

# Essential Drugs

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## Sexually transmitted diseases

Despite the intensive educational campaigns currently directed to the prevention of HIV infection, and reports from some countries that changes in sexual behaviour have stabilized or even reduced the level of some sexually transmitted diseases, the dramatic rise in their incidence that has occurred globally for several decades has not as yet been decisively stemmed. Since several hundreds of millions of new cases are still treated each year, the economic and social consequences as well as the health implications are considerable. Directly or indirectly, this burden of disease is responsible for much sterility, stillbirth, miscarriage, blindness, brain damage, disfigurement, cancer and even death.

It is vital that treatment is coupled with education of all persons at risk on avoidance of contact and prevention of transmission; that provision is made for tracing, treating and counselling sexual partners; and that screening for sexually transmitted disease is included as a vital component of routine antenatal care.

For reasons that remain uncertain, widespread changes in patterns of infection are also occurring. In many countries chlamydial infections, genital herpes, and warts are now more common than gonorrhoea and syphilis. At the same time, several infections have become unreliably responsive to the more readily-available antimicrobials. Strains of *Neisseria gonorrhoeae* with either chromosomal or plasmid mediated resistance to penicillin — and latterly to tetracycline — are now widespread. Multiresistant strains of *Haemophilus ducreyi* are emerging and resistance to metronidazole has been reported in *Trichomonas vaginalis*.

Other causative agents remain sensitive to most antimicrobial agents, but the treatment of all sexually transmitted diseases becomes more complicated in patients who are infected with the HIV virus or who are otherwise immunocompromised. Where facilities allow, all patients with suspected sexually transmitted disease should be evaluated for HIV, syphilis, gonorrhoea and chlamydia. When there is doubt whether oral

treatment arranged on an outpatient basis will be taken reliably, and particularly when sustained effective antimicrobial plasma concentrations are crucial to success, administration of drugs is best supervised by a health professional.

For these reasons, effective treatment is increasingly dependent upon access both to microbiological services and to expensive third-generation cephalosporins and fluoroquinolones. Wherever it is feasible, a laboratory service should be provided for screening and confirmatory testing. As a minimum, this should be equipped to perform light microscopy on wet mounts and Gram's stained slides, darkfield microscopy for *Treponema pallidum* and, when possible, detection of HIV antibodies.

The reality is that the existence of these facilities remains the exception rather than the rule. Most patients with sexually transmitted diseases are still treated according to prevailing local practices and on the basis of clinical signs alone. However, effective control and containment of the emergence of resistance will never be accomplished without rigorous laboratory control. Consideration of the epidemiology of these diseases over the past 50 years leaves no doubt that investment in the necessary facilities is highly cost-effective. For this reason, emphasis is placed in the following sections upon the importance of microbiological confirmation of the diagnosis and of the antibiotic sensitivity of the causative pathogen, even though this is presently unattainable in many clinical settings.

## Gonorrhoea

Gonorrhoea, which results from infection with the Gram-negative bacterium, *Neisseria gonorrhoeae*, now poses a considerable public health problem. The widespread emergence of strains resistant to penicillin, tetracycline and doxycycline has created a demand for expensive antibiotic therapy which strains health budgets everywhere and which remains unrealized in less developed countries.

Primary infection resulting from sexual contact may involve the mucosal surfaces of the urethra, the cervix, the rectum, the oropharynx or the conjunctivae. Gonococcal conjunctivitis and vulvovaginitis also occur in the newborn, as a result of contact

with endocervical infection in the mother during delivery.

The inflammatory response to urogenital infection is varied. In men, signs of rapidly progressive purulent urethritis typically occur within a few days. When treatment is inadequate or delayed, acute prostatitis, periurethral abscess and urethral stricture are likely to develop. In women, the initial endocervical infection may be either symptomless or marked by mild vaginal discharge. A substantial number of patients who are not treated early develop inflammatory disease of the pelvis which may result in chronic abdominal pain, menstrual disturbance, infertility or ectopic pregnancy.

Gonococcal conjunctivitis must be treated as a medical emergency. Whereas the inflammatory response can be mild in adults, it is always severe in infants in whom it progresses rapidly to corneal ulceration, perforation and blindness.

Haematogenous dissemination can occur if gonorrhoeal infections are not effectively treated at an early stage. Metastatic complications are varied. Typical and serious lesions include meningitis, endocarditis, and acute destructive monoarthritis with synovial effusion.

#### Confirming the diagnosis

In men, urethral discharge is the commonest presenting symptom of sexually transmitted disease. Gonococcal and chlamydial infections frequently coexist. Much less commonly, *Ureaplasma urealyticum*, *Trichomonas vaginalis*, and *Candida albicans* are involved in single or mixed infections. Focal intraurethral lesions, including herpes genitalis, warts, or a syphilitic chancre, are also sometimes responsible.

In women, gonorrhoea is a cause of infective vaginal discharge. Examination should be undertaken to exclude a focal lesion and endocervical and vaginal specimens should be examined microbiologically to establish or exclude candidosis, trichomoniasis and *Gardnerella vaginalis* infection.

Gonorrhoea can be confirmed in 90% of cases by demonstration of Gram-negative intracellular diplococci on a freshly-prepared slide. Ideally, cultures should be prepared when microscopy is negative. *Chlamydia trachomatis* cannot be demonstrated by direct microscopy and few clinics have appropriate culture facilities.

Blood samples should be taken for serology in all cases to exclude concurrent infection with syphilis.

#### Treatment

Since *Chlamydia trachomatis* — which is now the most prevalent cause of sexually transmitted urethritis — commonly co-exists with gonococcal infection, all patients with gonorrhoea should also be treated concurrently for chlamydial infection unless microbiological facilities exist to exclude it. All pregnant women should be screened for gonorrhoea both during their first antenatal visit and again — if they are considered to be at high risk — during the third trimester.

Antimicrobial therapy can be selected with confidence only when information is maintained on both the *in vitro* susceptibility of locally-prevalent strains of gonococci and the clinical efficacy of treatment. Specimens should be obtained routinely for culture 4 to 7 days after treatment to detect persistent infections. Resistance, when it is encountered, is of two types:

**Chromosomal resistance** rapidly rendered sulfonamides obsolescent as antigonorrhoeal agents. Strains have latterly emerged that are highly resistant — either singly or multiply — to penicillins, tetracyclines, spectinomycin, erythromycin, thiamphenicol and cephalosporins. Cross resistance between penicillin and second and third-generation cephalosporins has seriously compromised the value of cefoxitin and cefuroxime in the treatment of gonorrhoea in many areas. Reduced *in vitro* susceptibility of some strains to cefotaxime, ceftriaxone and newer quinolones has been reported more recently, but not as yet to an extent that impairs their clinical efficacy.

**Plasmid mediated resistance** has been recognized more recently and it spreads more rapidly. It has long compromised the value of penicillins and, more recently, of tetracyclines as antigonorrhoeal agents. Several different penicillinase plasmids have now been identified that code for the same TEM-1 beta lactamase, and at least one of these also confers some resistance against non beta-lactam antibiotics. In some areas strains carrying one of these plasmids have also been found to carry chromosomal resistance. Other strains exhibiting high levels of plasmid mediated resistance to tetracycline were first identified in North America in 1985. They have since been found in northern Europe and Africa but, otherwise, their prevalence remains uncertain.

WHO is establishing a network of regional coordinating surveillance centres to collate geographically-specific information on the susceptibility of

gonococci to reference antimicrobials and to promote the standardization of testing methods. The participation of laboratories in both developed and developing countries is encouraged.\*

### **Uncomplicated genital and anal infections**

Unless there are firm grounds for expecting the infection to be responsive to one of the less expensive antimicrobials, patients should receive a single intramuscular dose of either ceftriaxone, 250 mg, or spectinomycin, 2.0 g. A single oral dose of ciprofloxacin, 500 mg, is comparably effective, but it should not be administered during pregnancy.

In some countries, locally acquired strains of gonococci are also susceptible either to a single intramuscular dose of kanamycin, 2.0 g; or to an oral course of thiamphenicol, 2.5 g daily for 2 days; or trimethoprim (80 mg)/sulfamethoxazole (400 mg), 10 tablets once daily for three days.

