caused a mild pharyngitis in adult male volunteers inoculated orally, it is not known to do this naturally in children or adults. M. amphoriforme is a newly described species isolated from patients with chronic bronchitis, primarily those with B-cell deficiencies, and is phylogenetically related to pathogenic species such as M. pneumoniae and M. genitalium. The clinical im- portance of M. amphoriforme in the general population is unknown. M. faucium has been found in the throat of 25% of adults by PCR, more commonly in older individuals, but is not believed to be a cause of respiratory tract disease. History of M. pneumoniae In the late 1930s, nonbacterial pneumonias or primary atypical pneumonia were distinguished from typical lobar pneumonia. Patients from whom the ‘Eaton agent’ had been isolated in embryon- ated eggs often developed cold agglutinins. This agent was presumed to be a virus until it was found to be sensitive to chlortetracycline and gold salts. Its mycoplasmal nature was established by cultivation on a cell-free agar medium. The agent, M. pneumoniae, was estab- lished as a respiratory pathogen by studies based on isolation, ser- ology, volunteer inoculation, and vaccine protection. Clinical features of M. pneumoniae disease M. pneumoniae produces a range of effects from inapparent infec- tion and mild afebrile upper respiratory tract disease to severe pneu- monia. The most typical clinical syndrome is tracheobronchitis, often accompanied by upper respiratory tract manifestations such as acute pharyngitis. A clinical diagnosis of M. pneumoniae pneu- monia is impossible as it shares features of other nonbacterial pneumonias. Malaise and headache often precede chest symp- toms by 1 to 5 days, and pneumonia is seen radiographically be- fore physical signs such as rales are detectable. Usually, only one of the lower lobes is involved and the radiograph shows patchy opacities. Pneumonia develops in about 10% of those infected and about 20% of the pneumonia cases have bilateral opacities. Pleurisy and pleural effusions are unusual. The course of the disease is variable but often protracted. Symptoms may persist for several weeks and may relapse. The organisms can persist in respiratory secretions despite antibiotic therapy, particularly in patients with (a) (b) Fig. 8.6.46.2 (a) Fried-egg-like mycoplasma colonies (one ill-formed) and a larger bacterial colony. Transmission light microscopy, magnification ×43. (b) Section through mycoplasma colonies illustrating growth in the depth of the agar. Magnification ×78.

section 8 Infectious diseases 1298 hypogammaglobulinaemia where excretion may continue for months or years rather than weeks. Mortality is very low although a few very severe infections have been reported, usually in patients with immunodeficiency or sickle cell anaemia. In children, illness may be prolonged with paroxysmal cough followed by vomiting, simulating whooping cough. M. pneumoniae has been implicated in bronchial asthma, but this is controversial (see next). Extrapulmonary manifestations of M. pneumoniae infection Disease caused by M. pneumoniae is usually limited to the re- spiratory tract, but various extrapulmonary complications may occur during the course of the respiratory illness or subsequently (Table 8.6.46.3). Haemolytic crisis is precipitated by cold agglutinins (anti-I antibodies). This mycoplasma apparently alters the I antigen on erythrocytes sufficiently to stimulate an autoimmune response. A similar mechanism may be responsible for neurological and other complications. Invasion of the central nervous system cannot be discounted as M. pneumoniae has been isolated from cerebrospinal fluid in rare cases. Epidemiology of M. pneumoniae infections Pathology is age dependent. About one-quarter of infections in chil- dren aged 5 to 15 years result in pneumonia, whereas only about 7% of infections in young adults do so. Pneumonia is less frequent thereafter, but is more severe the older the patient. M. pneumoniae causes inapparent or mild upper respiratory tract symptoms more often than severe disease. It is responsible for a minority of all upper tract infections, usually attributable to viruses or streptococci. M. pneumoniae causes many lower respiratory tract infections (e.g. about 15–20% of all pneumonias in the United States of America). In populations such as military recruits it has been re- sponsible for up to 40% of acute pulmonary illness. M. pneumoniae infections occur globally. Infection is endemic in most areas and throughout the year, with a predilection for late summer and early autumn. Epidemic peaks have been observed about every 4 to 7 years. The incubation period ranges from 2 to 3 weeks. Spread from person to person occurs slowly, usually where there is continual or repeated close contact, as within a family. Immunopathological factors in the development of M. pneumoniae pneumonia The crucial step of adherence of M. pneumoniae organisms to re- spiratory mucosal epithelial cells, cytadsorption (Fig. 8.6.46.3), is mediated by the P1-protein and other specialized adhesins on the mycoplasmal surface. This is often followed by cellular invasion. In animals, there is peribronchiolar and perivascular pulmonary in- filtration mostly by T lymphocytes (Fig. 8.6.46.4). The pneumonia caused by M. pneumoniae is largely an immunopathological process since immunosuppression prevents pneumonia or diminishes its se- verity. A mycoplasmal polysaccharide–protein fraction is involved in the cell-mediated immune response, whereas the main antigenic determinant in complement fixation and other serological reactions is a glycolipid. After the initial lymphocyte response, polymorpho- nuclear leucocytes and macrophages appear in the bronchiolar

