8.6.6 Neisseria gonorrhoeae 1025

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8.6.6 Neisseria gonorrhoeae 1025 third dose in the second year of life. The vaccine reduces but does not eliminate carriage. A vaccine combining the components of Bexsero® with the conjugate polysaccharide A, C, W, Y is presently being tested. Such a vaccine could protect against all major serogroups except serogroup X. In October 2014 a new vaccine Trumenba® containing factor H binding protein (fHbp) subfamily A and B was licensed in the United States and Europe in 2017 for the age group 10–25 years. It is given as three doses at 0, 2, and 6 months. The use of this vaccine in other age groups and the influence on carriage has yet to be defined. Indications for vaccination Routine immunization with the A, C, Y, and W vaccine is advocated for people with documented deficiencies in the alternative pathway and late complement components. Non-outbreak situation Indications for vaccination are close contacts of an index case (in addition to antibiotic prophylaxis), travellers to high-risk areas, mili- tary recruits, persons with asplenia, HIV infection, and alcoholics. Outbreak situation Vaccination has been recommended if two or more persons are attacked by the same strain in a school class or day care centre, the at- tack rate exceeds 10 cases/100 000 population per 3 months, or the at- tack exceeds 1/1000 with three or more cases in a closed group setting. Epidemic situation An advocated threshold for mass vaccination is 15 cases/100 000 population per week for two consecutive weeks caused by the same strain.
A steadily increasing number of cases and an increase in the median age of the patients indicate an epidemic. Secondary prophylaxis Antibiotic prophylaxis Household contacts of an index case have 100 to 1000 times in- creased relative risk for developing meningococcal infections. Usually the second case occurs within 2 weeks of the index case if no eradication treatment is given. However, there is doubt about the effectiveness of eradication treatment when the causative strain belongs to serogroup B. Health authorities in most countries advise that close con- tacts have eradication treatment. Presently, adults receive 500 mg ciprofloxacin or 400 mg ofloxacin as a single dose. Pregnant women and children of less than 12 years should receive 250 mg and 125 mg ceftriaxone, respectively, as one intramuscular injection. Alternatively, children are treated with rifampicin 10 mg/kg, max- imum dose 600 mg, every 12 h for 48 h. FURTHER READING American Academy of Pediatrics (2012). Meningococcal infections. In: Red book, pp. 500–9. Elk Grove Village, IL. https://redbook.solu- tions.aap.org/chapter.aspx?sectionid=88187187&bookid=1484 Brower

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current guidelines, and challenges for future vaccine development. Hum Vaccin Immunother, 14, 1146–60. Frosch M, Maiden M (eds) (2006). Handbook of meningococcal disease. Wiley, Weinheim. Hellerud BC, et al. (2015). Massive organ inflammation in experi- mental and clinical meningococcal septic shock. Shock, 44, 458–69. Immunisation against infectious disease: The Green Book, Public Health England, 2017, Chap 22, page 1–24. Kristiansen PA, et al. (2015). Serogroup A meningococcal conjugate vaccines in Africa. Expert Rev Vaccines, 14, 1441–58. Lewis LA, Ram S (2014). Meningococcal disease and the complement system. Virulencei, 5, 98–126. Molyneux E, et al. (2011). 5 versus 10 days of treatment with ceftriaxone for bacterial meningitis in children: a double-blind randomised equivalence study. N Engl J Med, 377, 1837–45. Nathan N, et al. (2005). Ceftriaxone as effective as long-acting chloram- phenicol in short-course treatment of meningococcal meningitis during epidemics: a randomised non-inferiority study. Lancet, 366, 308–13. National Institute for Health and Care Excellence (NICE) (2010). Guidelines for bacterial meningitis and meningococcal septicaemia. https://www.nice.org.uk/guidance/CG102 Pace D (2013). Glycoconjugate vaccines. Expert Opin Biol Ther, 13, 11–33. Rollier CS, et al. (2015). The capsular group B meningococcal vaccine, 4CMenB: clinical experience and potential efficacy. Expert Opin Biol Ther, 15, 131–42. Rosenstein NE, et al. (2001). Meningococcal disease. N Engl J Med, 344, 1378–88. Sadarangani M, Feavers I, Pollard AJ (eds) (2016). Handbook of me- ningococcal disease management. Springer, Gewerbestrasse, Cham. Stephens DS, Greenwood B, Brandtzaeg P (2007). Epidemic meningitis, meningococcemia and Neisseria meningitidis. Lancet, 369, 2196–3210. Stoof SP, et al. (2015). Disease burden of invasive meningococcal disease in the Netherlands between June 1999 and June 2011: a subjective role for serogroup and clonal complex. Clin Infect Dis, 61, 1281–92. Van Deuren M, Brandtzaeg P, van der Meer JWM (2000). Update on meningococcal disease, with special emphasis on pathogenesis and clinical management. Clin Microbiol Rev, 13, 144–66. Welch SB, Nadel S (2003). Treatment of meningococcal infection. Arch Dis Child, 88, 608–14. 8.6.6 Neisseria gonorrhoeae Jackie Sherrard and Magnus Unemo ESSENTIALS Neisseria gonorrhoeae is a Gram-negative, intracellular diplococcus that is transmitted by direct inoculation of infected secretion from one mucosa to another. It primarily colonizes the columnar epithelium of lower genital tract, only occasionally spreading to the upper genital tract or causing systemic disease. Oropharyngeal and rectal infections