In the few areas where gonococci remain fully sensitive, a single dose of an appropriate penicillin taken together with probenecid, 1 g, is effective. Either amoxicillin, 3.0 g, or pivampicillin, 1.4 g, may be given orally; or procaine benzylpenicillin, 4.8 million units may be injected intramuscularly.

### **Pharyngeal infection**

Some of the regimens effective in genital gonorrhoea are unreliable in pharyngeal infections. Those most widely advocated are: a single intramuscular injection of ceftriaxone, 250 mg; or trimethoprim (80 mg)/sulfamethoxazole (400 mg), 10 tablets once daily for 5 days.

### **Disseminated infection**

Relatively high and extended parenteral dosage is necessary. For gonococcal arthritis and most other foci of infection, a 7-day course of either ceftriaxone, 1.0 g, given intramuscularly or intravenously; or spectinomycin, 2.0 g twice daily given intramuscularly is usually effective. When strains are known to be fully sensitive to penicillins, benzylpenicillin, 10 million units daily should be given intravenously for 3 days followed by amoxicillin, 500 mg orally for 4 days. When there is evidence of meningeal or endocardial involvement, treatment

should be extended to 2 weeks and 4 weeks respectively.

### **Gonococcal ophthalmia and conjunctivitis**

Since these conditions threaten sight and are rapidly progressive, adult patients should be admitted to hospital immediately and closely monitored until the infection has resolved. Antimicrobial therapy should be administered without delay and the eyes should be frequently irrigated with saline solution. A single intramuscular dose of either ceftriaxone, 250 mg, or spectinomycin, 2.0 g, is usually effective. When these are not available a single dose of intramuscular kanamycin, 2.0 g, may be substituted, or trimethoprim (80 mg)/sulfamethoxazole (400 mg) may be given orally in a single daily dose of 10 tablets for 3 days.

All infants born to mothers with gonococcal infection should immediately receive a single intramuscular dose of ceftriaxone, 50 mg/kg (to a maximum of 125 mg). If this is not available, kanamycin 25 mg/kg (to a maximum of 75 mg) may be substituted. Infants with signs of conjunctivitis should be isolated immediately and a rigorous system of barrier nursing instituted. Tetracycline ointment, 1%, should additionally be instilled into each eye hourly on the first day and 8-hourly for the next 10 days.

Where facilities for routine screening of pregnant women for gonococcal infection are not available, all infants should receive topical antigonococcal therapy immediately after birth. Tetracycline ointment 1% should be applied after gently cleaning the eyelids. Erythromycin ointment 1% is similarly effective, but more expensive. Silver nitrate eye drops 1% are more toxic.

### **Chlamydial infections**

#### **Lymphogranuloma venereum**

Lymphogranuloma venereum, which is highly prevalent in many tropical countries, was first associated with chlamydiae, a genus of obligate intracellular parasites, in the 1930s. The serotypes involved, L<sub>1</sub>, L<sub>2</sub> and L<sub>3</sub>, are distinct from those associated with other sexually transmitted chlamydial infections.

Infection results, after a latent period of days or months, in acute, fluctuant inguinal lymphadenopathy. Left untreated, the inflammatory masses, or

\* Programme of Sexually Transmitted Diseases, Global Surveillance Network for Gonococcal Antimicrobial Susceptibility, WHO Document VTD/90.452 (1990).]

buboes, extend into neighbouring tissues and frequently ulcerate to form chronic sinuses and fistulae. Although the disease is seen in its acute phases more frequently in men, the late sequelae are often more severe in women.

#### Treatment

The disease is usually responsive, in the acute stage, to an oral course of an appropriate antimicrobial, although treatment may need to be extended beyond 14 days. Tetracycline, 500 mg 4 times daily, or doxycycline, 100 mg twice daily, are both effective. When tetracyclines are inappropriate, they may be substituted either by erythromycin, 500 mg 4 times daily, or by a sulfonamide, such as sulfadiazine, 1 gm 4 times daily.

Fluctuant lymph nodes should be aspirated through healthy skin. Incision and drainage or excision of acutely inflamed nodes is contraindicated since it delays healing, but strictures, fistulae and other late sequelae may require surgical intervention.

#### Other chlamydial infections

Over the past thirty years other serotypes of chlamydiae (D-K) have become highly prevalent everywhere and they are now the most common sexually transmitted pathogens in industrialized countries. They are currently implicated in over half of all cases of nongonococcal urethritis in men. Infection may also result in epididymitis and, in active homosexuals, in chronic proctitis. In women, infection is more often asymptomatic or nonspecific in character, and it is associated more frequently with cervicitis, salpingitis and endometritis than with dysuria and pyuria. Reiter's syndrome, which is characterized by conjunctivitis, arthritis and urethritis, has also been associated with chlamydial infection.

Infection during pregnancy is associated with prematurity, low birth weight, neonatal death and postpartum endometritis. More than half the surviving infants born to women with cervical involvement develop purulent conjunctivitis (or chlamydial ophthalmia); others develop pneumonia; rarely, the vagina, pharynx and rectum may also be infected.

Urethritis, which is confirmed by demonstrating the presence of polymorphonuclear leukocytes in the discharge, is caused by several pathogens other than *C. trachomatis*. The most highly prevalent are

*N. gonorrhoeae* and *Ureaplasma urealyticum*. Less commonly, *Candida albicans* and *Herpes simplex* are implicated. However, in one-third of cases seen

in centres with fully equipped microbiological facilities no pathogen can be detected. Unless other causes of urethritis can be excluded with confidence by microscopy and culture, patients with presumed chlamydial infections and their recent sexual partners should also be treated concurrently for gonorrhoea.

#### Treatment

Chlamydial infections involving the urethra, the endocervix, the eye and the rectum usually respond to a 7-day oral course of tetracycline, 500 mg four times daily, or doxycycline, 100 mg twice daily. During pregnancy and in other situations in which tetracyclines are contraindicated, erythromycin, 500 mg four times daily for 7 days, or a sulfonamide in the event of intolerance, should be substituted.

Antimicrobial resistance to recommended regimens has not been reported, but patients should be advised to return for consultation if symptoms persist. Recurrence may result from failure to treat sexual partners or from non-compliance. When symptoms persist or recur after apparently adequate treatment, both patient and partners should be referred for laboratory investigation. Cultures for chlamydia should be taken 6 weeks after completion of treatment.

Where facilities exist, all pregnant women should be screened for chlamydial infection using direct immunofluorescence and rapid-culture techniques, initially during the first antenatal visit and again — for patients considered to be at high risk — during the third trimester. Pregnant women with gonorrhoea should be assumed also to have chlamydial infection and, in every instance, sexual partners should be treated simultaneously. Erythromycin at the above dosages is suitable for use during pregnancy. Tetracyclines are contraindicated because they are potentially toxic both for the fetus and for the mother.

Before neonatal conjunctivitis is treated as a chlamydial infection, gonorrhoea should be excluded microscopically. Erythromycin syrup is usually effective at a dosage of 50 mg/kg administered daily in 4 divided doses for 2 weeks. This regimen can be repeated should inclusion conjunctivitis recur on withdrawal of treatment. Topical therapy is not required. Infantile pneumonia requires more extended antimicrobial therapy.

#### Vaginitis

Vaginal discharge that occurs only premenstrually or at the time of ovulation, or that is associated with

the use of oral contraceptives or an intrauterine device, is likely to be physiological. Common pathological causes of diffuse vaginitis are candidiasis, chlamydiasis, trichomoniasis and *Gardnerella vaginalis* infections. Discharge is also associated both with focal infective lesions including syphilitic chancre, herpes and warts, and with non-infective conditions including cervical ectopion, polyps and neoplasms.

Diagnosis is confirmed microbiologically. Because candidosis, trichomoniasis and gonorrhoea may occur concurrently, tests for all three infections should be performed, particularly in high-risk patients. *Candida albicans* can usually be identified as Gram-positive spores and mycelia in smears taken from the vaginal wall. *Trichomonas vaginalis* is most reliably detected by dark-ground microscopy in a wet preparation of an isolate from the posterior fornix. *Neisseria gonorrhoea* can sometimes be demonstrated as Gram-negative intracellular cocci in isolates taken from the mucous membranes of the endocervix and the urethra but, because many infections are missed on microscopy, cultures should also be prepared. Facilities for isolating *Chlamydia trachomatis* are available only in the most highly equipped laboratories. *Gardnerella vaginalis* can often be seen on light microscopy attached to vaginal epithelial cells. The discharge may have a fish-like odour which is heightened by adding 5–10% potassium hydroxide to a few drops on a glass slide.