Table 8.6.46.1 Biological features, occurrence, and disease association of mycoplasmas of human origina Mycoplasma Metabolism of: Haemadsorption Frequency of detection in the: Cause of disease Respiratory tract Genitourinary tract Rectum Eye Blood M. amphoriforme Glucose Yes Rareb –c –c –c ?Yes M. buccale Arginine No Rare – – – – No M. faucium Arginine Yesd Common – – – – No M. fermentans Glucose, arginine No Common Rare – – Rare ?Yes M. genitalium Glucose Yes Very rare Common Common Rare ? Yes M. hominis Arginine No Rare Common Common Rare Very rare Yes M. lipophilum Arginine No Rare – – – – No M. orale Arginine Yesd Common – – – – No M. penetrans Glucose, arginine Yes – Rare Very rare – ? ? M. pirum Glucose, arginine No ? – Rare ? Very rare ? M. pneumoniae Glucose Yes Raree Very rare – – – Yes M. primatum Arginine No – Rare – – – No M. salivarium Arginine No Common Rare – – – Nof M. spermatophilum Arginine No – ?Rare ? ? ? Ureaplasma parvumg Urea Serotype 3 only Rare Common Common Rare Very rare ?Yes Ureaplasma urealyticumg Urea No Rare Common Common Rare Very rare Yes a Occasional

isolations of mycoplasma species of nonhuman origin not included. b Except in immunocompromised patients. c No reports of detection. d With chick erythrocytes only. e Except in disease outbreaks. f Except in hypogammaglobulinaemia. g Ureaplasmas have been divided into two species formerly described as biovars.

8.6.46 Mycoplasmas 1299 exudate. The slow evolution of the primary disease contrasts with an accelerated and often more intense host response to reinfection. Children between 2 and 5 years show serological evidence of infec- tion. The pneumonia that occurs in older people is considered to be an immunological overresponse to reinfection, with lung infiltra- tion by previously sensitized lymphocytes. Chronic respiratory disease Animal mycoplasmas are frequently associated with chronic illnesses, and so the possible role of mycoplasmas has been con- sidered in human chronic respiratory disease. M. pneumoniae often persists in the respiratory tract long after clinical recovery and occasionally the disease is protracted, but there is no evidence that M. pneumoniae is a primary cause of chronic bronchitis, or that it maintains chronic disease other than by possibly causing some acute exacerbations. M. salivarium, M. orale, and perhaps other mycoplasmas present in the oropharynx of healthy people spread to the lower respira- tory tract of people with chronic bronchitis. There is no hard evi- dence that these mycoplasmas cause acute exacerbations, but they may perpetuate an episode. Specific antibody responses follow such exacerbations more frequently than at other times, suggesting that mycoplasmas multiply and contribute to the tissue damage that is primarily due to viruses and bacteria. Table 8.6.46.2 Summary of the relationship between mycoplasmas and disease. Evidence for an association (A) between the indicated mycoplasmaa and disease, and for the causation (C) of disease M. pneumoniae M. fermentans Ureaplasmas M. hominis M. genitalium A C A C A C A C A C Upper respiratory tract disease +++ +++ – – + – – Bronchitis +++ +++ – – – – Pneumonia ++++ ++++ ++ + – – – Asthma ++ + NE NA – – Extrapulmonary sequelae of M. pneumoniae infection (see text) +++ +++ NA NA NA NA Nongonococcal urethritis NA – +++ +++ + - ++++ ++++ Chronic prostatitis NA NE ++ + – + – Epididymitis NA NE ++ ++ – +++ ++ Bartholinitis NA NE – + – NE Bacterial vaginosis NA NE ++ – ++++ + – Cervicitis NA – – – +++ +++ Pelvic inflammatory disease NA NE + + ++ ++ +++ +++ Infertility NA NE ++ – – ++b ++ Urinary calculi NA – ++ + – NE Pyelonephritis NA NE + – +++ + NE Chorioamnionitis NA + - +++ ++ +++ ++ NE Preterm labour/birth NA NE +++ ++ ++ ++ + + Spontaneous abortion NA + – +++ + ++ + + – Postabortal fever NA NE ++ + ++++ +++ NE Postpartum fever NA NE ++ + ++++ +++ NE Postpartum arthritis NA NE – +++ +++ NE Low birthweight NA NE ++ + ++ - NE Neonatal chronic lung disease NA NE +++ ++ ++ + NE Rheumatoid arthritis + – ++ – + – – + – Juvenile chronic arthritis ++ + NE – – NE Sexually acquired reactive arthritis/Reiter’s
disease – – ++ ++ – ++ ++ Arthritis in hypogammaglobulinaemia ++++ ++++ NE ++++ ++++ ++++ +++ NE Wound infections NA NE ++ + +++ +++ NE HIV infection – ++ – – – – NA, not appropriate to examine; NE, not examined; ++++, strong; +++, good; ++, moderate; +, weak; –, none. a See text for M. amphoriforme and other mycoplasmas. b Tubal factor infertility.