 are common in men who have sex with men but also occur in women. N. gonorrhoeae is almost exclusively transmitted by sexual activity. Clinical features Men—dysuria (50%) and urethral discharge (80%); complications (e.g. epididymitis, orchitis), are rare. Women—there are no specific symptoms in the absence of com- plications (e.g. salpingitis, bartholinitis). Oropharyngeal and rectal infections usually produce no symp- toms. Disseminated gonococcal infection is a comparatively benign bacteraemia affecting joints (particularly shoulder and knee) and skin; traditionally more common in women than men. Diagnosis—appropriate laboratory diagnostics are essential for the diagnosis of gonorrhoea. Microscopy of a Gram-stained or methy- lene blue smear from a genital site (male urethral or endo-

cervical) will give a presumptive diagnosis of gonorrhoea. Nucleic acid amp- lification tests are now the most sensitive tests for a confirmed diag- nosis of gonorrhoea but a single result from an extragenital site or from samples from low-prevalence populations should be verified using an additional nucleic acid amplification test with a different nucleic acid target. Culture is the most specific test and provides a viable organism for antimicrobial susceptibility testing but can lack sensitivity, particularly for oropharyngeal and rectal samples. Treatment—the gonococcus has adapted rapidly to prevalent anti- microbial usage, leading to resistance to all antibiotics used for treat- ment, notably penicillins, fluoroquinolones, macrolides, tetracycline, and cephalosporins. This development has resulted in major concerns internationally and the introduction of international and national ac- tion/response plans as well as dual antimicrobial therapy. In the United Kingdom as well as in Europe, Australia, United States, and Canada, re- commended first-line treatment of uncomplicated infection in adults is now ceftriaxone intramuscularly as a single dose plus azithromycin or- ally as a single dose. Spectinomycin intramuscularly plus azithromycin orally as a single dose is suitable for those with penicillin allergy. Introduction Gonorrhoea is an ancient disease. Galen coined its name in the 2nd century ad (from Greek words meaning ‘semen’ and ‘flow’), but there are older references including Chapter 15 of Leviticus in the Old Testament. The name of the causative obligate pathogenic bacterium, Neisseria gonorrhoeae, credits Albert Neisser with its discovery in 1879, although Hallier had described its characteristic microscopic appearance 7 years earlier. In the era of HIV/AIDS, gonococcal infections additionally play an important role as an indicator of risky sexual activity. Epidemiology The World Health Organization (WHO) estimated there were 78 million global cases of gonorrhoea among adults in 2012. In European Union/European Economic Area (EU/EEA), gonor- rhoea is the second most commonly reported sexually transmitted infection (STI) after chlamydial infections. However, the incidence in several EU/EEA countries is underestimated due to suboptimal diagnostics, testing, case reporting, and epidemiological surveil- lance. In 2016, 75 349 gonorrhoea cases (18.8 per 100 000 popu- lation) were reported in 27 EU/EEA countries (data unavailable from Austria, Germany, Greece, and Liechtenstein). The highest incidence was reported in the United Kingdom (61.4 per 100 000 population), which also reflects effective diagnostics, high levels of testing and a well-functioning epidemiological surveillance system. Young people (15–24 years of age) accounted for 36% of all EU/EEA cases. Forty-six per cent (46%) of the cases were reported in men who have sex with men. Since 2008, the incidence in United Kingdom has significantly increased and the reported incidence in EU/EEA has increased by more than 80%, which is mainly due to an increased number of cases in men, especially among men who Year 70 000 60 000 50 000 40 000 30 000 20 000 10 000 0 1918 1920 1922 1924 1926 1928 1930 1932 1934 1936 1938 1940 1942 1944 1946 1948 1950 1952 1954 1956 1958 1960 1962 1964 1966 1968 1970 1972 1974 1976 1978 1980 1982 1984 1986 1988 1990 1992 1994 1996 1998 2000 2002 2004 2006 2008 2010 2012 2014 2016 Total number of cases Benzyl- penicillin Sulphonamides Ampicillin Tetracyclines Erythromycin 3rd generation cephalosporins Fluoro- quinolones NHS Cefixime or ceftriaxone Ceftriaxone PLUS azithromycin Fig. 8.6.6.1 Reported cases of gonorrhoea and introduction of different treatments for gonorrhoea in England between 1918 and 2017 (Public Health England, formerly Health Protection Agency). NHS, National Health Service.

