Current recommended management of common STIs in primary care

Nadi Gupta MRCP and George Kinghorn OBE, MD, FRCP

Without effective treatment sexually transmitted infections can lead to serious complications. Our Drug review describes the current treatment options for the most commonly encountered STIs in general practice, followed by sources of further information.

Sexually transmitted infections (STIs) constitute a major public health problem. They can be detrimental to both physical and psychological health and, without effective treatment, can result in serious complications.

STIs are increasing in incidence. In 2010, England was in the bottom third of 43 countries in the World Health Organization’s European Region and North America for condom use among sexually active young people; previously, England was in the top 10.¹ In 2012, there were approximately 450,000 diagnoses of STIs made in England.² Of these, the most common were Chlamydia (46 per cent), genital warts (16 per cent), genital herpes (7 per cent) and gonorrhoea (6 per cent).

When comparing trends in diagnoses made at GUM clinics from 2011 to 2012, there was an increase in the following STIs: gonorrhoea (21 per cent; 21,024–25,525), trichomoniasis (6 per cent; 6280–6638), genital herpes (2 per cent; 31,318–32,021) and infectious syphilis (1 per cent; 2939–2978). The impact of STIs remains greatest in young heterosexuals under the age of 25 years and in men who have sex with men (MSM). Large increases in STI diagnoses were seen in MSM, including a 37 per cent increase in gonorrhoea diagnoses.²

The common STIs encountered in the general practice setting are Chlamydia trachomatis, Neisseria gonorrhoeae, genital warts, genital herpes and Trichomonas vaginalis.

The aim of this article is to describe the available treatment options for the most commonly encountered STIs and highlight the significant changes in recent years. It is beyond the remit of the article to discuss the detailed treatment of syphilis, lymphogranuloma venereum (LGV) and HIV infection. Although the most common and important side-effects and interactions will be discussed, reference to the product literature and the BNF will provide a more comprehensive list. Readers are also encouraged to read the British Association for Sexual Health and HIV (BASHH) guidelines for more detailed information (see Resources).
Bacterial infections

Genital Chlamydia

Chlamydia is the commonest bacterial STI, with 206,912 diagnoses made in 2012. One in ten sexually active young people aged between 16 and 24 years have genital C. trachomatis infection. Furthermore, results from the national Chlamydia screening programme demonstrate a high level of asymptomatic infection reinforcing the need for screening in community settings.

Women may develop pelvic inflammatory disease, which can lead to ectopic pregnancy and infertility. In men, complications include urethritis and epididymitis.

LGV is an STI caused by one of three invasive serovars of C. trachomatis. Since 2003, there have been a series of LGV outbreaks reported across Europe occurring mostly among HIV-positive MSM. In the recent MSM outbreaks the majority of cases presented with proctitis. Patients may report rectal pain, anorectal bleeding, mucoid and/or haemopurulent rectal discharge, tenesmus and constipation. It is important to take a rectal swab for STI screening in any patient reporting receptive anal intercourse.

Chlamydia, like other acute bacterial and viral STIs, is associated with an increased risk of HIV transmission and acquisition. The consequences of these complications represent a considerable health and economic burden.

### What’s new in the treatment of STIs

- new RCGP/BASHH guidelines on the management of STIs have been produced specifically for pragmatic use in the primary-care setting (see Resources)
- a test of cure at 3 months post-treatment of Chlamydia trachomatis is recommended in all patients under 25 years of age
- doxycycline may be more efficacious than azithromycin in patients with rectal chlamydial infection
- there are increasing rates of resistance of Neisseria gonorrhoeae to cephalosporins: a test of cure at 2 weeks post-treatment is recommended in all patients with gonorrhoea
- the prevalence of genital warts is likely to decrease in the UK following the introduction of the quadrivalent HPV vaccine programme
- syphilis has re-emerged in the UK mainly among men who have sex with men and rates of infectious syphilis are at their highest since the 1950s
- rates of HIV are increasing with around one-quarter of patients unaware of their infection