section 8 Infectious diseases 1300 M. amphoriforme was recovered from the respiratory tract of pa- tients with chronic bronchitis, most of whom were B-cell deficient. Recovery may depend on the eradication of this organism but its role in the general population is unknown. The role of M. pneumoniae in asthma is controversial. Acute M. pneumoniae infection is associated with wheezing and the or- ganism has been found, mainly by PCR, more frequently in subjects with asthma than in those without. However, no causal relationship has so far been established. Genitourinary and

related infections Nongonococcal urethritis and its complications M. genitalium, (Table 8.6.46.1, Fig. 8.6.46.5a), is strongly associ- ated with acute nongonococcal urethritis (Tables 8.6.46.2; 8.6.46.4). It has been detected almost independently of Chlamydia tracho matis by PCR in about 25% of cases compared with significantly fewer (about 6%) healthy controls. It also causes urethritis experi- mentally in male chimpanzees and adheres to and enters epithelial cells (Fig. 8.6.46.5b). Intracellular M. genitalium may be partially protected from antimicrobials resulting in persistent or recurrent nongonococcal urethritis. Most recently, M. genitalium has been associated with balanoposthitis in men with acute nongonococcal urethritis. Table 8.6.46.3 Extrapulmonary manifestations of M. pneumoniae infections System Manifestations Estimated frequency Cardiovascular Myocarditis, pericarditis <5% Dermatological Urticaria, erythema multiforme, Stevens–Johnson syndrome, other rashes Some skin involvement in about 25% Gastrointestinal Anorexia, nausea, vomiting, and transient diarrhoea 15–45% Hepatitis ? Pancreatitis ? Genitourinary Acute glomerulonephritis Insignificant Haematological Cold agglutinin production About 50% Haemolytic anaemia ? Thrombocytopenia ? Intravascular coagulation

> 50 reported cases Musculoskeletal Myalgia, arthralgia, arthritis 15–45% Neurological Meningitis, meningoencephalitis, ascending paralysis, transient myelitis, cranial nerve palsy, poliomyelitis-like illness <5% in a few studies based on serology Fig. 8.6.46.3 Electron micrograph of ciliated epithelial cells in the tracheal mucosa of a hamster infected with M. pneumoniae. Note cilia (c) and individual organisms (m), some with a specialized terminal structure oriented towards the membrane of the host cell (arrows). Magnification ×9880. Fig. 8.6.46.4 Pneumonia 2 weeks after intranasal inoculation of a hamster with M. pneumoniae. Note peribronchiolar and perivascular infiltration of mononuclear cells, predominantly lymphocytes. Haematoxylin and eosin, magnification ×98.

8.6.46 Mycoplasmas 1301 Although M. hominis has been isolated from about 20% of pa- tients with acute nongonococcal urethritis, it has not been impli- cated as a cause. The role of ureaplasmas in nongonococcal urethritis has been contentious for many years. The results of most qualitative studies have failed to demonstrate a significant difference be- tween the prevalence of ureaplasmas in men with or without acute nongonococcal urethritis, but there are some quantitative data indicating higher titres of organisms in men with disease. There are two species of human ureaplasmas, U. urealyticum and U. par vum. PCR assays of clinical specimens have shown an association between U. urealyticum and acute nongonococcal urethritis, par- ticularly when the organism was present in high titres, whereas this seems not the case for U. parvum. Intraurethral inoculation of first-passage ureaplasma strains produced a mild urethritis and an antibody response in male chimpanzees and the disease responded to tetracycline therapy. Four investigators who inoculated them- selves intraurethrally developed urethritis. In one study, two re- ceived cloned U. urealyticum, serotype 5, isolated from a patient with acute nongonococcal urethritis in whom no other potentially pathogenic microorganisms could be detected, although M. geni talium was not sought at that time. Both developed symptoms and signs of urethritis which responded to treatment with minocycline. Another volunteer experiment suggested that ureaplasmas may cause disease the first few times they gain access to the urethra but later insults

