6: Sexually transmitted infections: new diagnostic approaches and treatments

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New technologies have made diagnosis and screening easier for patients and clinicians

Abstract

- Commercially available nucleic acid amplification assays (eg, polymerase or ligase chain reaction) are now the "gold standard" tests for genital chlamydial infection and also have a role in screening for gonococcal infection.
- Single-dose oral antibiotics are available for treatment of *Chlamydia trachomatis*, *Neisseria gonorrhoeae* and *Trichomonas vaginalis* infections.
- Strains of *N. gonorrhoeae* in urban Australia are often penicillin resistant, while strains from South East Asia and those in homosexually active men may show high-level resistance to quinolones.
- Imiquimod, a novel immune-response modifier, is now available for effective, safe, self-administered treatment of genital warts.
- The Pap smear remains the cornerstone of screening for precursor lesions of cervical cancer, but human papillomavirus genotyping may have a role in clinical decision-making for women with equivocal or early precancerous lesions.
- Treatment of primary genital herpes changes the clinical course, and long-term suppressive therapy is effective for those with multiple recurrences.

MJA 2002; 176: 551–557

SEXUALLY TRANSMITTED INFECTIONS (STIs) remain endemic in Australia and have significant individual and public health consequences.

New diagnostic tests based on nucleic acid amplification have had no greater effect on patient care than in this area. Indeed, the first polymerase chain reaction (PCR) test to be commercially marketed was for detecting genital chlamydial infection. In addition, new drugs have substantially improved treatment of several STIs (eg, azithromycin for chlamydial infection and imiquimod for genital warts). In this article, we discuss recent advances in diagnosis and treatment of important STIs in Australia.

Common presentations of STIs and the recommended investigations are summarised in Box 1. However, most STIs are asymptomatic or produce mild symptoms that do not bring affected people to medical attention. These STIs will be detected only through screening and contact tracing. Patients with a suspected or diagnosed STI should be screened for other STIs, with the tests performed dependent on the probability of specific infections in the individual. Partners of those diagnosed with an STI should be screened and treated empirically.

Chlamydial infection

Infection with *Chlamydia trachomatis* is often asymptomatic and causes cervicitis, endometritis and pelvic inflammatory disease in women, with the sequelae of tubal factor infertility and ectopic pregnancy. In men, it causes urethritis, epididymo-orchitis and prostatitis (Box 2). Infection with *C. trachomatis* is the third most common notifiable disease in Australia, with 16 770 cases reported in 2000 (Communicable Diseases System, personal communication[1]). As most infections in women are asymptomatic, notification data may under-represent the true incidence of disease in the community. There are no agreed national screening guidelines for *C. trachomatis* infection, but candidates for screening include sexually active young women attending for Pap smears, contraceptive advice, antenatal care or termination of pregnancy, if indicated by their sexual history (case history, Box 3).

Laboratory diagnosis

Nucleic acid amplification techniques have largely replaced tissue culture, non-amplification DNA probe assays and other rapid antigen assays (eg, direct immunofluorescence and enzyme immunoassay) as the "gold standard" for diagnosis of *C. trachomatis* because of their greater sensitivity.[2] Nucleic acid amplification techniques may use samples

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1: Common presentations of sexually transmitted infections and recommended investigations*