 have sex with men. In the United Kingdom since the Second World War, the peak incidence of reported gonorrhoea cases in 1946 re- sulted from a combination of returning infected soldiers and ascer- tainment bias (Fig. 8.6.6.1). Changing incidence thereafter seemed independent of the availability of effective antibiotics. The rising numbers of infections

since the late 1950s, peaking in 1974, coin- cided with the introduction of the oral contraceptive pill, greater sexual promiscuity, effective diagnostics (culture) in women, and an increasing availability of different classes of effective antibiotics and was mainly unrelated to antimicrobial resistance. The rapid fall in incidence in the late 1980s coincided with a self-imposed regime of safer sex in the general population and particularly in the men who have sex with men community, which was primarily due to the awareness of spread of HIV. The rates of complications of gonorrhoea have declined in parts of the world where diagnosis and treatment of STIs is readily avail- able. However, the availability of effective antimicrobial agents for gonorrhoea is declining worldwide as resistance rapidly emerges to current agents. Changes in N. gonorrhoeae have been driven, until now, mainly by antibiotic pressures. An intriguing and worrying problem, with the increasing use of nucleic acid amplification tests (NAATs) for diagnosis, is the evolution of strains that become ‘invisible’ to the NAAT as a result of altered or loss of the target sequence; this has al- ready happened with NAATs for Chlamydia trachomatis in Sweden in 2006 as well as with porA pseudogene NAATs for N. gonorrhoeae in several countries. Pathogenesis N. gonorrhoeae has evolved mechanisms for evading host defences and causing repeated infections. Major outer membrane antigens exposed to the immune response are pili, lipo-oligosaccharide, and major outer membrane proteins, for example, PorB, Opa, and Rmp. N. gonorrhoeae primarily colonizes the columnar epithelium of the lower genital tract, only occasionally spreading to the upper genital tract or causing systemic disease. To colonize successfully, the organism must attach to and invade the epithelial layer to avoid being swept away by cervical secretions in women or urine in men. Iron is essential to replication; N. gonorrhoeae expresses transferrin or lactoferrin receptors on its surface. In vivo, gonococci resist the bactericidal activity of serum by sialylation of lipo- oligosaccharide. In vitro, most strains become serum sensitive. Pili, Opa, and lipo- oligosaccharide antigens can alter the part of the molecule reacting with the immune response. This antigenic variation occurs at a fre- quency higher than the normal mutation rate. On each encounter between the organism and the host, the gonococcus presents a range of immunologically distinct proteins that are not recognized by the host. Host cell receptors are complex carbohydrates, glycosamines, lipoproteins, and glycoproteins. Signs and symptoms of gonorrhoea Classically, urethral gonorrhoea in men causes discharge (>80%) and dysuria (>50%) although the severity and frequency of the dys- uria has diminished in recent years. The diagnostic thick, profuse, purulent, white or off-white exudate is less often seen and men more commonly complain of a mucopurulent or scanty mucoid discharge. Even if untreated, the discharge might, after some weeks, diminish to a simple clear mucus or resolve completely; asymptomatic patients (<10%) thus include presymptomatic, postsymptomatic, and unob- servant men. Rectal and urethral gonorrhoea acquired by fellatio is increasingly seen in men who have sex with men practising ‘safe’ sex. Uncomplicated gonorrhoea in women affects the cervix (90%), ur- ethra (75%), rectum (40%), or oropharynx (5–15%). Initially, there are no specific symptoms. Gonococcal cervicitis might result in an increased purulent or mucopurulent exudate from the os, which can present as an increased vaginal discharge (50%). This vaginal discharge has no specific characteristic. Dysuria (12%), without fre- quency, is not found consistently enough to make it a diagnostically helpful symptom. The occasional urethral discharge is not profuse enough to cause symptoms. Rectal infection can occur without anal intercourse and rarely produces slight dampness or discharge. Abdominal pain signifies spread to the pelvic organs. Rectal and oropharyngeal infections are asymptomatic in most cases. Development of a sore throat after oral sex does not indicate any particular STI. Complications Complications in men which include tysonitis (infection of the Tyson’s or preputial glands, Fig. 8.6.6.2), epididymitis, prostatitis, periurethral abscess, and infection of the median