### First-line and alternative treatments for uncomplicated Chlamydia trachomatis infection

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Mechanism of action</th>
<th>Efficacy</th>
<th>Principal side-effects</th>
<th>Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st line</td>
<td>azithromycin</td>
<td>1g po single dose</td>
<td>inhibits protein synthesis</td>
<td>&gt;95%</td>
<td>occasional: GI intolerance, diarrhoea, nausea, abdominal pain</td>
</tr>
<tr>
<td>1st line (particularly if rectal infection)</td>
<td>doxycycline</td>
<td>100mg bd po for 7 days</td>
<td>inhibits protein synthesis</td>
<td>&gt;95%</td>
<td>occasional: oesophagitis, hepatitis, GI intolerance, candidosis, photosensitivity stains teeth in children &lt;12 years</td>
</tr>
<tr>
<td>Alternative</td>
<td>erythromycin</td>
<td>500mg qds for 7 days or 500mg bd po for 14 days</td>
<td>inhibits protein synthesis</td>
<td>77–95%</td>
<td>frequent: GI intolerance occasional: stomatitis, cholestatic hepatitis, rash (higher likelihood of side-effects with qds regimen)</td>
</tr>
<tr>
<td>Alternative</td>
<td>ofloxacin</td>
<td>200mg bd or 400mg od po for 7 days</td>
<td>disrupts bacterial DNA replication</td>
<td>similar to doxycycline but more expensive</td>
<td>occasional: GI intolerance, headache, malaise, insomnia, restlessness</td>
</tr>
<tr>
<td>Alternative</td>
<td>tetracycline</td>
<td>500mg qds po for 7 days</td>
<td>inhibits protein synthesis</td>
<td>94–99%</td>
<td>frequent: GI upset, stains teeth in children &lt;12 years occasional: hepatotoxicity, photosensitivity</td>
</tr>
</tbody>
</table>

Table 1. First-line and alternative treatments for uncomplicated Chlamydia trachomatis infection
The antibiotics available to treat uncomplicated genital infection are summarised in Table 1. First-line therapy is usually with azithromycin or doxycycline. Recent evidence suggests that doxycycline may be more effective than azithromycin in the treatment of rectal infection. If LGV is suspected then referral to genitourinary medicine is recommended as a prolonged course of antibiotics is required. Contact tracing of sexual partners should be pursued, and patients should be advised to avoid sexual intercourse until they and their partner(s) have finished treatment.

The national Chlamydia screening programme has recently recommended retesting for Chlamydia three months post-treatment in all patients under 25 years of age. Studies show that around 10–15 per cent of young adults diagnosed with Chlamydia also test positive at their next test.

Pregnancy Erythromycin is safe for use in pregnancy but less efficacious. Current BASHH and RCGP guidelines recommend a test of cure in pregnancy five weeks after therapy in pregnancy or after six weeks if azithromycin is used.

Azithromycin may be taken in pregnancy but the manufacturers advise that it should only be used if there is no alternative.

Gonorrhoea (see Figure 1)
Gonorrhoea, caused by N. gonorrhoeae, is the second most common bacterial STI in the UK. There are higher rates in young people, MSM and black ethnic groups.

The complications of gonorrhoea include epididymitis, prostatitis, pelvic inflammatory disease and disseminated gonococcal infection.

Co-infection with C. trachomatis is common (up to 20 per cent of men and 40 per cent of women with gonorrhoea), and it is essential that screening for C. trachomatis is performed as a matter of routine. The sites of infection are the urethra, endocervix, pharynx, conjunctiva and rectum.

Table 2 summarises the main antibiotics used in the management of uncomplicated gonorrhoea. Treatment guidelines are changing in view of the growing concern regarding antimicrobial resistance and decreasing sensitivity of the gonococcus to extended-spectrum cephalosporins. In 2011, Japan and France reported N. gonorrhoeae strains that were resistant to ceftriaxone (Rocephin) and most other antibiotics. UK surveillance data from 2012 demonstrate evidence of isolates exhibiting decreased susceptibility to ceftriaxone, and overall

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<tr>
<td><strong>1st line</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ceftriaxone (with 1g azithromycin co-treatment)</td>
<td>500mg im single dose</td>
<td>disrupts synthesis of bacterial cell wall</td>
<td>occasional: allergic reaction, diarrhoea, eosinophilia</td>
<td>probenecid</td>
</tr>
<tr>
<td>spectinomycin</td>
<td>2g im single dose</td>
<td>inhibits protein synthesis</td>
<td>occasional: urticaria, rash, pruritus</td>
<td>none</td>
</tr>
<tr>
<td>cefixime</td>
<td>400mg po single dose</td>
<td>disrupts synthesis of bacterial cell wall</td>
<td>frequent: diarrhoea, nausea occasional: allergic reaction, diarrhoea, eosinophilia</td>
<td>probenecid</td>
</tr>
<tr>
<td>ciprofloxacin</td>
<td>500mg po single dose</td>
<td>disrupts bacterial DNA replication</td>
<td>occasional: GI intolerance, headache, malaise, insomnia, restlessness</td>
<td>sucralfate, antacids, theophylline, warfarin</td>
</tr>
<tr>
<td>ofloxacin</td>
<td>400mg po single dose</td>
<td>disrupts bacterial DNA replication</td>
<td>occasional: GI intolerance, headache, malaise, insomnia, restlessness</td>
<td>antacids, sucralfate, procainamide</td>
</tr>
</tbody>
</table>