result in colonization without disease, accounting per- haps for their frequent occurrence in the urethras of healthy men. At present, it is not part of standard patient management to search for ureaplasmas in men with nongonococcal urethritis. Epididymitis and chronic prostatitis Ureaplasmas may be a rare cause of epididymitis since they have been recovered from the urethra and epididymal aspirate fluid of a patient with acute nonchlamydial, nongonococcal epididymitis, with a specific antibody response. M. genitalium has not been sought in aspirates, but it has been found in the urethra without other known pathogens (Table 8.6.46.4). Information linking prostatic infection with acute ureaplasmal urethral infection is scanty, although ureaplasmas have been iso- lated more frequently and in greater numbers from patients with acute urethroprostatitis than from controls. Most of those with more than 103 organisms in expressed prostatic fluid responded to tetra- cycline therapy. In contrast, ureaplasmas have not been found, and M. genitalium only rarely found, in prostatic biopsy specimens from patients with chronic abacterial prostatitis. M. hominis is not associ- ated with prostatitis. Pelvic inflammatory disease (Chapter 9.8) Microorganisms in the vagina and lower cervix may ascend to and cause inflammation of the fallopian tubes and adjacent pelvic structures (Tables 8.6.46.2; 8.6.46.4). M. hominis has been isolated from inflamed fallopian tubes, tubo-ovarian ab- scesses, and pelvic abscesses or fluid. Laparoscopy samples have yielded M. hominis from the tubes of about 10% of women with salpingitis but not from those of healthy women. However, they may be present in mixed infections with bacterial vaginosis- associated bacteria as M. hominis is strongly associated with bac- terial vaginosis (Chapter 9.4). M. hominis antibody was found in approximately one-half of salpingitis patients, but in only 10% of healthy women. Although ureaplasmas have been isolated directly from the fallopian tubes of a very small proportion of patients with acute salpingitis, from pelvic fluid, and from a tubo-ovarian abscess, it seems that they are of little importance in acute pelvic inflamma- tory disease. Nucleic acid amplification tests (NAATs) have established that M. genitalium is involved in at least some cases of pelvic inflamma- tory disease. It is a cause of cervicitis and its presence in the cervix or upper genital tract is associated significantly with histological endometritis. It has rarely been detected in tubes but in one study of women with pelvic inflammatory disease, an antibody response was detected to M. genitalium but not to M. hominis or C. trachomatis in one-third of the patients. Other studies have not shown this associ- ation but M. genitalium has been related serologically to tubal factor infertility. Fallopian-tube organ culture studies have shown that gono- cocci destroy the epithelium, M. genitalium causes some damage, M. hominis organisms multiply but only produce swelling of some cilia, and ureaplasmas cause no damage. This differential effect may be a true reflection of the pathogenic potential of these microorgan- isms in vivo but, as the immune system is not operational, failure to demonstrate damage does not confirm avirulence. Inoculation of M. hominis or M. genitalium into primates caused a self-limited acute salpingitis and parametritis with an antibody response, whereas ureaplasmas had no effect. (a) (b) Fig. 8.6.46.5 (a) Electron micrograph of M. genitalium, negatively stained to show flask-shaped appearance and terminal specialized structure (arrow). Magnification ×90 000. (b) Electron micrograph of M. genitalium adhering to a Vero cell by the terminal structure. Magnification ×60 000. From Tully JG, et al. (1983) Mycoplasma genitalium, a new species from the human urogenital tract. Int J Syst Bacteriol, 33, 387, with permission.

 Effects of mycoplasmas on pregnancy Preterm birth The involvement of genital mycoplasmas is debated but ureaplasma infection of the amniotic fluid is associated with preterm labour. M. hominis probably plays a part through its involvement with bac- terial vaginosis, a known cause of preterm labour. M. hominis and ureaplasmas are unlikely to