Presentation	Possible causes	Investigations*
Urethritis (dysuria, discharge, frequency)	*Common causes* *Chlamydia trachomatis* (most important cause in heterosexual contact; commonly asymptomatic) *Neisseria gonorrhoeae* (especially in homosexually active men and after heterosexual contact overseas) *Trichomonas vaginalis* (consider in remote populations and if overseas contact) *Mycoplasma genitalium*, *Mycoplasma hominis*, *Ureaplasma urealyticum* (importance as pathogens not clear: associated with urethritis but considered normal flora) Herpes simplex virus (HSV) types 1 and 2 (uncommon cause of intermittent, recurrent attacks of urethritis) *Other bacterial causes* *Neisseria meningitidis*	■ First-catch urine (does not have to be first void of the day) for PCR or LCR for *C. trachomatis* (± *N. gonorrhoeae*, depending on pre-test probability of infection) ■ Urethral swab for microscopy and culture (not routinely recommended unless pus is visible at meatus; culture is necessary for antibiotic susceptibility testing of *N. gonorrhoeae*) ■ Microscopy of wet preparation and special culture (if *T. vaginalis* suspected) ■ Urethral swab for viral culture (if HSV suspected)
Cervicitis (usually asymptomatic)	*C. trachomatis* *N. gonorrhoeae*	■ Urine, cervical or vaginal swab for PCR or LCR for *C. trachomatis* and *N. gonorrhoeae* ■ Cervical swab for microscopy and culture for *N. gonorrhoeae*
Vaginal discharge (usually not sexually transmitted)	*Candida albicans* (most common cause) Bacterial vaginosis (caused by changes in normal vaginal flora) *T. vaginalis* (sexually transmitted)	■ High vaginal swab for microscopy and culture ■ Microscopy of wet preparation and special culture (if *T. vaginalis* suspected)
Pelvic inflammatory disease (pelvic pain, menstrual irregularities, dyspareunia, may be silent)	*STI-related* *C. trachomatis* *N. gonorrhoeae* *Non-STI-related* Mixed pathogens — anaerobes, facultative bacteria and *Mycoplasma* spp.	■ Urine, cervical or vaginal swab for PCR or LCR for *C. trachomatis* and *N. gonorrhoeae* ■ Cervical swab for microscopy and culture for *N. gonorrhoeae* ■ Pelvic ultrasound examination ■ Possible laparoscopy in severe cases
Genital warts (typical warty lesions in anogenital area)	Human papillomavirus (most commonly types 6 and 11; occasionally other types)	■ Clinical diagnosis ■ Biopsy if atypical lesions or doubt about diagnosis
Anogenital ulceration	*Infective causes* HSV-1 and HSV-2 (most common cause outside remote Australia) Syphilis (*Treponema pallidum*) Donovanosis (*Klebsiella granulomatis*) Chancroid (*Haemophilus ducreyi*) (not endemic in Australia) Lymphogranuloma venereum (rare) *Non-infective causes* Aphthous ulceration Behçet's disease Trauma Drug reaction	■ Viral culture (± PCR for HSV-1 and HSV-2) ■ Routine microscopy and culture of swab specimen (*H. ducreyi* is difficult to culture on routine media) ■ Serological tests for syphilis ■ Giemsa staining of smear or biopsy (PCR available in some centres) (if donovanosis suspected) ■ Dark ground microscopy (available only in some centres) (if syphilis suspected) ■ Biopsy for histopathological examination and special staining (if non-infective cause suspected)

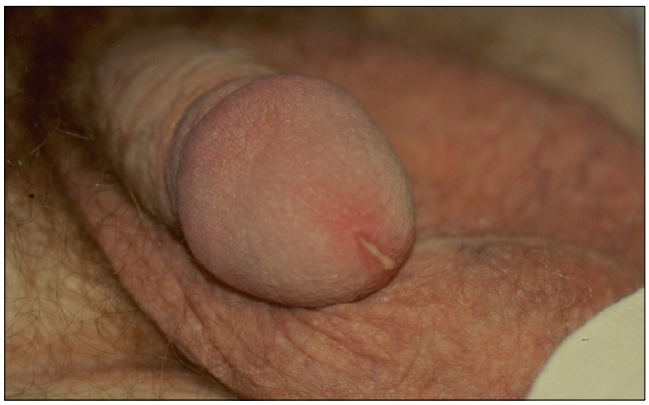
PCR = polymerase chain reaction. LCR = ligase chain reaction. STI = sexually transmitted infection.
*Routine screening for other STIs (including HIV) should also be offered to patients with any of these presentations.

collected from the cervix and vagina, but are also easily adapted to self-sampling with self-inserted swabs, tampons or first-void urine.[3,4] Most laboratories use PCR, ligase chain reaction or strand displacement amplification. These techniques can be performed in less than 24 hours, but most tests are "batched" and performed several times a week.

Management

A major advance in treatment of *C. trachomatis* infection has been the introduction of azithromycin (Box 4); clinical trials have found that a single oral dose of this drug has equivalent efficacy to a seven-day course of twice-daily oral doxycycline when compliance is high.[5] Both drugs achieve cure rates greater than 95%. If compliance is likely to be suboptimal, then azithromycin is more cost effective.[6] Azithromycin is also effective for treatment of non-specific urethritis (ie, cases with negative results for chlamydia and gonococcus).[7] Its risk in pregnancy is categorised as B1, and it can be used safely during pregnancy and breastfeeding.[8] A seven-day course of erythromycin, roxithromycin or amoxycillin has been recommended for use in pregnancy, but, as these agents are less effective, careful follow-up and retesting after three weeks is highly recommended.[9]

2: Chlamydial urethritis



Urethritis in a heterosexual man who presented with dysuria and yellowish discharge. A swab of the discharge showed no growth on culture, but was positive by polymerase chain reaction for Chlamydia trachomatis.