Table 2. First-line and alternative treatments for uncomplicated anogenital gonorrhoea

The antibiotics available to treat uncomplicated genital infection are summarised in Table 1. First-line therapy is usually with azithromycin or doxycycline. Recent evidence suggests that doxycycline may be more effective than azithromycin in the treatment of rectal infection. If LGV is suspected then referral to genitourinary medicine is recommended as a prolonged course of antibiotics is required. Contact tracing of sexual partners should be pursued, and patients should be advised to avoid sexual intercourse until they and their partner(s) have finished treatment.

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prevalence of azithromycin resistance increased slightly to 0.7 per cent. Ciprofloxacin resistance was found in 25 per cent of isolates and therefore quinolones are no longer recommended unless the isolate is known to be sensitive.

Contact tracing of sexual partners should be pursued, and patients should be advised to avoid sexual intercourse until they and their partner(s) have finished treatment. A test of cure at two weeks post-treatment is recommended in all patients.

Intramuscular ceftriaxone plus co-treatment with azithromycin (regardless of Chlamydia result) is the current first-line recommended treatment. Oral cefixime (unlicensed indication) plus co-treatment with azithromycin is second line (in those who decline parenteral therapy).

Pregnancy The cephalosporins are safe for use in pregnancy.

Syphilis
There has been a marked increase in the number of cases of early syphilis observed since the late 1990s. Epidemics of infectious syphilis are continuing, especially among MSM.

Syphilis is caused by the spirochaete Treponema pallidum and has an incubation period of 9–90 days. The primary ulcer (chancre) usually occurs at the site of inoculation that is usually the genital or perianal area. The lesion is classically solitary and painless but can be multiple and painful. The primary chancre spontaneously resolves after a few weeks and may go unnoticed by the patient.

Secondary syphilis develops four to eight weeks later. It has a wide variety of presentations and may mimic many other diseases and can be easily misdiagnosed as glandular fever. Clinical features of secondary syphilis include rash, lymphadenopathy, mouth ulcers, fever and malaise. The symptoms and signs resolve without treatment. Long-term complications of untreated syphilis are neurological disease, cardiovascular disease and granulomatous skin lesions (gumma) that occur years later.

Diagnosis is based on history, clinical features and serological confirmation. Left untreated, it can lead to serious complications and even death. Suspect and proven cases should always be referred.

Parenteral penicillin is the treatment of choice for all stages of syphilis.

Viral infections
Genital warts (see Figure 2)
Genital warts are caused by infection with human papilloma virus (HPV) and are the most prevalent viral STI diagnosed in the UK. Infection may not be clinically apparent.

Table 3. Treatments available for genital warts

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dose</th>
<th>Mechanism of action</th>
<th>Side-effects</th>
<th>Clearance at end of treatment</th>
<th>Recurrence rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cryotherapy with liquid nitrogen</td>
<td>apply until a ‘halo’ forms a few millimetres around the lesion, every 1–2 weeks</td>
<td>cytolysis at dermo-epidermal junction</td>
<td>local irritation/occasional scarring</td>
<td>63–92%</td>
<td>0–39%</td>
</tr>
<tr>
<td>Podophyllotoxin (0.15% cream)</td>
<td>apply bd x 3 days a week, repeat up to 4 months</td>
<td>antimitotic agent</td>
<td>localised reaction</td>
<td>42–88%</td>
<td>10–91%</td>
</tr>
<tr>
<td>5% imiquimod cream</td>
<td>3 x a week, wash off 10 hours later – repeat up to 4 months</td>
<td>induces a cytokine response – response to treatment may be delayed for some weeks</td>
<td>localised irritation</td>
<td>50–62%</td>
<td>13–19%</td>
</tr>
<tr>
<td>Surgical</td>
<td>refer</td>
<td>excision</td>
<td>infection, bleeding</td>
<td>89–93%</td>
<td>36%</td>
</tr>
</tbody>
</table>

Figure 2. Drug treatments for genital warts include podophyllotoxin and imiquimod creams.
There are over 100 documented genotypes, most being benign. However, certain genotypes are associated with an increased risk of anogenital neoplasia; specifically in the UK, genotypes 16 and 18 are associated with the greatest risk. However, most visible warts are due to types 6 and 11, which are the least likely to have neoplastic potential.