cause low birthweight in otherwise normal full-term infants. The role of M. genitalium is controversial; it has been associated with preterm birth in some but not all studies. Postabortal and postpartum fever M. hominis has been isolated from the blood, with an antibody re- sponse, in up to 10% of women with fever after abortion, but not from those without fever. However, a pure culture of M. hominis in blood is needed before it can be accepted as a cause of fever. The role of ureaplasmas is unclear. Patients with postabortal or postpartum fever of mycoplasmal origin usually recover without antibiotic treatment. Neonatal infections Whether transmitted in utero or during birth, ureaplasmas may be isolated from the throats and tracheal aspirates of some neonates. Ureaplasma-infected infants of very low birthweight (<1000 g) have died or have developed chronic lung disease twice as often as uninfected infants of similar birth weight or those of over 1000 g. However, the pathogenicity of ureaplasmas is uncertain since erythromycin treatment has failed to prevent disease in two trials. M. hominis has very rarely been implicated in pneumonia soon after birth but the other bacteria present could be responsible. Table 8.6.46.4 Causal relationship of M. genitalium, M. hominis, and ureaplasmas with human genitourinary, reproductive,
and perinatal disease Disease Evidence suggesting a causal relationship of: Comments on the relationship M. genitalium M. hominis Ureaplasmas Nongonococcal urethritis Strong None Good U. urealyticum in high titres is associated with nongonococcal urethritis but U. parvum is not. Chronic prostatitis None None Weak None of the microorganisms appears to be a cause Epididymitis Some None Some Ureaplasmas isolated from the epididymis in one case of acute disease Urinary calculi ? None Weak Experimentally, ureaplasmas cause bladder calculi in male rats but so far little evidence for a cause of natural human disease Pyelonephritis ? Weak None M. hominis possibly causes some cases of acute pyelonephritis and exacerbations Reiter’s disease/sexually acquired reactive arthritis Some None Some M. genitalium detected in joint of one patient; ureaplasmas are related on the basis of lymphocytic response to specific antigen Bartholinitis ? Very weak None Doubtful whether M. hominis is involved Bacterial vaginosis None Weak None M. hominis and to a lesser extent ureaplasmas are associated with bacterial vaginosis, but a causal relationship is unproved Cervicitis Good None None M. genitalium is associated with nongonococcal, nonchlamydial cervicitis Pelvic inflammatory disease Good Some Weak M. genitalium is associated serologically and has been detected in the upper genital tract of patients with endometritis and salpingitis; M. hominis probably causes a small proportion of cases, but very doubtful that ureaplasmas do Postabortal fever ? Good Weak M. hominis, and to a much lesser extent ureaplasmas, are responsible for some cases, but the proportion is unknown Postpartum fever ? Good Weak M. hominis, and to a much lesser extent ureaplasmas, are responsible for some cases, but the proportion is unknown Infertility Some None None M. genitalium is associated serologically to tubal factor infertility; ureaplasmas are associated with reduced sperm motility, but a causal relationship is unproved Preterm birth Weak Some Some/good M. genitalium associated in a few studies, but not in others. Considerable evidence for the involvement of ureaplasmas, less so for M. hominis; both possibly as part of bacterial vaginosis Spontaneous abortion and stillbirth ? Weak Weak Maternal and fetal infections are associated with spontaneous abortion, but a causal relationship is unproved Chorioamnionitis ? Some Some An association exists with ureaplasmas, but a causal relationship is unproved Low birth weight ? None Weak An association exists with ureaplasmas in some studies, but a causal relationship is unproved Neonatal meningitis ? Some Some A rare event Neonatal lung disease ? Weak Some M. hominis has been involved in pneumonia soon after birth; ureaplasmas possibly involved in premature infants weighing less than 1000 g

8.6.46 Mycoplasmas 1303 Mycoplasmal infection should be considered in cases of neo- natal disease of the central nervous system in which the results of bacteriological staining and culture are negative. M. hominis or ureaplasmas have been found in the cerebrospinal fluid of neo- nates with meningitis or brain abscess. Joint infections Arthritis Mycoplasmas cause several animal arthritides and PCR testing showed M. fermentans and ureaplasma DNA in more than 20% of patients with rheumatoid arthritis and other chronic inflam- matory disorders, in contrast to those with noninflammatory dis- orders. The significance of these findings is unknown. M. hominis has been isolated from septic joints, usually hip, that have developed in mothers after childbirth. The arthritis re- sponds to tetracycline therapy and the diagnosis should be con- sidered in a post-partum arthritis which is unaffected by β-lactam antibiotics. Arthritis may occur soon after or concomitant with non gonococcal urethritis (sexually acquired reactive arthritis) or the arthritis may be associated with conjunctivitis and ureth- ritis. M. genitalium causes uncomplicated nongonococcal ur- ethritis and ureaplasmas do so to a lesser extent, but previous antimicrobial treatment usually prevents adequate investigation of patients with arthritis. M. genitalium has been detected in the synovial fluid of a patient with sexually acquired reactive arth- ritis and clinical experience has shown that this condition is not uncommon after M. genitalium-positive nongonococcal ureth- ritis, but no causal link has been established. The latter is also true in the case of some patients whose synovial lymphocytes have been shown to proliferate in vitro in response to ureaplasmal antigens. Wound infections M. hominis has occasionally been linked to fever in patients with burns, trauma, or wound infections. It is most common in fever after surgery on the urogenital tract, but also in mediastinitis; ureaplasmas are also likely to be present, but neither these nor M. hominis will be found unless specifically sought. Kidney transplant patients occasionally develop mixed infections with ureaplasmas and M. hominis, which in severe cases may create fistulas. A rare wound infection is ‘seal finger’ or ‘blubber finger’, which is well known in Arctic regions where the handling of sea mammals is part of daily living. A few days after a seal bite, oedema of the affected finger develops with swelling of the interphalangeal joint adjacent to the lesion. It is extremely painful, suppuration can occur, extensive surgery may be needed, and re- sidual dysfunction is possible. The infection usually responds rapidly to tetracyclines but macrolides are inefficient. An un- named, rapidly growing new mycoplasma species can be re-covered from the lesions. Mycoplasmas in immunodeficiency states Urethritis and arthritis in patients with hypogammaglobulinaemia Prolonged urethrocystitis with persistent ureaplasmal infection has been seen in a few patients with hypogammaglobulinaemia. In addition, arthritis of mycoplasmal aetiology (Fig. 8.6.46.6a, b) should be considered in patients with this immune deficiency who develop an abacterial septic arthritis. M. pneumoniae, M. homi nis, M. salivarium, and, in particular, ureaplasmas have been isolated from synovial fluids of at least 40% of these patients. In addition, vigilance should be kept for infection by mycoplasmas of nonhuman origin. The arthritis usually responds to tetracyc- lines or other antimicrobials to which the organisms are sensitive. Intravenous and combination therapy should be considered to avoid antimicrobial resistance developing due to suboptimal drug concentrations at the infection site. Administration of specific antiserum against the mycoplasma in question may be helpful in a few patients when antimicrobial therapy fails. Mycoplasmas in HIV-infected patients Although M. fermentans was distributed widely in tissues taken at autopsy from some patients with AIDS, no association has been found with the stage of the disease, CD4 count, plasma HIV-1 viral load, or rate of progression of the illness. M. penetrans, which avidly invades eukaryotic cells, was isolated from urine sediments of a few HIV-1-positive men who have sex with men. While it is possible that M. fermentans, M. penetrans, or other mycoplasmas might proliferate in this immunodeficiency