### **Candidosis**

Most infections are cured by nystatin pessaries, 100 000 units. Two inserted nightly for two weeks are usually effective, but in some areas doses as high as 1 000 000 units nightly are required. More rapid cures can be obtained with more expensive imidazole preparations such as clotrimazole or miconazole, 200 mg daily intravaginally for three days. Vulval irritation may be relieved by local nystatin or clotrimazole cream. A relapse shortly after initial therapy should be treated with a longer course of an imidazole: for example, clotrimazole 100 mg daily for 12 days.

If infection is recurrent, other possible predisposing factors including use of oral contraceptives and tight or insulating clothing should be discussed with the patient.

### **Trichomoniasis**

Metronidazole, 2.0 g in a single oral dose, cures the large majority of infections. The cure rate increases to more than 90% when sexual partners, who are

usually asymptomatic, are treated simultaneously. Coincident bacterial vaginitis attenuates the effectiveness of the treatment. Patients who do not respond satisfactorily to single doses should receive metronidazole, 800 mg at 12-hour intervals for 5 days. This should also clear any local bacterial infection.

Because metronidazole has been demonstrated to be teratogenic in animals at massive dosage, trichomoniasis is best managed by local therapy during pregnancy and lactation. Pessaries of clotrimazole will at least attenuate symptoms.

Infants with symptomatic trichomoniasis or with asymptomatic infection persisting after the fourth month should receive metronidazole, 5mg/kg orally, three times daily for 3 days.

### **Gardnerella infections**

Oral metronidazole, 400 mg twice daily for 5 days is highly effective, but reinfection can occur if partners are not evaluated and treated as appropriate.

## **Pelvic inflammatory disease**

Acute pelvic inflammatory disease, primarily involving the endometrium and fallopian tubes, is often a consequence of sexually transmitted disease. The pathological agents most commonly involved are *Neisseria gonorrhoeae* and *Chlamydia trachomatis*. Colonization of the latter is favoured by the use of oral contraceptive preparations. However, bacteria present in the normal vaginal flora, including *Streptococcus* species, *Escherichia coli*, *Haemophilus influenzae* and anaerobes such as *Bacteroides* spp, *Peptostreptococcus* and *Peptococcus*, are also frequently implicated. It is possible that the ascent of these organisms into the endometrial cavity is facilitated by trauma to the endocervical canal from an intrauterine device.

The condition is a frequent cause of pain, dyspareunia, vaginal discharge, dysuria, fever, and sometimes of nausea and vomiting. Untreated, the chronic inflammatory reaction may result in long-term sequelae, including persistent abdominal discomfort, sterility, tubal pregnancy and menstrual disturbances. The diagnosis should be considered in all sexually active women complaining of lower abdominal pain, and — because it can also be asymptomatic — in all women with sexually transmitted disease.

Ideally, all patients in whom the diagnosis is established should be admitted to hospital. Where

this is not feasible, priority should be given to those with severe disease that is unresponsive to ambulatory treatment, adolescents, pregnant women, patients with a suspected pelvic abscess, and those who have signs suggestive of appendicitis or ectopic pregnancy.

#### Treatment

If an intrauterine device is in place it should be removed.

Since mixed infections are common and precise microbiological diagnosis is rarely feasible, a treatment regimen should be chosen that is active against each of the commonly implicated organisms. The objective is to relieve symptoms and, in particular, to arrest progressive tubal damage.

Ambulatory patients have been successfully treated with single dose therapy for uncomplicated gonorrhoea, followed by a ten-day oral course of doxycycline or tetracycline for chlamydial infection taken concurrently with metronidazole, 500 mg three times daily, for anaerobic infections. However, evidence of potential carcinogenicity and teratogenicity has aroused reservations about the routine use of metronidazole for a commonly occurring condition in young women.

Regimens based on cefoxitin (active against *N. gonorrhoeae*, *Enterobacteriaceae* and anaerobes) and doxycycline (active against *C. trachomatis*) are now widely used, while a combination of clindamycin (active against anaerobes and Gram-positive aerobic organisms) and gentamicin (active against Gram-negative aerobic organisms including *N. gonorrhoeae*) is sometimes favoured for treatment of pelvic abscess. Other regimens based on penicillins in combination with beta-lactam inhibitors, quinolones, monolactams and carba-penems are still being evaluated.

Severely ill, hospitalized patients should receive intravenous antimicrobial therapy — either cefoxitin, 2 g four times daily, plus doxycycline 100 mg twice daily; or gentamicin, 1.5 mg/kg 8-hourly together with clindamycin, 900 mg three times daily — for a minimum of 4 days and for at least 48 hours after clinical improvement, followed by oral doxycycline or tetracycline for 10 days.

## Syphilis

After many years of decline resulting from the success of penicillin therapy, syphilis, which is caused by the spirochaetal organism, *Treponema*

*pallidum*, is again increasing in incidence in many industrialized countries. In less developed countries, where the disease has remained relatively common, the primary illness frequently remains untreated and the late sequelae of the disease are still encountered.

Transmission results almost exclusively from direct contact with infected lesions or, during pregnancy, from congenital infection of the fetus. The primary genital ulcers (or chancres) — which are typically solitary, "punched out", indurated, painless lesions with a clear exudate — appear between 9 to 90 days after exposure and heal spontaneously within a few weeks. Although the chancre has distinctive morphological characteristics, it should be differentiated microbiologically from other causes of ulceration including herpes genitalis, chancroid, and Behçet's disease.

Untreated, and within a period of 6 months, the disease enters the secondary phase which is characterized by a transient pleomorphic skin rash and generalized low-grade lymphadenopathy, accompanied occasionally by focal involvement of the eye, the meninges, parotid glands or viscera. Similar episodes, which never persist for more than a few weeks, may recur within the first three years. Infectivity subsides after this time, although women who remain untreated almost invariably infect their progeny for 10 years or more after initial infection.

Infection of the central nervous system may occur in any patient with untreated syphilis of more than two years' duration. From 5 to 50 years may elapse after the disease becomes quiescent before the tertiary manifestations — benign late syphilis and cardiovascular syphilis — become evident.

Fetal infection may occur at any time throughout pregnancy, and infectivity approaches 100% when the mother has untreated primary or secondary disease. Clinical evidence of infection is often not present at birth and it may readily be missed until the lesions of late syphilis begin to appear during childhood. However, preventive measures adopted in more affluent countries have been highly successful with the result that congenital syphilis has been virtually eliminated where pregnant women are screened routinely for the disease.

#### Confirming the diagnosis

Clinical suspicion of syphilis can be difficult to confirm. During the primary and secondary phases of the disease repeated searches should be made

for spirochaetes in exudates from lesions using dark-ground microscopy. Serological tests do not become positive for at least two weeks after the appearance of the primary lesion. Two of these tests are specific for treponemal diseases: the absorbed fluorescent treponemal antibody test and the treponema pallidum haemagglutination test. The first usually becomes positive late in the primary stage, while the second often takes somewhat longer to develop. Subsequently, both tests often remain positive for life even when prompt, effective treatment is given. For this reason, quantitative but less specific tests, the Venereal Disease Research Laboratory Test (VDRL) and the rapid plasma reagin test (RPR), are widely used to assess the stage and activity of the disease. These are flocculation tests that depend upon the presence and titre of a less specific antibody (reagin) in the serum.

All pregnant women should be screened for syphilis, using a non-treponemal test, both during their first antenatal visit and again — if they are considered to be at high risk — at least in the third trimester. Pregnant patients who are positive on serological testing should be examined clinically for evidence of infection. If no abnormal signs are detected two further separate blood specimens should be submitted for serology within 4 weeks. If the disease cannot then be excluded with reasonable certainty the patient should receive antisyphilitic treatment. If it is certain that a seropositive patient has been treated adequately in the past, retreatment is unnecessary unless the VDRL titre rises 4-fold or more on sequential testing, or recent sexual contacts are indicative of recurrence. Following treatment, the VDRL titre should be estimated at monthly intervals up to the time of delivery in order to detect reinfection or relapse.