raphe are rare in the United Kingdom and other developed countries. If the urogenital infection is undetected or not appropriately treated, spread to the endometrium, fallopian tubes, and pelvic adnexae is the most common complication (5%) in women. It usually occurs at, or soon after, the menstrual period, probably resulting from retrograde flow of menses. Pelvic pain might be unilateral causing confusion with acute appendicitis. Pelvic inflammatory disease can result in severe sequelae such as infertility or ectopic pregnancy. Coincidental infection with C. trachomatis is sufficiently common to justify treatment of both organisms. Infection of Bartholin's, Skene's, or periurethral glands is now rare in the United Kingdom and other developed countries. Vertical transmission can occur at the time of delivery, resulting in purulent conjunctivitis in the neonate which characteristically develops in the first week of life. Fig. 8.6.6.2 Gonococcal urethritis and tysonitis. Courtesy of Peter Greenhouse.

section 8 Infectious diseases 1028 Perihepatitis (Fitz-Hugh–Curtis syndrome) occurs more frequently with C. trachomatis than with N. gonorrhoeae. Right hypochondrial pain, referred to the shoulder, occasionally with pleural effusion and rub, might lead to referral to a surgical or general medical clinician rather than a genitourinary physician. Disseminated gonococcal infection is rare but traditionally more common in women than men, reflecting the lack of genital symptoms in women. It has traditionally been caused mainly by penicillin-sensitive organisms and is a comparatively benign bacteraemia affecting joints and skin. The shoulder and knee are most commonly affected, followed by wrist, elbow, and small joints of the hands and feet, often with an associated tenosynovitis. The pathognomonic painless, usually 4 to 10, skin lesions evolve through vesicular, pustular, and haemorrhagic stages before healing (Figs. 8.6.6.3, 8.6.6.4). Erythema nodosum-like lesions have been described. Systemic symptoms are minimal. White cell count and erythrocyte sedimentation rate are usually not greatly raised. The response to appropriate antibiotic treatment is rapid, but joints may need to be aspirated. Blood or joint fluid culture can yield gonococci, but the quickest diagnosis usually comes from anogenital and throat NAAT. In both sexes, gonococcal infection is associated with increased risk of acquisition and transmission of HIV due to genital tract inflammation. Diagnosis Microscopy Microscopy (×1000) of an appropriately methylene blue- or Gram-stained smear is the first line in diagnosis. For adequate diagnosis, Gram-negative intracellular (within the cytoplasm of a polymorphonuclear leucocyte) diplococci should be identified (Fig. 8.6.6.5). In samples from the male urethra (Fig. 8.6.6.6), microscopy is sensitive (identifying up to 98% of culture positives in symptomatic men and rather fewer in those without symptoms) and highly specific (<1% will be found on culture to be Neisseria meningitidis or other bacterial species). Microscopy of stained samples from the cervix is much less sensitive (≤55%) and comprises a suboptimal specificity, but when positive, immediate treatment is enabled. Because of the preponderance of other Neisseria species in the oropharynx, microscopy of stained samples from this site is not helpful. Microscopy of stained smears from blind anorectal swabs is not recommended because of the large number of other Gram-negative cocci present in faecal flora. However, microscopy of stained smear of a rectal discharge taken through a proctoscope can be helpful. Laboratory detection of N. gonorrhoeae Isolation (culture) of N. gonorrhoeae was the previous diagnostic gold standard because of its high sensitivity and 100% specificity (if adequate species confirmation is performed), but can be hampered by inadequacies in sample taking, storage, transport to the laboratory, and culture methodology, including culture media used. NAATs have been shown to be more sensitive than culture for gonococcal infection. NAATs are significantly more sensitive than culture in samples from the oropharynx and rectum, although they are not currently licensed for use at these sites, but cross-reacting other Neisseria

species can reduce specificity and require confirmation using a second NAAT with a different nucleic acid target. Because NAATs are the standard test methodology for C. trachomatis infection, commercial kits offering testing for both organisms have become the norm. Care is needed in their use in low-prevalence populations; false-positives, resulting in a low positive predictive value, may be unacceptably common. Culture is recommended fol- lowing a positive NAAT test, to allow susceptibility testing of the Fig. 8.6.6.3 Disseminated gonococcal infection, haemorrhagic vesiculopustule. Fig. 8.6.6.4 Disseminated gonococcal infection: healing lesions with desquamation and deposition of haemosiderin. Fig. 8.6.6.5 Gram-stained urethral discharge showing Gram-negative intracellular diplococci.