state, there is no convincing evidence that they are important for the development of AIDS. (a) (b) Fig. 8.6.46.6 (a) Damage to the knee joint of a hypogammaglobulinaemic patient caused by U. urealyticum infection. (b) Sinus connected with the shoulder joint of a patient with hypogammaglobulinaemia; ureaplasmas were isolated repeatedly from the sinus exudate. Courtesy of A. D. B. Webster.

 Conditions of rare or equivocal mycoplasmal aetiology Bacterial vaginosis (Chapter 9.4) M. hominis organisms may well have a role in the pathogenesis of bacterial vaginosis in which they occur in very large numbers, but proof is impossible due to the variety of other bacteria pre- sent in profusion. Ureaplasmas are less likely to be pathogenic and M. genitalium does not seem to be involved at all. Pyelonephritis Over 30 years ago M. hominis was isolated, sometimes in pure cul- ture, from the upper urinary tract of almost 10% of patients with acute pyelonephritis, occasionally accompanied by an antibody re- sponse, but not from patients with noninfectious urinary tract dis- eases. However, there has never been confirmation that M. hominis is a cause of acute pyelonephritis or acute exacerbations of chronic pyelonephritis. Urinary calculi Animal model and human isolation studies have suggested that ureaplasmas, which have a urease, could be involved in the devel- opment of urinary calculi, but proof is lacking. Other conditions There is no confirmation that ureaplasmas are a cause of male or female infertility, but M. genitalium may be responsible for tubal factor infertility in some instances (see earlier). There is no credible evidence that mycoplasmas are related to fibromyalgia, chronic fatigue syndrome, or the Gulf War syndrome. Laboratory diagnosis of mycoplasmal infections M. pneumoniae infection The diagnosis is made by molecular methods (NAATs), and/ or serology and in special cases by culture. The complex culture media for M. pneumoniae isolation contain glucose, selective anti- biotics, and a pH indicator (phenol red). The fluid medium, in- oculated with the clinical specimen, is incubated at 37° C and a colour change (red to yellow) signals the fermentation of glucose (Table 8.6.46.1) with production of acid, due to multiplication of the organisms. This preliminary identification may be confirmed by subculturing to agar medium and demonstrating inhibition of colony development by specific antiserum (Fig. 8.6.46.7) or by immunofluorescence of colonies with an M. pneumoniae-specific antibody. Culture may take as long as 5 weeks, and consequently it is of limited value in clinical diagnosis. Rapid detection of M. pneumoniae by a NAAT has become routine in most settings. Serological testing by commercially available enzyme immuno- assays specific for IgM and/or IgG is used more routinely. IgM detection is not reliable in reinfection, which is most often the case in adults and as IgG reactivity remains for years, an increase in IgG titre is often required. The complement-fixation test is still undertaken in some laboratories. Recent infection is indi- cated by a fourfold or greater rise in antibody, but this occurs in only about 80% of cases. A high titre (1:128 or greater) in a single serum is suggestive but not proof of infection. The complement- fixation test does not distinguish between M. pneumoniae and M. genitalium. Cold agglutinins, detected by agglutination of O Rh-negative erythrocytes at 4° C, also correlate with specific IgM and are suggestive of a recent M. pneumoniae infection, but the test is rarely used as it is not specific. Genitourinary and other infections Swabs from the urethra or cervix/vagina have a slightly higher sensitivity for mycoplasmal isolation than urine specimens. Ureaplasmas and M. hominis usually show evidence of growth in culture media within 1 to 5 days. Primary isolation of M. geni talium in this way is difficult and can take 50 days or more, so that a NAAT is required for detection. Unfortunately, up to now, com- mercial tests have not met Food and Drug Administration (FDA) approval but CE-marked assays have been introduced in Europe, making testing available in many settings. Several