The risk of congenital syphilis is remote if the mother has been treated with penicillin during pregnancy. Passive transfer of antibodies from a previously infected mother can invalidate postnatal serological diagnosis of active disease in the child for as long as 12 weeks. None the less, any seropositive infant of a seropositive mother should be treated promptly. It is no longer considered justifiable to wait for three months to obtain serological confirmation of the diagnosis. An infected infant of a mother infected late in pregnancy may be both asymptomatic and seronegative at birth. Such infants should also be treated immediately, particularly when it is impossible to monitor their clinical and serological status reliably,

or when it is uncertain whether the mother has received adequate treatment with penicillin.

Abnormalities in the cerebrospinal fluid may develop in any patient with syphilis. They occur in the early stages with sufficient frequency for some clinicians to require a sample to be examined routinely one year after treatment before discharging the patient as cured. This examination is also vital in the investigation of suspected neurosyphilis. The disease should be excluded in any patient who presents with cranial nerve lesions, or optic or auditory symptoms of uncertain cause. Negative serological tests virtually exclude neurosyphilis, but positive tests require careful interpretation. Because they are persistent, they may provide evidence of previous as well as current infection.

Radiological assessment, as well as serological testing, is important in the diagnosis and subsequent management of cardiovascular syphilis.

#### **Treatment**

All patients and their contacts should be additionally tested and treated, as appropriate, for chlamydial infection, gonorrhoea and human immunodeficiency virus.

#### **Early syphilis**

In cases of not more than 2 years' duration, two alternative regimens are widely used: either a single intramuscular injection of benzathine benzylpenicillin, 2.4 million units (given, because of the large volume, as two injections at separate sites); or a 10-day intramuscular course of procaine benzylpenicillin, 1.2 million units daily.

However, some authorities recommend that all patients with either secondary or latent syphilis should receive more prolonged treatment: either intramuscular benzathine benzylpenicillin, 2.4 million units once weekly for 3 consecutive weeks; or intramuscular procaine benzylpenicillin, 1.2 million units daily for 2 weeks.

#### **Late syphilis (other than neurosyphilis)**

Prolonged courses of penicillin should be administered to all patients with benign late syphilis, cardiovascular syphilis, and latent syphilis that is likely to be of more than 2 years' duration. This may be given either as a 3-week intramuscular course of procaine benzylpenicillin, 1.2 million units daily, or as 3 consecutive weekly intramuscular injections of benzathine benzylpenicillin, each of 2.4 million units.

### **Neurosyphilis**

Higher dosages are necessary in patients with neurosyphilis to ensure that penicillin levels in the cerebrospinal fluid do not fall below the minimum inhibitory concentration throughout the period of treatment. This is most reliably achieved by administering benzylpenicillin, 4 million units, intravenously every 4 hours for 2 weeks. Alternatively, provided that compliance is assured, single daily intramuscular injections of procaine benzylpenicillin, 1.2 million units, can be given for 2 weeks in combination with oral probenecid, 500 mg 4 times daily.

### **Syphilis in pregnancy**

Syphilis should be treated immediately at all stages of pregnancy in accordance with the foregoing regimens. Treated patients should remain under close supervision throughout pregnancy to ensure that any reinfection is promptly diagnosed and treated.

### **Congenital syphilis**

In children aged up to 2 years, congenital syphilis usually responds well to adequate doses of penicillin, although recovery may be slow in seriously ill patients with extensive involvement of the skin, mucous membranes, bone and viscera. Pneumonia and other intercurrent infections can rapidly supervene, particularly when there are signs of malnutrition.

When the cerebrospinal fluid is abnormal the infant should receive a 10-day course either of benzylpenicillin, 50 000 units/kg daily in 2 divided doses intravenously, or in one daily dose intramuscularly. When the cerebrospinal fluid is normal, opinion is divided as to whether a 10-day course is required, or whether reliance can be placed in a single intramuscular injection of benzathine benzylpenicillin, 50 000 units/kg.

In children older than 2 years, higher and sustained blood concentrations of penicillin are required. Benzylpenicillin should be given for 2 weeks in a dose of at least 200 000 to 300 000 units/kg daily, rising on a weight adjusted basis to 1.2 million units/kg daily.

### **Patients allergic to penicillin**

Non-pregnant adult patients with early syphilis who are allergic to penicillin should receive a 2-week oral course of either tetracycline, 500 mg four times daily; or doxycycline, 100 mg twice daily. For patients with late syphilis this regimen should be extended for at least one additional week.

Pregnant patients with early syphilis and confirmed allergy to penicillin are seriously disadvantaged because they cannot be given tetracyclines. It is consequently important to assess and, when appropriate, to confirm by skin testing any unsupported report of allergy in such a patient. An attempt at desensitization should be considered. Various alternative treatments have been proposed, but formal proof of efficacy is lacking. These include oral erythromycin, 500 mg, which is sometimes administered 4 times daily for 3 weeks or, alternatively, in women with no history of anaphylaxis, an extended course of a third-generation cephalosporin.

Children with congenital syphilis and confirmed allergy to penicillins should receive erythromycin 7.5 to 12.5 mg/kg daily in 4 divided doses for a period of 30 days. During the first month of life the risk of allergy can safely be discounted.

### **Post-treatment follow-up**

Patients with early syphilis who have been treated with adequate doses of penicillins should be evaluated clinically and serologically after 3 months, 6 months and 12 months to assess the effect of treatment and to detect possible reinfection. Patients treated with other antibiotics should be evaluated more frequently. Nontreponemal tests may remain positive at low titres indefinitely even after adequate treatment.

Patients with cardiovascular syphilis or neurosyphilis should remain under observation for at least 3 years. In addition to clinical and serological evaluations, examination of cerebrospinal fluid and assessment of radiological changes may also be necessary. Retreatment should be considered when:

- clinical signs or symptoms of active syphilis persist or recur;
- a high titre nontreponemal test, such as a VDRL of 1:8, persists for 1 year or, in a pregnant woman, for 3 months;
- a lower titre nontreponemal test increases by 4-fold or more.

The cerebrospinal fluid should be examined before treatment, unless there are conclusive grounds for establishing a diagnosis of early syphilis due to reinfection. In all other circumstances patients should be assumed to have late syphilis and be treated accordingly.

## Genital herpes simplex

Genital herpes, which can be caused by the ubiquitous herpes simplex virus, but more frequently by a variant (HSV-2), increased considerably in prevalence among young adults throughout the 1980s, particularly in North America. The disease is painful, recurrent and without cure.

Primary infection is usually signalled within a week by an extremely painful vesicular eruption, on the external genitalia or other foci of sexual contact which subsequently ulcerates and resolves with crusting. This resolves spontaneously and completely within 3 weeks, but the virus remains latent within the involved sensory nerve ganglia. Recurrences, which are usually milder and shorter than the primary attack, are often preceded by local tingling and paraesthesiae. Typically, they occur 3 or 4 times each year and they are liable to recur indefinitely. The incidence of the disease and the frequency and severity of the attacks is greater in patients who are immunodeficient, most commonly as a result of HIV infection.

In the longer term, HSV-2 infection in women may increase the risk of cervical carcinoma. Although the association remains contested, annual cytological examinations are recommended.

The evidence for placental transmission of infection is inconclusive. If it occurs it is likely to result in fetal death and spontaneous abortion. Neonatal infection can occur if the mother's infection is active at the time of delivery. The risk is low and is greatest during the primary infection. The disease can remain focal in the skin, the eyes, and the oral cavity, but in its disseminated form it can be fatal within a few weeks and cause permanent brain damage in survivors. When active genital lesions are present the possibility of delivery by Caesarian section should be considered. Genital cultures taken late in pregnancy are poor predictors of shedding during delivery.

### Confirming the diagnosis

Definitive diagnosis is dependent upon culture and identification of the herpes virus but, in practice, this is often not possible. Treatment is then determined solely on medical history and clinical examination. Syphilis and other causes of genital ulceration should be excluded beforehand.

### Treatment

Patients should be warned that they are infectious to their partner when the lesions are present and that they should abstain from sexual activity as soon as they become aware of prodromal symptoms.

Topical treatment has little palliative effect, but pain may be partially relieved by simple analgesics. Bathing the lesions with saline is soothing and may facilitate micturition when this is painful. Urinary retention resulting from uncontrollable pain can necessitate hospital admission.

Although no radical cure is possible, the antiviral agent, aciclovir, inhibits replication of the virus to an extent that markedly reduces viral shedding. Treatment is extremely costly, but systemic therapy, when started early, may inhibit the formation of new lesions and also significantly accelerate healing, particularly during the first attack.