Treatment is usually for cosmetic rather than medical purposes. All treatments have significant failure and relapse rates, and no single treatment is considered to be better than another. There are multiple treatments available; Table 3 illustrates some of the most commonly used. By stimulating the immune response, imiquimod (Aldara) may have a lower relapse rate. Podophyllotoxin can be used as a 0.15 per cent cream (Warticon Cream) or a 0.5 per cent solution. The solution is an option when treating warts that are easily visible and accessible to the patient: in practice, this means that it is more appropriate in males.

Other treatments available in specialist settings include curettage, trichloroacetic acid, laser therapy and electrosurgery. These too have significant failure and relapse rates.

Patients should be reviewed to assess progress. Different options may need to be tried if the patient is not tolerating the treatment or if there is a poor response. *Pregnancy* Cryotherapy is safe for use in pregnancy; podophyllotoxin, however, is contraindicated.

With the roll-out of quadrivalent HPV vaccine (Gardasil) in the UK, the prevalence of genital warts is expected to decline. *Genital herpes (see Figure 3)*

Genital herpes is the commonest ulcerative STI in the UK and its prevalence is increasing. Herpes simplex virus (HSV) types 1 and 2 both cause genital and orolabial herpes. Studies demonstrate an increasing proportion of genital herpes cases associated with HSV type 1, most often resulting from orogenital transmission. The presence of genital ulcers also increases the likelihood of HIV transmission.

Disease episodes may be initial (primary) or recurrent, and symptomatic or asymptomatic. Primary genital herpes can be very painful and distressing. Most clinicians make a clinical diagnosis and prescribe immediate treatment after taking
swabs for HSV; full STI screening is important but is usually deferred until lesions have healed.

General advice includes saline bathing, analgesia and 2 per cent lidocaine gel. Oral antiviral drugs reduce the severity and duration of the episode, and are indicated within five days of the start of the episode and while new lesions are still forming. Topical agents are not as effective as oral.

The three antiviral drugs all have similar efficacy but differ in cost. It is the authors’ preference to use valaciclovir for primary genital herpes as it achieves a high plasma drug concentration more rapidly, and aciclovir for recurrent infection.

Treatment of recurrent genital herpes could be episodic or suppressive. Episodic treatment, usually for three days, should ideally be patient initiated. Patients experiencing frequent outbreaks may be considered for suppressive treatment with aciclovir 400mg twice daily, usually for a maximum of one year. Failure of suppressive treatment is usually due to inadequate dosing, poor adherence and rarely malabsorption. Aciclovir resistance is another possible cause of treatment failure and is more likely in patients with HIV.

Referral to a GUM clinic is recommended for management §during pregnancy and for those considering suppression therapy.

Table 4 summarises the treatment options.

Human immunodeficiency virus
By the end of 2011 an estimated 96 000 people were living with HIV in the UK, approximately one-quarter of whom were undiagnosed and unaware of their infection. Transmission rates in MSM remain high but the proportion of those heterosexually infected within the UK has increased. Heterosexual acquisition now predominates among diagnosed cases worldwide.

HIV is a chronic treatable condition. The advent of highly active antiretroviral therapy (HAART) has transformed the prognosis with patients now living into old age. However, many people with early infection are clinically well and asymptomatic. All clinicians are encouraged to consider HIV infection as a differential diagnosis and to promote early testing to decrease morbidity and mortality and to prevent onward transmission.

It can take up to three months for antibodies to be detected in the blood (window period). Therefore, if the initial negative HIV test blood test was taken within the first three months of possible exposure, repeat testing is advised.

Protozoal infection
Trichomoniasis (see Figure 4)
Trichomoniasis is caused by the flagellate protozoan *T. vaginalis* (TV) and is one of the commonest STIs worldwide. The prevalence in GUM clinics is higher than in general practice, where it commonly co-exists with other STIs. It is associated with older age groups and nonwhite ethnicity. TV is associated with premature labour, low birth weight, prostatitis and HIV transmission.