8.6.6 Neisseria gonorrhoeae 1029 organism. In general, only validated and quality-assured laboratory methods should be used for diagnosis of gonorrhoea. Isolation and identification of N. gonorrhoeae N. gonorrhoeae requires an enriched culture medium, such as (modi- fied) Thayer–Martin or modified New York City which consist of gonococcal (GC) agar base supplemented with a source of iron (lysed horse blood) and essential amino acids and glucose, and incubation in moist atmospheric conditions enriched with 5–7% carbon di- oxide at 37°C. Appropriate specimen collection, storage, and efficient transport to the laboratory are crucial for successful isolation. Specimens are taken from appropriate sites using disposable loops or swabs for inoculation in the clinic or transfer to the labora- tory in transport medium. Isolation is enhanced by adding antibiotics to the medium to suppress other organisms that colonize the anogenital tract. Vancomycin or lincomycin inhibit Gram-positive organisms, colistin and trimethoprim inhibit other Gram-negative organisms, and amphotericin B or nystatin inhibit yeasts. Gram-negative cocci on primary isolation that are oxidase positive (produce cytochrome c oxidase) are considered to be Neisseria species. In the developed world, confirmation of species identity as N. gonor- rhoeae is considered normal practice. This is frequently achieved using carbohydrate utilization tests, either alone or in combination with detection of the enzyme prolyliminopeptidase in commercial kits; N. gonorrhoeae differs from other species in that it utilizes glucose only during growth. An alternative approach is to use immunological re- agents such as coagglutination tests (e.g. Phadebact Monoclonal GC test) that utilize antibodies against antigenic epitopes on the N. gonor- rhoeae major outer membrane protein PorB (Por or PI). These sensitive and specific reagents can identify colonies directly from the primary isolation medium and a result can be obtained on the same day as the organism is isolated. Correct identification of N. gonorrhoeae is always desirable but is most important in cases of sexual or child abuse when more than one identification test should be used to confirm an isolate as N. gonorrhoeae. In recent years, NAATs have become commonly used for species verification of N. gonorrhoeae. Molecular detection of N. gonorrhoeae NAATs have historically not been used as extensively for N. gonor- rhoeae as for C. trachomatis, with which it commonly coexists. This is because the NAATs initially failed to offer much advantage over Gram staining and culture for urogenital specimens, most particu- larly earlier generations of NAATs had a clearly suboptimal speci- ficity for N. gonorrhoeae, and NAATs do not provide an organism for antimicrobial susceptibility testing. However, the increasing pressure to screen more patients attending for sexual healthcare, or asymptomatic individuals in other healthcare settings, together with the evolution of improved commercial NAATs, has signifi- cantly escalated their use. The sensitivity of NAATs is high, they are less affected by suboptimal handling or transport of specimens and can be used with specimens such as urine (recommended for males) or self-taken swabs (recommended for females). NAATs are also rapid, allow automation, and enable simultaneous detection of several STIs. However, despite the fact that the specificity of newer

generations of N. gonorrhoeae NAATs has improved, confirmation using a second NAAT with a different nucleic acid target remains recommended in low-prevalence populations and for extragenital specimens. Furthermore, the performance characteristics of the various commercially available or in-house N. gonorrhoeae NAATs differ significantly. No molecular tests are available for complete determination of antibiotic susceptibility and, accordingly, a rep- resentative sample of viable organisms will be required for surveil- lance purposes to guide antimicrobial therapy. Substantial research is ongoing internationally to develop molecular tests for prediction of antimicrobial resistance or susceptibility for surveillance and, ideally, to guide individually tailored treatment. Epidemiological typing This has been used to study evolution and bacterial population gen- etics, identify specific strains transmitted globally in specific popu- lations and/or in core groups, identify temporal and geographic changes in strain types and the emergence and transmission of in- dividual strains (e.g. antimicrobial resistant strains), establish strain identity/difference in contact tracing, reinfection, or test of cure, confirm/disprove treatment failures, resolve forensic issues, and confirm presumed epidemiological connections or discriminate iso- lates of suspected sexual networks clusters and outbreaks. Molecular typing has largely replaced phenotypic typing methods (auxotyping (based on nutritional requirement) and serovar determination (based on reactivity with monoclonal antibodies)) because it is more robust, reproducible, objective, and discriminating. Sequence-based methods, such as the N. gonorrhoeae multiantigen sequence typing (NG-MAST), which examines diversity in two more variable genes (porB and tbpB), have proved useful in many countries. However, N. gonorrhoeae is highly competent for genetic exchange during its entire life and particularly genes with products exposed to the immune response can have high mutational and recombinational rates. Accordingly, a highly discriminatory typing method, such as NG-MAST, is more appropriate for short-term studies such as ana- lysis of sexual networks or outbreaks, rather than long-term tem- poral studies or comparisons at different geographical locations, nationally and particularly internationally. The combination of an appropriate typing method and detailed epidemiological, anti- microbial resistance and behavioural data can provide information that can be used for public health purposes, and has been proven on a national level in United Kingdom as well as on a European level. Ideally, it would be possible to apply such information when designing public health preventive measures and interventions. In Fig. 8.6.6.6 Urethral swab for gonorrhoea. Courtesy of Peter Greenhouse.