Primary attacks are usually treated with a 7-day oral course of aciclovir, 200 mg five times daily. In subsequent attacks, 5 day courses of treatment may suffice. Severe attacks in immunocompromised patients, which are characterized by widespread mucocutaneous involvement, should be treated in hospital with intravenous aciclovir, 5 mg/kg, every 8 hours until the lesions resolve, and for not less than 5 days.

Continuous suppressive therapy with aciclovir, 200 mg 3 times daily, has been claimed to markedly decrease the rate of recurrences among patients experiencing more than six episodes yearly. At present, there is no indication that this regimen gives rise either to cumulative toxicity or to the development of resistance.

Secondary infections should be treated with an appropriate antibiotic. Trimethoprim/sulfamethoxazole has the advantage, in some situations, that it has no antitreponemal activity and, consequently, does not mask syphilis.

Infants born to women with active genital ulcers or positive herpes virus cultures should be isolated and examined frequently for signs of infection. When possible, cultures for herpes virus should be taken at 24 and 48 hours after birth. In some centres all infants born to a mother with a primary infection are presumptively treated with intravenous aciclovir at the above dosage without awaiting confirmation of infection.

## Chancroid

Chancroid, which results from infection by *Haemophilus ducreyi*, is the most common cause of genital ulceration in developing countries and it has been associated with increased rates of HIV infection. It is seen most frequently in men — typically on the prepuce, following a short incubation period of 1–8 days, and it is characterized by extremely painful, soft, destructive lesions, with undermined ragged edges and enlarged inguinal lymph nodes. Clinically, and in the absence of laboratory confirmation, the disease is readily confused with syphilis and genital herpes.

Secondary fusospirochaetal infection of advanced untreated lesions can result in destructive ulceration of the entire external genital region, with stenotic lesions, sinus formation and, in women, rectovaginal fistula.

### Treatment

Fluctuant lymph nodes may need to be aspirated through intact skin when the patient is first seen. Effective antimicrobial therapy usually results in rapid healing of the ulcerative lesion and resolution of lymph node enlargement within 14 days, but a high degree of resistance to therapy has been reported in patients with HIV infection.

A single intramuscular dose of ceftriaxone, 250 mg, is highly effective, as is erythromycin given orally at a dose of 500 mg three times daily for 7 days. A single oral dose of ciprofloxacin, 500 mg, has been claimed to be useful in the presence of HIV infection, but the results of confirmatory studies are still awaited. Benzylpenicillin should always be administered at the same time when facilities for darkfield examination and serological diagnosis of syphilis are not available. Resistance of *H. ducreyi* to sulfonamides, tetracyclines and penicillins now renders these compounds largely ineffective. None the less, in some countries trimethoprim (80 mg)/sulfamethoxazole (400 mg), 2 tablets twice daily for 7 days is still used with success.

## Granuloma inguinale

Granuloma inguinale is a chronic granulomatous infection, usually involving the genitalia and perineum, that is caused by a Gram-negative encapsulated bacterium, *Calymmatobacterium granulomatis* (formerly referred to as *Donovania granulomatis*) that occurs almost exclusively in tropical and subtropical regions. It is believed to be sexually transmitted, but it is not highly contagious.

The primary lesion, which appears after an incubation period ranging from 9–90 days, starts as a papule and slowly develops into a painless, indurated granulomatous ulcer. Lymph nodes become enlarged only when secondary infection supervenes. Secondary fusospirochaetosis results in large, painful and foul-smelling destructive lesions. Untreated, the lesion may involve the whole of the external genitalia, the inguinal region and the anus. Healing then results in intense scarring and stenotic lesions that require surgery. Cancerous change can occur in long-standing lesions.

### Treatment

Most infections are cured by a 2-week course of trimethoprim (80 mg)/sulfamethoxazole (400 mg), 2 tablets twice daily. Intramuscular streptomycin, which is also effective, is no longer recommended because of its ototoxicity and the need to reserve it for the treatment of tuberculosis.

Unresponsive infections have been treated successfully with a variety of regimens. Those most widely used are oral tetracycline, 500 mg four times daily for 2 weeks; chloramphenicol, 500 mg orally four times daily for 3 weeks; or gentamicin 1 mg/kg intramuscularly 3 times daily for 3 weeks.

The treatment of pregnant patients poses difficulties because of the potential toxicity of these antibiotics. Erythromycin alone has proved disappointing. Better results are claimed when it is administered in combination with lincomycin (each at an oral dose of 500 mg four times daily for 2 weeks), but this is associated with a risk of pseudomembranous colitis.

## Genital warts

Genital warts are caused by a papillomavirus which cannot be cultured. They are nearly always transmitted by sexual contact and are usually asymptomatic. They occur most commonly on the external genitalia, but the perineum, anus, oral cavity and rectum — and in women, the vagina and cervix — may also be involved. They are diagnosed solely on their clinical features and need to be distinguished, in particular, from condylomata lata of secondary syphilis and molluscum contagiosum.

Many patients have other sexually transmitted diseases. They should be examined to exclude gonorrhoea and non-gonococcal urethritis and also, in women, vaginal infection due to chlamydiae, candida, trichomonas or *Gardnerella vaginalis*.

Serological tests for syphilis should also be undertaken.

Women should also be examined by colposcopy for cervical warts. Because of uncertainty regarding risk of malignant change, they should be encouraged to undergo annual cytology testing.

#### Treatment

Local caustic applications are most frequently used, but treatment failures are frequent. Podophyllum resin, 10–25% in compound tincture of benzoin, should be applied carefully and sparingly to the lesions at weekly intervals, avoiding normal tissue. Where it is available, podophyllotoxin is a less toxic alternative which can be applied by the patient. Trichloroacetic acid applied directly to the wart is less effective and the treated area should be powdered with talc or sodium bicarbonate to remove excess acid. Podophyllum resin applied to vaginal mucosa or to meatal warts should be allowed to dry before it comes into apposition with normal epithelium. External applications should be removed by washing after 1–4 hours. Podophyllin is readily absorbed, locally destructive and teratogenic. Neither podophyllotoxin or podophyllum resin should be applied to large skin surfaces, nor should they be used during pregnancy or lactation.

Surgical removal, electrocautery, cryosurgery and laser treatment may be used when topical applications have failed or when they are contraindicated.

Electrosurgical removal under urethroscopy is preferred for urethral warts, which should be suspected when meatal warts are recurrent. Intraurethral instillation of 5% fluorouracil cream may be effective, but the technique remains to be fully evaluated.

## ACICLOVIR

*tablet 200 mg*

*powder for injection 250 mg in vial*

Aciclovir, a synthetic purine nucleoside analogue derived from guanine is an antiviral agent. It acts against herpes viruses by interfering with DNA synthesis and inhibiting viral replication.

Absorption from the gastrointestinal tract is variable and incomplete. It is widely distributed in tissues and body fluids and is excreted in the urine primarily unchanged.

#### Uses

Treatment of primary genital herpes simplex.

#### Dosage and administration

*Adults with normal immune status:* 200 mg five times daily orally for 7 days.

*Immunocompromised patients:* 5 mg/kg every 8 hours for at least 5 days.

#### Contraindications

Aciclovir should not be used in uncomplicated herpes simplex infections in other sites in immunocompetent persons.

Known hypersensitivity.

#### Precautions

Aciclovir should be administered by slow infusion over a period of one hour to avoid acute impairment of renal function. Adequate hydration should be maintained.

#### Use in pregnancy

Experimental animal studies have demonstrated mutagenic effects. Aciclovir should not be used during pregnancy.

#### Adverse effects

Headache, nausea and vomiting are the most frequent adverse effects following oral administration.

Transient renal impairment may occur during intravenous therapy, possibly as a result of crystallization in the renal tubules. This usually responds rapidly to dosage reduction or withdrawal of the drug. Haemodialysis is necessary in extreme cases of acute renal failure.

#### Overdosage

Since aciclovir is incompletely absorbed from the gastrointestinal tract, oral overdosage is unlikely to have serious effects.

#### Storage

Tablets should be stored in tightly-closed containers below 25 °C.

Aciclovir for injection should be stored between 2 and 8 °C.