Complicated chlamydial infections, such as epididymitis or pelvic inflammatory disease (PID), require longer therapy, but treatment recommendations vary greatly. For PID in general, broad-spectrum antimicrobials have been advised (Box 4), as the infection usually involves mixed endogenous vaginal flora, particularly if it occurs postpartum or after gynaecological instrumentation, miscarriage, termination of pregnancy, or insertion of an intrauterine contraceptive device. If PID is sexually acquired, an antibiotic to cover *Neiserria gonorrhoeae* is also required. As the definitive diagnosis of PID requires laparoscopy, and as the severity and number of episodes of untreated disease contribute to the risk of subsequent complications (chronic pelvic pain, infertility and ectopic pregnancy),[10] therapy must be based on clinical features.

Gonorrhoea

Gonorrhoea has similar symptoms, signs and sequelae to chlamydial infection, although symptomatic disease may be more common, especially in men. Rates of gonorrhoea in Australia are currently at their highest for nearly 20 years and double those of 10 years ago.[11] Three groups are primarily affected: men who have sex with men (the group with the greatest increase), Indigenous Australians in remote settings, and people who have heterosexual contact overseas. Other heterosexual cases are uncommon.[11]

Laboratory diagnosis

Culture of *Neisseria gonorrhoeae* from a urethral or endocervical swab remains the standard diagnostic method, as information on antibiotic susceptibility is essential. However nucleic acid amplification of urine, cervical and vaginal specimens has an important role in diagnosis of this fastidious organism, especially where prevalence is high and where there may be delay between specimen collection and processing. A PCR assay for both *C. trachomatis* and *N. gonorrhoeae* is available in a single tube. Because specificity is lower for *N. gonorrhoeae* than for *C. trachomatis*,[12] it is recommended that all positive results for *N. gonorrhoeae* should be confirmed by amplification of an alternative target (such as the 16S rRNA gene) or preferably by culture. A ligase chain reaction test for *N. gonorrheae* is also available. Testing for both organisms is currently available through the Medicare schedule.

3: Case history — opportunistic screening for sexually transmitted infections

Presentation: A 17-year-old female student from an inner-city high school presented to her general practitioner requesting a first prescription for the oral contraceptive pill.

History: The GP took a thorough sexual history. The patient began sexual activity 6 months previously, had had five sexual partners and never used condoms. She had no genital symptoms.

Management: The GP explained to the patient that she was at risk of having acquired a sexually transmitted infection and suggested that, as she was reluctant to undergo a speculum examination, she obtain a self-inserted swab specimen for a polymerase chain reaction (PCR) test for *Chlamydia trachomatis*.

A week later, the patient returned for the result of the PCR test, which was positive for *C. trachomatis*. She was treated with a single oral dose of azithromycin (1 g). The GP discussed with her the need to contact her sexual partners, gave her a "form" letter for them and explained that, as chlamydia is a notifiable disease, the laboratory would report a positive result to the local public health unit. The GP also discussed the need for a Pap smear in the next 12 to 18 months, counselled the patient about safer sex practices and arranged a follow-up visit in two weeks.

At follow-up, the girl reported that she had contacted one partner but was too embarrassed to talk to the others. The GP obtained her permission to contact the other partners and their phone numbers.

- *The GP adopted an approach to screening for sexually transmitted infections (STIs) that was appropriate to the age, sexual behaviour and urban residence of the patient. (The approach to symptomatic patients differs and is outlined in Box 1.)*
- C. trachomatis *infection is the most common curable STI affecting young heterosexual people in Australia and has important reproductive sequelae.*
- Neisseria gonorrhoeae *could have been included in the PCR test, but the positive predictive value (proportion of positive tests that truly represent the presence of infection) would have been low because of the low pre-test probability of disease in this young, heterosexual, urban woman.*
- *Similarly, we believe that screening for other STIs need not be routinely offered at the initial consultation with a patient such as this. However, once an STI is diagnosed, HIV testing should be offered. Many clinicians would also test for syphilis and offer hepatitis B vaccination at the first visit.*
- *Pap smears are not recommended for women aged under 18 years unless they have been sexually active for two years or more.*
- *If the GP was unable to contact the girl's sexual contacts, the case should have been referred to the relevant public health authority or sexual health centre.*

Management

Treatment is summarised in Box 4. Infections acquired in remote Australia are almost universally penicillin-sensitive (although the minimum inhibitory concentration for new isolates has been slowly rising over time), and oral amoxycillin with probenecid can be used. Infections acquired in other parts of Australia are often penicillin-resistant,[13] and intramuscular ceftriaxone or the oral quinolone ciprofloxacin should be used. However, there has been a recent increase in the incidence of quinolone resistance in isolates obtained from homosexually active men in New South Wales,[13] and from heterosexual people infected in South East Asia. Where local data indicate that quinolone resistance is rare, ciprofloxacin can be used for empirical therapy; otherwise, intramuscular ceftriaxone should be used in the first instance. When treating gonococcal infection, antibiotic therapy should also cover possible chlamydial co-infection.