 recent years, whole genome sequencing has become more access- ible, user-friendly, and cost-effective. Whole genome sequencing provides ideal discriminatory and more accurate data that can be ap- plied to microepidemiological (short-term), macroepidemiological (long-term), and evolutionary studies, and allows molecular predic- tion of antimicrobial susceptibility or resistance. Antimicrobial resistance N. gonorrhoeae was originally inherently susceptible to most antimicro- bial agents but with increased usage both chromosomally mediated and plasmid-mediated resistance has developed to all antimicrobials available for treatment of gonorrhoea. Penicillin was used as first-line therapy for many years, until in 1989 when WHO issued new guide- lines for the treatment of gonorrhoea following increasing levels of plasmid-mediated and chromosomally mediated resistance worldwide. Alternative treatments were recommended: ciprofloxacin (a fluoro- quinolone), ceftriaxone (a third-generation cephalosporin), or spec- tinomycin (an aminocyclitol), with penicillin recommended only if the gonococcal population was known to be susceptible. Ciprofloxacin was the treatment of choice in the United Kingdom because it is ad- ministered orally and was highly effective and inexpensive, whereas in the United States of America ceftriaxone was more widely used. In 2002 resistance to ciprofloxacin

reached levels over 5% in England and Wales resulting in a change in guidelines for first-line therapy to a third-generation cephalosporin (i.e. ceftriaxone or cefixime). In 2011, reports of treatment failure to the oral third-generation cephalosporins such as cefixime and in vitro surveillance data indicating increasing prevalence of resistance to cefixime were worrying and national guide- lines in the United Kingdom were revised to recommend the inject- able agent ceftriaxone 500 mg intramuscularly plus azithromycin 1 g oral single dose as first line. The lack of new alternative treatments after ceftriaxone is a major concern internationally and raises the pos- sibility of gonorrhoea as a potentially untreatable infection. In recent years, the drug pipeline has fortunately opened slightly again and a few new antimicrobials for future treatment of gonorrhoea have been developed. Particularly the novel spiropyrimidinetrione, zoliflodacin, (ETX0914 or AZD0914), is promising and currently in randomized clinical trials for treatment of gonorrhoea. Chromosomally mediated resistance Decreased susceptibility to penicillin was detected as early as 1958 but this could be overcome by increasing the dose of penicillin and by adding probenecid. It was not until the 1970s that strains began to appear with minimum inhibitory concentrations (MIC) to peni- cillin of more than 1.0 mg/litre and posed a therapeutic problem. Chromosomal resistance to penicillin in N. gonorrhoeae is the re- sult of the cumulative effects of mutations at multiple loci: penA (decreasing the drug affinity to the main lethal target penicillin- binding protein 2 (PBP2)), mtrR (increasing the drug efflux through an overexpressed MtrCDE efflux pump), penB (decreasing the drug influx through the porin PorB), ponA (decreasing the drug affinity to the second target PBP1), and penC (or pilQ; decreasing the drug influx through the secretin PilQ). Resistance to ciprofloxacin emerged initially in N. gonorrhoeae strains primarily originating from the Western Pacific region, par- ticularly Japan, with single nucleotide polymorphisms in the DNA gyrase gene gyrA and the topoisomerase IV gene parC. These are the main resistance-determining loci, however, mutations in the gyrB gene and overexpressed efflux pumps, such as NorM, might also in- crease the MIC further. Fluoroquinolone-resistant gonorrhoea is now endemic and highly prevalent in most countries globally. In vitro and clinical resistance to third-generation cephalosporins appear also to have initially emerged in the Western Pacific region, particularly in Japan. Therapeutic failure of the oral cephalosporin, cefixime, has now been verified in many countries. Rare failures to treat pharyngeal gonorrhoea with ceftriaxone have also been veri- fied in several countries. The main mechanism of resistance to third- generation cephalosporins is specific mosaic penA alleles, encoding mosaic PBP2 with a remodelled target with less affinity for the drug. The mtrR and penB resistance determinants (see earlier) further in- crease the MIC of the third-generation cephalosporins. The emer- gence of resistance to ceftriaxone, which is the last remaining option for empiric first-line monotherapy is a major concern globally. Azithromycin, primarily used for chlamydial infection, is being used also for gonorrhoea, particularly in the currently recommended, dual antimicrobial therapy. However, resistance has emerged, pos- sibly under selective pressure of the lower 1-g dose recommended for chlamydial infection compared to the 2-g dose for gonorrhoea. The azithromycin resistance is mostly due to specific single nucleo- tide polymorphisms in the 23S rRNA (decreasing the drug affinity to the target 23S rRNA), but also the mtrR resistance determinant, uptake of erm genes encoding 23S rRNA methylases and additional efflux pumps (MacAB efflux pump and Mef effux pump) increase the MIC of azithromycin. Since 2015, an outbreak of N. gonorrhoeae with high-level resistance (MIC ≥256 mg/litre) has been recorded in England. It is of grave concern that the first gonococcal strain with ceftriaxone resistance combined with high-level resistance to azithromycin globally was identified in the United Kingdom in 2018. Spectinomycin can be an alternative for treatment of gonorrhoea as resistance is only reported very sporadically worldwide. However, if spectinomycin is used frequently, resistance