**BENZYL PENICILLIN**

powder for injection, 600 mg (= 1 million IU), 3 g (= 5 million IU) (as sodium or potassium salt) in 5 ml-vial

**BENZATHINE BENZYL PENICILLIN**

powder for injection, 1.44 g benzylpenicillin (= 2.4 million IU) in 5-ml vial

**PROCAINE BENZYL PENICILLIN**

powder for injection 1g (= 1 million IU), 3 g (= 3 million IU)

Benzylpenicillin is a beta-lactam derivative of *Penicillium*. It is bactericidal against *Streptococci*, *Neisseriae*, many anaerobes and spirochaetes. It must be administered parenterally because it is degraded in the gastric juice. After intramuscular injection, peak plasma concentrations are reached within 15–30 minutes. It is widely distributed throughout the body, has a plasma half-life of 30 minutes and is excreted mainly in the urine.

Repository formulations of benzylpenicillin are available for parenteral use. They are designed to provide a tissue depot from which the drug is slowly absorbed over a period of 12 hours to several days. Procaine benzylpenicillin produces a peak plasma concentration within 1–3 hours. It is excreted over a period of several days while benzathine benzylpenicillin is detectable in the urine for several weeks.

**Uses**

Primary, secondary and latent syphilis of less than one year's duration should be treated with either procaine or benzathine benzylpenicillin.

Latent syphilis, neurosyphilis or cardiovascular syphilis require intensive intravenous therapy with benzylpenicillin.

Early congenital syphilis may be treated with either benzylpenicillin or procaine benzylpenicillin but children aged two years or more require intravenous benzylpenicillin.

Value in the treatment of gonorrhoea is limited to the few remaining areas where gonococci remain fully sensitive to penicillins.

**Dosage and Administration**

Benzylpenicillin and its repository formulations must be administered parenterally.

The powder for injection should be diluted in water for injection in accordance with the manufacturer's directions.

**Primary, secondary and latent syphilis:**

Benzathine benzylpenicillin 2.4 million IU i.m. in a single session, or  
Procaine benzylpenicillin 1.2 million IU daily i.m. for 10 consecutive days.

**Latent syphilis, neurosyphilis or cardiovascular syphilis:**

Benzylpenicillin 12–24 million IU i.m. in divided doses for 14 days.

**Early congenital syphilis:**

Benzylpenicillin 50 000 IU/kg i.m. or i.v. in two divided doses for 10 days or  
Procaine benzylpenicillin 50 000 IU/kg i.m. daily for 10 days.

**Congenital syphilis of two or more years' duration:**

Benzylpenicillin 20 000 IU/kg i.v. daily in divided doses for 14 days.

**Gonorrhoea in areas where gonococci remain fully sensitive:**

Procaine benzylpenicillin 4.8 million IU i.m. as a single dose.

**Contraindications**

Known hypersensitivity to penicillins or cephalosporins.

**Precautions**

Facilities should be available for treating anaphylaxis whenever penicillins are used.

Patients should be questioned carefully about previous allergic reactions.

If skin rashes develop during treatment, the patient should be transferred to a different class of antibiotic.

Rapid intravenous administration of large doses of benzylpenicillin may cause hyperkalaemia, dysrhythmias and cardiac arrest, particularly in patients with impaired renal function.

**Use in pregnancy**

There is no evidence of teratogenicity with benzylpenicillin or its repository formulations. They can be used during pregnancy.

Desensitization should be attempted of pregnant women with syphilis who are allergic to penicillins.

**Adverse reactions**

Hypersensitivity reactions range in severity from skin rashes to immediate anaphylaxis.

Pain and sterile inflammation can occur at the site of intramuscular injection and phlebitis or thrombophlebitis sometimes occurs after intravenous administration.

Accidental injection into a peripheral nerve causes pain and dysfunction. Unduly high concentrations of benzylpenicillin in the central nervous system can result in confusion, convulsions, coma and fatal encephalopathy.

Interstitial nephritis has been reported and neutropenia and thrombocytopenia have occurred.

#### Overdosage

Overdosage can cause convulsions, paralysis and even death.

Emesis and gastric lavage may be of value if instituted within a few hours of injection. Excessive blood concentrations can be lowered by haemodialysis.

#### Storage

Powder for injection should be stored at temperatures between 2 and 8 °C.

## CEFTRIAZONE

*powder for injection 250 mg*

Ceftriazone is a third-generation cephalosporin derived from *Cephalosporium acremonium*. It is highly active against Gram-negative cocci and Gram-negative bacilli. Like benzylpenicillin, it has a beta-lactam ring.

After intramuscular administration, ceftriazone is distributed widely throughout the body. It has a relatively long plasma half-life of about eight hours and is excreted as unchanged drug both in the urine and bile.

#### Uses

Treatment of penicillin-resistant gonococcal infections.

Treatment of chancroid caused by beta-lactam-resistant *Haemophilus ducreyi*.

Treatment of pelvic inflammatory disease together with tetracycline.

#### Dosage and administration

Ceftriazone must be administered parenterally.

**Uncomplicated congenital and pharyngeal gonococcal infection:**

250 mg i.m. as a single dose

**Disseminated gonococcal infection:**

1 g daily i.m. or i.v. for 7 days.

**Neonatal gonococcal ophthalmia:**

50 mg/kg i.m. as a single dose.

**Chancroid:**

250 mg i.m. as a single dose.

**Pelvic inflammatory disease:**

250 mg i.m. as a single dose, followed by doxycycline 100 mg twice daily for 10 days.

#### Contraindications

Known hypersensitivity to other beta-lactam antibiotics.

#### Precautions

Blood concentrations of liver enzymes may rise transiently.

#### Use in pregnancy

There is no evidence that ceftriazone is teratogenic. It may be used during pregnancy.

#### Adverse effects

Hypersensitivity reactions are the most common adverse effects. Skin rashes are relatively frequent, while urticaria, bronchospasm and anaphylaxis are uncommon. Nausea, vomiting and diarrhoea have been reported. Rarely, antibiotic-associated pseudomembranous colitis due to *Clostridium difficile* occurs. When this is suspected, treatment should be immediately discontinued.

Reversible cholestatic jaundice has been reported.

#### Storage

Powder for injection should be stored in tightly closed containers, protected from light.

## CIPROFLOXACIN

*tablet 250 mg (as hydrochloride)*

Ciprofloxacin is a synthetic quinolone which acts as a specific inhibitor of bacterial DNA gyrase. It has a broad spectrum of antibacterial efficacy against both Gram-negative and Gram-positive aerobic organisms. Reports of chromosome resistance have been reported but as yet are of little clinical significance.

It is rapidly absorbed from the gastrointestinal tract; it has a plasma half-life of 3–5 hours and is excreted in the urine mainly as unchanged drug.

**Uses**

Treatment of penicillin-resistant gonorrhoea.  
Treatment of chancroid in patients with HIV.

**Dosage and administration**

**Uncomplicated anal and genital gonorrhoea and chancroid infections:** 500 mg in a single dose.

**Contraindications**

Hypersensitivity to any quinolone.  
Pregnancy, adolescents and children since arthropathy has been induced in weight-bearing joints of young animals.

**Precautions**

Reduced dosage should be considered in patients with hepatic or renal impairment.  
Ciprofloxacin should be administered cautiously to patients with epilepsy since seizures may be precipitated.  
Adequate fluid intake must be assured since crystalluria may occur.

**Adverse effects**

Ciprofloxacin is generally well tolerated. The most frequently reported adverse effects are nausea, diarrhoea, vomiting, dyspepsia, abdominal pain, headache, restlessness, rash, dizziness and pruritus.

**Drug interactions**

Plasma concentrations of theophylline may be raised.  
Prolonged bleeding time has been reported in patients receiving anticoagulants concurrently.

**Overdosage**

Gastric lavage is of value if performed promptly.  
Electrolyte balance must be maintained. Serum concentrations of ciprofloxacin may be lowered by dialysis.

**Storage**

Tablets should be stored in well-closed containers.

**ERYTHROMYCIN**

*enteric coated tablets 250 mg (as stearate or ethylsuccinate)*

*oral suspension 125 mg (as stearate or ethylsuccinate)/5 ml*

Erythromycin is a macrolide antibiotic produced by *Streptomyces erythreus*. It has selective bacteriostatic activity against both streptococci and staphylococci and some Gram-positive bacilli.