of these assays combine M. genitalium detection with detection of macrolide re- sistance mediating mutations in the 23S rRNA gene. This allows treatment to be directed to the most appropriate antibiotics, such as recommended in the European guideline on M. genitalium in- fections. PCR assays have also been used to identify M. fermentans and U. urealyticum/U. parvum. In particular, quantitative assays for U. urealyticum show some promise for clinically relevant diag- nosis in male acute nongonococcal urethritis. M. hominis cultured on agar medium produces colonies of ca 200 to 300 µm diameter, whereas ureaplasma colonies are tiny (15–60 µm) (Fig. 8.6.46.8a) but can be seen more easily on medium containing manganous sulphate (Fig. 8.6.46.8b). M. hominis may grow on ordinary blood agar where it produces nonhaemolytic pinpoint colonies after extended incubation. Ureaplasma colonies Fig. 8.6.46.7 Mycoplasma identification by agar growth inhibition. Colony development inhibited around a filter-paper disc impregnated with specific antiserum. Note also antibody–antigen precipitation at edge of inhibition zone.

 are too small to be detected on blood agar, but occasionally a scrape from the agar surface will yield ureaplasmas when inocu- lated into ureaplasma medium. In a few research laboratories only, serological tests have been used to detect antibodies to M. hominis, M. genitalium, and the ureaplasmas. Treatment M. pneumoniae infections M. pneumoniae is sensitive to the bacteriostatic tetracyclines and macrolides. The newer macrolides, such as clarithromycin and azithromycin, are very active in vitro, but their clinical effect is not documented extensively in randomized clinical trials. The newer quinolones, such as moxifloxacin, are also highly active in vitro. They should not be used as first-line therapy but, as they are bacteri- cidal, they may have a role in immunosuppressed patients. Recently, a rapid increase in high-level macrolide resistance in M. pneumoniae has been reported among infected patients in Asia, but in Europe the prevalence of resistance is still below 10% in most settings. In a controlled trial, tetracycline significantly reduced the duration of fever, pulmonary infiltration, and other signs and symptoms of M. pneumoniae infection. In practice, antimicrobials may be less ef- fective because correct treatment is initiated at a late stage. Nevertheless, treatment with an antimicrobial is worthwhile. Due to the lower fre- quency of gastrointestinal side effects, newer macrolides such as azithromycin and clarithromycin are preferred when macrolides are indicated, as in children. Successful treatment of disease with bacterio- static drugs does not always correlate with eradication of organisms from the respiratory tract. Relapse can be avoided by giving antibiotics for at least 10 days. It is uncertain whether early treatment prevents complications but it should start as soon as possible, even if there is only clinical evidence and a suggestive single antibody titre. Corticosteroids in conjunction with antimicrobials appear to have been helpful in pa- tients with severe pneumonia and erythema multiforme. Genitourinary and other infections Antimicrobial susceptibility of the mycoplasma species found most commonly in the urogenital tract is presented in Table 8.6.46.5 as a combination of in vitro susceptibility data and clinical experience. Treatment must take into account the fact that several different micro- organisms may be involved and that a precise microbiological diag- nosis is not available. Patients with nongonococcal urethritis should ideally receive an antibiotic with activity against C. trachomatis, urea- plasmas, and M. genitalium. Azithromycin is being used increasingly for chlamydial infections and is also active against a wide range of mycoplasmas, including M. genitalium and, to a lesser extent, urea- plasmas. However, high-level macrolide resistance is common with prevalence figures of 15% where doxycycline is used for first-line treatment of nongonococcal urethritis and cervicitis, to over 40% in most settings where azithromycin 1 g is used as first-line therapy. For the treatment of symptomatic nongonococcal urethritis, recent European Guidelines on the Management of nongonococcal ureth-