might quickly be selected. Spectinomycin also has poor efficacy (just above 52%) against pharyngeal gonorrhoea and can be difficult to access in many countries, including the United Kingdom. High-level resistance to spectinomycin (MIC >1024 mg/litre) is due to a single nucleo- tide polymorphism in the 16S rRNA gene or, more rarely, specific mutations in the rpsE gene (encoding the 30S ribosomal protein S5), which decrease the drug affinity for the ribosomal target. Plasmid-mediated resistance N. gonorrhoeae exhibiting plasmid-mediated high-level resistance to penicillin was first described in 1976. Simultaneous reports ap- peared of two strains, one from Africa carrying a plasmid of 3.2 MDa (5599 base pair) and the second from the Far East carrying a plasmid of 4.4 MDa (7426 base pair). Both plasmids encoded the TEM-1 type β-lactamase (penicillinase). Penicillinase-producing N. gon- orrhoeae carrying the African (3.2-MDa) and Asian (4.4-MDa) plasmids have now disseminated worldwide although their preva- lence is greatest in countries of the developing world. Penicillinase- producing N. gonorrhoeae carrying plasmids of differing size have been described, such as the Rio/Toronto, Nimes, New Zealand, and Johannesburg plasmids, but these have had more limited spread. The Asian plasmid appears to be the ancestral plasmid from which the other plasmids evolved, through deletions and/or insertions.

8.6.6 Neisseria gonorrhoeae 1031 In 1985, plasmid-mediated resistance to tetracycline was first de- tected. This high-level resistance (MIC ≥16 mg/litre) is due to the acquisition of the tetM determinant by the conjugative plasmid of N. gonorrhoeae resulting in a plasmid of 25.2 MDa. Tetracycline is not the treatment of choice for gonorrhoea but was commonly used, par- ticularly in African countries, until the emergence of high-level resist- ance to tetracycline, because it was inexpensive and readily available. Antimicrobial susceptibility testing The primary aim of antimicrobial susceptibility testing of N. gonor- rhoeae is to predict therapeutic failure. However, it is also important to monitor temporal drifts in susceptibility and to detect the emer- gence of resistant strains to therapies recommended, which should inform revisions of the guidelines for empiric treatment of gonor- rhoea. The quantitative agar dilution method determines the MICs of antimicrobials and is the gold standard method. However, particularly for testing a low number of isolates, agar dilution method is laborious and not appropriate for routine antimicrobial susceptibility testing. Instead, the quantitative Etest for MIC determination is commonly used internationally. Etests, which are strips that contain a gradient of concentrations of antibiotics and give a MIC, are very useful for laboratories testing small numbers of strains, albeit still an expensive choice. A qualitative susceptibility testing can also be performed using a disc diffusion method. This determination of zone sizes of inhibition around antibiotic-containing discs has been the method of choice by most clinical laboratories in the United Kingdom. However, N. gonor- rhoeae is a fastidious organism and different strains significantly vary in their growth patterns and therefore this method can be difficult to quality assure, control, and interpret. Accordingly, for adequate repro- ducibility and interpretation to appropriately reflect the MIC values of given antibiotics, these methods require considerable quality as- surance and appropriate quality controls. Determination of the full MIC might not be necessary for most clinical laboratories. However, for susceptibility testing of cefixime and ceftriaxone, Etests are par- ticularly useful, reliable, and are preferable to disc testing. When disc diffusion methods are used, any new, emerging, or rare antimicrobial resistance should be confirmed by MIC determination. Treatment of gonococcal infection Since the spectrum of antibiotic resistance is continually chan- ging, up-to-date advice regarding resistance and treatment should be sought, for example from the websites of the Public Health England (PHE; formerly Health Protection Agency (HPA)), the British Association of Sexual Health and HIV (BASHH), and the International Union against STIs (IUSTI) European STI guidelines. In the United Kingdom, first-line treatment of uncomplicated uro- genital, rectal, or