There are various drugs that have been administered in the form of topical preparations but these are largely ineffective; eradication requires systemic treatment. Metronidazole is the drug of

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Table 4. Treatments available for genital herpes

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Mechanism of action</th>
<th>Efficacy</th>
<th>Principal side-effects</th>
<th>Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1st line</strong></td>
<td><strong>aciclovir</strong></td>
<td>400mg 3 x day for 5 days</td>
<td>converted by viral thymidine kinase and cellular enzymes into active form – inhibits viral DNA polymerase</td>
<td>significant reduction in duration of lesions and viral shedding</td>
<td>usually none occasional: rash, nausea, diarrhoea, renal and hepatic dysfunction</td>
</tr>
<tr>
<td><strong>1st line</strong></td>
<td><strong>valaciclovir</strong></td>
<td>500mg bd for 5 days</td>
<td>converted into aciclovir</td>
<td>as above</td>
<td>usually none occasional: headache, dizziness, nausea and diarrhoea</td>
</tr>
<tr>
<td><strong>1st line</strong></td>
<td><strong>famciclovir</strong></td>
<td>250mg 3 x day for 5 days</td>
<td>converted into penciclovir then active form – inhibits viral DNA polymerase</td>
<td>as above</td>
<td>as for valaciclovir</td>
</tr>
</tbody>
</table>

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![Figure 3. Genital herpes: oral antiviral drugs reduce the severity and duration; the three currently available are equally effective](image-url)
choice (see Table 5). A single dose has the advantage of improved compliance and being cheaper, although there is some evidence to suggest that the failure rate is higher, though not significantly, especially if the partners are not treated concurrently.

Patients should be advised to avoid sexual intercourse until they and their partner(s) have finished treatment. Partners should have a full STI screen and be treated for trichomoniasis irrespective of the results of investigations.

In the event of persistent treatment failure with metronidazole, there are other treatments available such as tinidazole (Fasigyn). Referral is advised.

**Pregnancy** A course of metronidazole for one week is recommended; the manufacturers advise that single high-dose metronidazole should be avoided in pregnancy.

### Conclusion

The involvement of primary-care clinicians in the diagnosis and management of STIs is now encouraged by the Department of Health. It should be emphasised that optimal management of any diagnosed STIs should include screening for other STIs, partner notification and follow-up test of cure where appropriate. Patients should be given a detailed explanation of their condition with particular emphasis on the long-term health implications for themselves and their partners.

Early diagnosis and treatment of STIs not only alleviates symptoms and reduces complications, but also reduces the period of infectivity and onward transmission.

### References


### Declaration of interests

None to declare.

Dr Gupta is a consultant in genitourinary medicine, Rotherham NHS Foundation Trust, and George Kinghorn is honorary professor in genitourinary medicine, Royal Hallamshire Hospital, Sheffield
1. Which one of the following statements is false?
   a. In 2010, England was among the top 10 of 43 countries in the World Health Organization’s European Region and North America for condom use among sexually active young people.
   2. Diagnoses of gonorrhoea in genitourinary medicine clinics increased by 21 per cent between 2011 and 2012.
   3. In 2012, there were approximately 450 000 diagnoses of STIs made in England.
   4. The impact of STIs is greatest in young heterosexuals under the age of 25 years and in men who have sex with men.

2. Genital infection by Chlamydia trachomatis
   b. Is often asymptomatic.
   c. Usually presents as proctitis in men who have sex with men.
   d. Should be treated with doxycycline in pregnant women.

3. In the diagnosis and treatment of gonorrhoea
   a. In the UK in 2012, there was evidence of decreasing susceptibility to ceftaxime.
   b. The sites of infection are exclusively genital.
   c. Patients should routinely be screened for C. trachomatis infection.
   d. Oral cephalaxine plus azithromycin is the preferred treatment for patients who decline parenteral therapy.

4. Considerations when treating STIs in primary care include
   a. Quinolones are not recommended for the treatment of N. gonorrhoeae infection unless the isolate is known to be sensitive.
   b. Doxycycline may be more effective than azithromycin for the treatment of rectal infection by C. trachomatis.
   c. A test of cure at two weeks post-treatment is recommended in all patients with gonorrhoea.
   d. Parenteral penicillin is the treatment of choice only for primary syphilis.

5. Which one of the following statements about viral infections is false?
   a. Most visible genital warts are due to types that are the least likely to have neoplastic potential.
   b. The UK prevalence of genital herpes is decreasing.
   c. Recurrent genital herpes can be treated by patient-initiated episodic oral antiviral therapy.
   d. It is believed that about a quarter of people with HIV in the UK are undiagnosed and unaware of their infection.

6. In the management of genital infection
   a. If an initial HIV blood test taken within the first three months of possible exposure is negative, HIV infection can be excluded.
   b. Failure of suppressive treatment of genital herpes with an oral antiviral is usually due to inadequate dosing, poor adherence and rarely malabsorption.
   c. Imiquimod cream may be associated with a lower relapse rate than other treatments for genital warts.
   d. Valaciclovir, aciclovir and famciclovir are equally effective in the treatment of genital herpes.

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**Resources**

**Guidelines**