ritis recommend doxycycline 100 mg bd for 7 days. If this fails, infec- tions should be treated with azithromycin 500 mg on day 1 followed by 250 mg daily on days 2–5. If macrolide resistance is present or de- velops, moxifloxacin 400 mg daily for 7–10 days is the only treatment option in many European countries. Strains with dual resistance to azithromycin and moxifloxacin have been reported with increasing frequency in the Asian-Pacific region and in high-risk populations in the USA with a prevalence as high as 30% reported in one study. Such infections require treatment with alternative antibiotics such as pristinamycin which is difficult to source outside of France and which only eradicates 75% of the infections. A broad-spectrum antibiotic should also be included in the treatment of pelvic inflammatory disease to cover C. trachoma tis, M. hominis and other bacterial vaginosis-associated bacteria and M. genitalium. Since 20% or more of M. hominis strains are resistant to tetracyclines, other antibiotics such as clindamycin or fluoroquinolones may be needed. Prevention of infection M. pneumoniae infection or disease may occur despite high titres of serum mycoplasmacidal antibody. The correlation be- tween the presence of IgA in respiratory secretions and resist- ance to M. pneumoniae disease endorses the importance of local (a) (b)
Fig. 8.6.46.8 (a) A ureaplasma colony (15 µm diameter) (arrow) adjacent to colonies of M. hominis (130 µm diameter) grown from urethral exudate. Oblique light, magnification ×68. (b) Dark ureaplasma colonies with colonies of M. hominis on agar containing manganous sulphate. Magnification ×136.

 immune factors in resistance. IgA could prevent attachment of organisms to respiratory epithelial cells. Protective immunity also depends on the severity of infection. Thus, in one study, patients with nonpneumonic illness were susceptible to an epi- demic occurring 5 years later, whereas those with M. pneumo niae pneumonia were protected until the following epidemic 10 years later. No effective vaccine has been developed for human use. Vaccination against M. pneumoniae has been attempted. Formalin- inactivated vaccines prevented mycoplasmal pneumonia in only one- to two-thirds of subjects, perhaps because they failed to stimulate cell-mediated immunity and/or local antibody. Live attenuated vaccines, containing temperature-sensitive mutants of M. pneumoniae, have not been considered safe for general human use. Recombinant DNA vaccines involving P1 and other proteins, or a recombinant vaccine developed by cloning part of the M. pneumoniae P1 gene into an adenovirus vector, may offer greater success in the future. No vaccine is available for M. genitalium or the other urogenital mycoplasmas, but M. genitalium infection as well as most other bacterial STIs is preventable by correct use of condoms. FURTHER READING Frølund M, et al. (2016). Urethritis-associated pathogens in urine from men with nongonococcal urethritis: a case-control study. Acta Derm Venereol, 96, 689–94. Haggerty CL (2008). Evidence for a role of Mycoplasma genitalium in pelvic inflammatory disease. Curr Opin Infect Dis, 21, 65–9. Herrmann R, Ruppert T (2006). Proteome of Mycoplasma pneumo niae. Methods Biochem Anal, 49, 39–56. Horner P, Blee K, Adams E (2014). Time to manage Mycoplasma gen italium as an STI: but not with azithromycin 1g! Curr Opin Infect Dis, 27, 68–74. Jensen JS (2006). Mycoplasma genitalium infections: diagnosis, clinical aspects, and pathogenesis. Dan Med Bull, 53, 1–27. Jensen, JS, Bradshaw C (2015). Management of Mycoplasma genitalium infections—can we hit a moving target? BMC Infect Dis, 15, 343. Lis R, Rowhani-Rahbar A, Manhart LE (2015). Mycoplasma genitalium infection and female reproductive disease: a meta-analysis. Clin Infect Dis, 61, 418–26. McGarrity GJ, Kotani H, Butler GH (1992). Mycoplasmas in tissue culture cells. In: Maniloff J (ed) Mycoplasmas: molecular biology and pathogenesis, pp. 445–54. American Society for Microbiology, Washington, DC. Razin S, Yogev D, Naot Y (1998). Molecular biology and pathogenicity of mycoplasmas. Microbiol Mol Biol Rev, 62, 1094–156. Sutherland ER, Martin RJ (2007). Asthma and atypical bacterial infec- tion. Chest, 132, 1962–6.

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Table 8.6.46.5 Susceptibility of some genital mycoplasmas to various antibiotics. A combination of in vitro susceptibility data and clinical efficacy is given where such experience is available

Antibiotics	M. hominis	M. fermentans	U. urealyticum	M. genitalium
Tetracyclines				
Tetracycline	+	+	+	±
Doxycycline	++	++	++	±
Macrolides				
Erythromycin	–	±	+	+
Clarithromycin	–	±	++	++ a
Azithromycin	–	±	+	+++a
Lincosamides				
Clindamycin	+++	++	±	±
Quinolones				
Ciprofloxacin	+	++	+	±
Ofloxacin	+	++	+	±
Moxifloxacin	++	+++	++	++b

+++, extremely sensitive; ++, highly sensitive; +, moderately sensitive; ±, weakly sensitive; –, insensitive; a, high-level macrolide resistance may be common in settings where azithromycin 1 g single dose is commonly used. bMoxifloxacin resistance is increasingly detected.

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