Because it is inactivated by gastric juices, oral formulations are enteric-coated. It diffuses rapidly into all tissues except the brain and cerebrospinal fluid, and readily crosses the placental barrier. The plasma half-life is approximately 90 minutes. It is partially demethylated in the liver and excreted largely via the bile and faeces.

**Uses**

- *Chlamydia trachomatis* infections in patients unable to take tetracycline.
- Confirmed ophthalmia neonatorum.
- Lymphogranuloma venereum as an alternative to tetracycline.
- Syphilis in penicillin-allergic pregnant patients.

**Dosage**

**Chlamydia:** 500 mg orally four times daily for 7 days.

**Ophthalmia neonatorum:** 50 mg/kg of oral suspension daily for 14 days.

**Lymphogranuloma venereum:** 500 mg four times daily for 14 days.

**Syphilis:** 500 mg orally four times daily for 30 days.

The effectiveness of erythromycin in syphilis is doubtful and it must be used only as a drug of last resort.

**Contraindications**

Known hypersensitivity to erythromycin.

**Precautions**

Hepatic function should be monitored in patients with a previous history of liver disease.

**Adverse effects**

Nausea, vomiting and diarrhoea can occur.  
Cholestatic hepatitis, which may present with symptoms suggestive of acute cholecystitis, occasionally complicates prolonged courses of treatment. Symptoms resolve rapidly when the drug is withdrawn.  
Anaphylaxis and other hypersensitivity reactions are rare.

**Drug interactions**

Erythromycin, chloramphenicol, and clindamycin which have a similar bacteriostatic action tend to be mutually antagonistic when administered together. Erythromycin decreases the rate of metabolism of carbamazepine and warfarin in the liver to a degree that can warrant readjustment of dosage.

**Overdosage**

Symptoms of overdosage include severe nausea, vomiting, diarrhoea and hearing loss. Induction of emesis or gastric lavage may be of value if undertaken within a few hours of ingestion.

**Storage**

Tablets and suspension should be stored in tightly-closed containers.

**METRONIDAZOLE**

*tablet 200 mg, 250 mg, 400 mg, 500 mg*  
*suspension 200 mg/5 ml*

A 5-nitroimidazole derivative with anti-microbial activity against anaerobic bacteria and some protozoa, including *Trichomonas vaginalis*. Metronidazole is almost completely absorbed following oral administration. Its plasma half-life is about 8 hours and it is excreted, largely in the urine, both unchanged and as metabolites.

**Uses**

Treatment of confirmed trichomoniasis.

Trichomoniasis in neonates persisting for more than 4 weeks.

Treatment of vaginitis due to *Gardnerella vaginalis*.

**Dosage and administration**

Metronidazole should be administered preferably with or immediately after meals.

**Trichomoniasis:**

*Adults:* 2 g in a single oral dose, or 200 to 250 mg three times daily for 7 days.

*Infants more than 4 weeks old:* 20 mg/kg daily for 5 days in divided doses.

**Gardnerella infections:**

*Adults:* 400 mg twice daily for 5 days.

**Contraindications**

- Known hypersensitivity.
- Early pregnancy.
- Chronic alcohol dependence.

**Precautions**

Patients should be warned not to take alcohol during treatment since disulfiram-like reactions can occur.

**Use in pregnancy and lactation**

Metronidazole should not be used to treat trichomoniasis during early pregnancy. For symptomatic relief, clotrimazole 100 mg may be given as

a vaginal suppository daily for 7 days. Breast-feeding should be interrupted until 24 hours after cessation of treatment since metronidazole is excreted in milk.

**Adverse effects**

In general, metronidazole is well tolerated, but mild symptoms of headache, gastrointestinal irritation and a persistent metallic taste are common. Less frequently, drowsiness, rashes and darkening of urine occur.

More serious reactions are rare and usually occur only during extended courses of treatment. They include stomatitis and candidiasis, reversible leukopenia, and sensory peripheral neuropathy, which is usually mild and rapidly reversible. Ataxia and epileptiform seizures have been reported among patients receiving dosages considerably higher than those currently recommended.

**Drug interactions**

The action of oral anticoagulants is potentiated. Alcohol may induce abdominal pain, vomiting, flushing and headache.

Phenobarbital and corticosteroids lower plasma levels of metronidazole whereas cimetidine raises them.

**Overdosage**

No specific treatment exists. Emesis or gastric lavage may be of value within a few hours of ingestion.

**Storage**

Tablets and suspension should be kept in well-closed containers, protected from light.

**MICONAZOLE**

*cream, 2% (nitrate)*

A synthetic imidazole antifungal agent active against both dermatophytes and yeasts, and Gram-positive cocci (*Staphylococcus* and *Streptococcus* spp).

**Uses**

A specially formulated cream is used for treatment of vaginal candidosis.

**Dosage**

*Vaginal candidosis:* 10 ml cream should be inserted high into the vagina on 7 consecutive nights.

**Contraindications**

Known hypersensitivity to miconazole.  
Severe liver impairment.

**Precautions**

Treatment should be discontinued if irritation or sensitivity occurs. It should not come in contact with the eyes.

**Use in pregnancy**

Topically-applied miconazole is not systemically absorbed and can be used safely during pregnancy and lactation.

**Adverse effects**

Irritation and burning occasionally occur.

**Storage**

Store preparations in a cool place, protected from light.

**NYSTATIN**

*ointment or cream: 100 000 IU*

An antifungal polyene antibiotic derived from *Streptomyces noursei* which is effective against infections caused by a wide range of yeasts and yeast-like fungi.

**Uses**

Treatment of vaginal candidosis.

**Dosage and administration**

100 000 IU cream inserted high into the vagina nightly for at least 2 weeks.

Administration should be continued for 48 hours after clinical cure. Higher doses and a longer period of treatment may be necessary in immunocompromised patients.

**Contraindications and precautions**

Discontinue treatment if symptoms of irritation or sensitization occur.

**Use in pregnancy**

Nystatin does not cross the placental barrier and no special precautions are required during pregnancy.

**Adverse effects**

Mild and transient nausea, vomiting and diarrhoea may occur after oral administration. Irritation rarely occurs after topical application.

**Storage**

Nystatin ointment or cream should be stored in well-closed containers, protected from light and below 15 °C.

**PODOPHYLLUM RESIN**

*solution 10 %*

Podophyllum resin is a powdered mixture of resins extracted from the roots of *Podophyllum peltatum*. A solution is prepared by forming a paste with benzoin in alcohol. It is a caustic keratolytic agent for topical application.

**Uses**

Topical treatment of genital warts (condylomata acuminata).

**Dosage and administration**

A 10% solution should be applied to the affected area. Care must be taken to avoid contact with normal tissue. The solution should be thoroughly rinsed off after 1–4 hours.

Therapy may be repeated once or twice weekly for no more than a total of four applications.

The active ingredient podophyllotoxin is available in some countries. It is less corrosive and may be applied without medical supervision.

**Contraindications**

Podophyllum resin should not be applied to large areas of skin, nor should it be used in the treatment of cervical, urethral, anorectal or oral warts.

**Use in pregnancy**

Treatment is contraindicated during pregnancy since podophyllum resin is both teratogenic and fetotoxic.

**Precautions**

Preparations of podophyllum resin should be used only under close medical supervision because of potentially serious local and systemic toxicity that can result from prolonged or excessive applications. Systemic absorption is enhanced when applications are made to friable, bleeding warts.

**Adverse effects**

Systemic effects resulting from excessive cutaneous absorption include nausea, vomiting, abdominal pain and diarrhoea.

Transient leukopenia and thrombocytopenia sometimes provide evidence of bone-marrow depression.

Gross over-application can result in serious neurotoxicity. The signs, which are characteristically delayed in onset are slow to resolve. They include visual and auditory hallucinations, delusions, disorientation, confusion and delirium.

**Storage**

Topical solution should be kept in tightly closed containers, protected from light and excessive heat. The shelf-life of the resin is variable and some formulations may begin to degrade within a few days.

**SPECTINOMYCIN**

*powder for injection 2 g (as hydrochloride) in vial*

Spectinomycin is produced from *Streptomyces spectabilis*. It is most effective against *Neisseria gonorrhoeae* in which it selectively inhibits protein synthesis.

It is rapidly absorbed after intramuscular injection and peak plasma concentrations occur after one hour. It is not significantly bound to plasma proteins and is excreted unchanged in the urine.

**Uses**

Uncomplicated anogenital and disseminated gonorrhoea.  
Gonococcal ophthalmia.