oropharyngeal infection in adults is ceftriaxone intramuscularly with azithromycin orally. Spectinomycin intramus- cularly, also with azithromycin orally, is an alternative and is suitable for those with penicillin allergy. Both regimens can be used to treat infection in pregnant or breastfeeding women. When an infection is confirmed by laboratory testing before treatment to be susceptible, ciprofloxacin orally as a single dose, ofloxacin orally as a single dose or cefixime orally as a single dose can also be used. Azithromycin should not be used on its own for treatment of gonorrhoea because of the ease of selection of resistance and presence of high-level resistance in the United Kingdom as well as in many other countries globally. Pelvic infection and epididymo-orchitis might be due to N. gonor- rhoeae, C. trachomatis, mixed anaerobes or any combination of organ- isms, and treatment regimens reflect this. British guidelines suggest that gonococcal pelvic infection and perihepatitis should be treated with parenteral antibiotics. Ceftriaxone intramuscularly or intraven- ously as a single dose with doxycycline and metronidazole, both twice daily intravenously or orally for 14 days, are recommended. For gono- coccal epididymo-orchitis, the treatment is a single dose of ceftriaxone intramuscularly plus doxycycline orally twice daily for 2 weeks. For disseminated gonococcal infection, British guidelines suggest ceftriaxone intramuscularly or intravenously daily; or cefotaxime intravenously every 8 h; or spectinomycin intramuscularly every 12 h continuing for 7 days. This can be switched 24–48 h after symp- toms improve to an oral regimen such as cefixime twice daily or, if quinolone resistance is excluded, ciprofloxacin or ofloxacin twice daily. Laboratory testing should provide full antibiotic susceptibil-ities of the causative organism. Individuals infected with gonorrhoea should be given a detailed explanation of their infection with emphasis on the long-term im- plications for the health of themselves and their partner(s). Patients should also be advised to abstain from sexual intercourse until they and their partner(s) have completed treatment. Finally, patients should be screened for other STIs and their partners identified and, ideally, tested for infection before treatment. Both the United Kingdom national guideline for management of gonorrhoea in adults, and the European guideline on the diagnosis and treatment of gonorrhoea in adults recommend a test of cure in all cases of gonorrhoea. Where resource or practical considerations require test of cure to be selective, priority should be given to pa- tients with persisting symptoms or signs, pharyngeal infection (sig- nificantly harder to eradicate with any treatment), and treatment with a regimen other than the first-line recommendation. FURTHER READING Barlow D, Phillips I (1978). Gonorrhoea in women: diagnostic, clin- ical and laboratory aspects. Lancet, i, 761–4. Bignell CJ, Fitzgerald M (2011). UK National guideline for the manage- ment of gonorrhoea in adults, 2011. https://www.bashh.org/guidelines Bignell C, Unemo M (2013). 2012 European guideline on the diagnosis and treatment of gonorrhoea in adults. Int J STD AIDS, 24, 85–92. Eyre DW, et al. (2018). Gonorrhoea treatment failure caused by a Neisseria gonorrhoeae strain with combined ceftriaxone and high-level azithromycin resistance, England, February 2018. Euro Surveill. Fifer H, et al. (2016). Failure of dual antimicrobial therapy in treatment of gonorrhea. N Engl J Med, 374, 2504–6. Harris SR, et al. (2018). Public health surveillance of multidrug- resistant clones of Neisseria gonorrhoeae in Europe: a genomic survey. Lancet Infect Dis, pii, S1473-3099 (18)30225-1. doi: 10.1016/ S1473-3099(18)30225-1. Hook III EW, Handsfield HH (2008). Gonococcal infections in the adult. In: Holmes KK, et al. (eds) Sexually transmitted diseases, 4th edition, Chapter 35. McGraw Hill, New York, NY. Ison CA, et al. (2013). Current and future treatment options for gonor- rhoea. Sex Transm Infect, 89 Suppl 4, iv52–6.

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