**Dosage and administration**

**Uncomplicated anogenital infections:**  
2 g i.m. as a single dose.

**Disseminated gonococcal infections:**

2 g i.m. twice daily for 7 days.

**Gonococcal ophthalmia:**

2 g i.m. as a single dose.

**Contraindications**

Known hypersensitivity.

**Precautions**

In patients with renal impairment spectinomycin should be used only when alternative therapies are inappropriate.

**Use in pregnancy**

Safety in pregnancy has not been established. It should be used in pregnant women only if the need outweighs any possible risk to the fetus.

**Adverse reactions**

Hypersensitivity reactions occur rarely. Pain at injection site, nausea, fever, dizziness and urticaria have been reported.

**Storage**

Powder for injection should be stored in vials.

**SULFAMETHOXAZOLE/  
TRIMETHOPRIM**

*tablet 100 mg + 40 mg, 400 mg + 80 mg,  
800 mg + 160 mg*

The two components of this combination product have a similar antimicrobial spectrum. They operate synergistically because they independently inhibit different steps in the enzymic synthesis of tetrahydrofolic acid, an essential metabolic process in susceptible organisms.

Trimethoprim is absorbed more rapidly and is more widely distributed in tissues than sulfamethoxazole. Both compounds enter the cerebrospinal fluid; they are extensively bound to plasma proteins, and each is excreted largely unchanged in the urine at a rate that gives a plasma half-life of about 10 hours.

**Uses**

Treatment of chancroid and gonorrhoea in those areas where strains remain sensitive.  
Treatment of granuloma inguinale.

**Dosage and administration**

**Chancroid:** sulfamethoxazole 400 mg + trimethoprim 80 mg two times daily for 7 days.

**Gonorrhoea:** sulfamethoxazole 4000 mg + trimethoprim 800 mg as a single dose for 3 days.

**Granuloma inguinale:** sulfamethoxazole 800 mg + trimethoprim 160 mg twice daily for 14 days.

**Contraindications**

Known hypersensitivity.  
Severe hepatic or renal dysfunction.

**Precautions**

Treatment should be suspended immediately should a rash, or any other manifestation of sulfonamide hypersensitivity occur. The risk of sulfonamide crystalluria is decreased by maintaining a urinary output of at least 1.5 litres daily. Whenever possible, plasma sulfonamide concentrations should be determined periodically. Peak plasma concentrations should be maintained at about 40 micrograms/ml.

Patients must be advised to seek medical advice should they develop a sore throat or fever during treatment. This advice can be of greater value than routine monitoring of the white cell count.

Elderly patients may be more susceptible to severe adverse reactions, especially blood dyscrasias. Treatment should not be unnecessarily prolonged. Supplementary calcium folinate may prevent megaloblastic anaemia.

#### Use in pregnancy

Because the disease is life-threatening, treatment should in no circumstance be delayed.

#### Adverse effects

Nausea, vomiting, glossitis and skin rashes are common.

Trimethoprim may induce a megaloblastic anaemia responsive to folic acid.

Sulfonamide-induced hypersensitivity reactions can be severe. They include life-threatening cutaneous reactions such as erythema multiforme (Stevens-Johnson syndrome) and toxic epidermal necrolysis.

Other reactions include granulocytopenia, agranulocytosis, aplastic anaemia, thrombocytopenic purpura and toxic hepatitis. Occasionally, haemolysis may occur in individuals deficient in glucose-6-phosphate dehydrogenase.

#### Drug interactions

Maintenance requirements for sulfonamides and coumarin anticoagulants are often reduced as a result of their displacement from plasma proteins by sulfamethoxazole.

Concomitant use of other inhibitors of folate metabolism (such as pyrimethamine, methotrexate and certain anticonvulsants) increases the risk of megaloblastic anaemia.

#### Overdosage

Symptoms of acute overdosage include vomiting, dizziness and confusion followed by visual disturbances, petechiae, purpura and jaundice.

Crystalluria, haematuria and anuria may also occur. Emesis or gastric lavage may be of value within a few hours of ingestion. Provided urinary output is satisfactory, a high fluid intake should be maintained. Haemodialysis may be of value in eliminating some of the drug. Otherwise, treatment is symptomatic and supportive.

#### Storage

Tablets should be stored, protected from light, in well-closed containers.

## TETRACYCLINE

capsule or tablet, 250 mg (hydrochloride)

eye ointment 1% (hydrochloride)

Tetracycline is a broad-spectrum antibiotic derived from a species of *Streptomyces* that induces bacteriostasis by inhibiting protein synthesis. It is selectively concentrated in susceptible organisms. Absorption from the alkaline contents of the intestine is slow. Peak plasma concentrations occur within 4 hours and decay with a half-life of about 8 hours. Excretion is effected primarily by filtration into the urine. An enterohepatic circulation results in high concentrations accumulating in the liver and bile. Bacteriostatic concentrations are maintained for up to 6 hours after topical administration.

Tetracycline crosses the placenta and is excreted into breast milk.

#### Uses

Treatment of *Chlamydia trachomatis* infections; lymphogranuloma venereum; syphilis in penicillin-allergic non-pregnant patients; and granuloma inguinale.

Prevention and treatment of conjunctivitis of the newborn due to *N. gonorrhoeae* and *C. trachomatis*.

#### Dosage

***Chlamydia trachomatis***: 500 mg orally four times daily for 7 days.

***Lymphogranuloma venereum and granuloma inguinale***: 500 mg orally four times daily for 14 days.

***Syphilis***: 500 mg orally four times daily for 15 days. In neurosyphilis and late syphilis, treatment should be continued for a further 15 days.

***Prevention of ophthalmia neonatorum***: A single application of the ointment should be sufficient.

***Treatment of ophthalmia neonatorum***: Ointment should be applied to the conjunctiva 4 times daily for 14 days together with systemic therapy. The treatment may be reduced to 4 days if there is no evidence of conjunctivitis.

#### Contraindications

Known hypersensitivity.  
Severe renal impairment.

**Precautions**

Troublesome oesophagitis may be averted if the patient is propped up while swallowing capsules, which should be washed down immediately with a glass of water.

Time-expired tetracycline capsules or tablets should be discarded. Degraded tetracycline has been reported to induce renal dysfunction indistinguishable from the Fanconi syndrome and skin lesions similar to those of systemic lupus erythematosus.

**Use in pregnancy and early childhood**

Tetracycline is generally contraindicated in pregnancy and during early childhood because impaired calcification can result in abnormal osteogenesis, permanent staining of teeth and also, on occasion, hypoplasia of dental enamel.

**Adverse effects**

Phototoxic reactions occasionally result in porphyria-like skin changes and pigmentation of the nails.

Hypersensitivity reactions are rare. Morbilliform rashes, urticaria, fixed drug eruptions, exfoliative dermatitis, cheilosis, glossitis, pruritus and vaginitis are described. Angioedema, anaphylaxis and pseudotumor cerebri have been reported.

**Storage**

Tetracycline capsules or tablets should be kept in well-closed containers, protected from light.

**DOXYCYCLINE**

capsules, 100 mg (as hyclate)

Doxycycline is derived from and closely related to oxytetracycline, and shares an identical spectrum of antibiotic activity. It differs from the tetracyclines in that it is more extensively absorbed and more lipid-soluble, and it possesses a longer serum half-life that is independent of the patient's renal status.

**Uses**

Treatment of *Chlamydia trachomatis* infections; lymphogranuloma venereum; syphilis in penicillin-allergic non-pregnant patients; granuloma inguinale; pelvic inflammatory disease (together with a third-generation cephalosporin).

**Dosage**

*Chlamydia trachomatis*: 100 mg orally twice daily for 7 days.

*Lymphogranuloma venereum and granuloma inguinale*: 100 mg orally twice daily for 14 days.

*Syphilis*: 100 mg orally twice daily for 15 days. In neurosyphilis and late syphilis, treatment should be continued for a further 15 days.

*Pelvic inflammatory disease*: 100 mg twice daily for 10–14 days.

**Contraindications**

Known hypersensitivity.

[Precautions, use in pregnancy, adverse effects

**The information in this section is subject to consultation prior to definitive publication in the WHO Model Prescribing Information series. Comments, which are invited at this stage, should be referred to:  
Division of Drug Management and Policies, World Health Organization, 1211 Geneva 27, Switzerland**