Penicillin alone is not sufficient for pharyngeal and anorectal infections, even with penicillin-sensitive strains. Therefore, in homosexually active men, ceftriaxone or ciprofloxacin is required. Urethral and anorectal infection will be cured in over 98% of cases, whereas for pharyngeal infection the cure rate is lower (about 90%).[9]

Trichomonas vaginalis infection

Infection with the protozoan *Trichomonas vaginalis* is the most common treatable STI in the world. Prevalence has fallen progressively in the developed world over the past 20 years, but in women living in remote areas of Australia may be as high as 25%.[14]

Laboratory diagnosis

T. vaginalis may be diagnosed by Pap smear (which has poor sensitivity and specificity), culture or microscopy of a wet preparation. Enzyme immunoassay (EIA) and immunofluorescence tests are available but not widely used. In-house nucleic acid amplification methods are used by some Australian laboratories and have high sensitivity and specificity[15] compared with the "gold standard" of culture. They have been used to detect the organism in urine, self-inserted swabs and self-collected tampon samples and are suitable where access to medical personnel is limited.

Management

Trichomonal infection is treated with a single dose of metronidazole or tinidazole (Box 4). Most studies of treatment efficacy have been conducted in women, and there is a surprising lack of evidence regarding their efficacy in men.

Trichomonal infection in pregnancy is associated with premature rupture of membranes and premature labour. However, a recent study showed that treatment of asymptomatic infection during pregnancy is also associated with an increased rate of premature labour.[16] This highlights the need to prevent and treat infections in women of childbearing age before pregnancy.

4: Treatment of sexually transmitted infections (1)*

Chlamydial and other non-gonococcal urethritis and cervicitis

Azithromycin (1 g orally, as a single dose) *or* doxycycline (100 mg orally, 12-hourly for 7 days).

Gonorrhoea

Ceftriaxone (250 mg intramuscularly) *or* ciprofloxacin (500 mg orally, as a single dose)

plus either azithromycin (1 g orally, as a single dose) *or* doxycycline (100 mg orally, 12-hourly for 7 days).

Where prevalence of penicillin-resistant N. gonorrhoeae *is low (eg, remote areas of Australia) use*

Amoxycillin (3 g) *plus* probenecid (1 g) *plus* azithromycin (1 g orally, as a single dose).

Pelvic inflammatory disease (sexually acquired)

Mild to moderate infection

Doxycycline (100 mg orally, 12-hourly for 14 days)

plus either metronidazole (400 mg orally, 12-hourly) *or* tinidazole (500 mg orally, daily for 14 days)

plus either ceftriaxone (250 mg intramuscularly) *or* ciprofloxacin (500 mg orally, as a single dose).

If adherence to a 2-week course of doxycycline is likely to be suboptimal, doxycycline may be replaced by azithromycin (1 g orally on Days 1 and 8), although no clinical trial has assessed this.

Severe infection

Metronidazole (500 mg intravenously, 12-hourly)

plus doxycycline (100 mg orally, 12-hourly)

plus either cefotaxime (1 g intravenously, 8-hourly) *or* ceftriaxone (1 g intravenously, daily).

Continue until there is substantial clinical improvement, and then use oral therapy (as for mild to moderate infection) to complete 2 weeks of total treatment.

Pelvic inflammatory disease (non-sexually acquired)

Mild to moderate infection

Amoxycillin clavulanate (875/125 mg orally, 12-hourly for 7–10 days)

plus doxycycline (100 mg orally, 12-hourly for 7–10 days).

Azithromycin is being investigated as an alternative.

If the patient is pregnant or breastfeeding

Substitute roxithromycin (300 mg orally, daily for 14 days) for doxycycline.

Trichomoniasis

Tinidazole *or* metronidazole (2 g orally, as a single dose).

Candidiasis

Clotrimazole (2% vaginal cream for 3 nights or 500 mg pessary as a single dose).

* Adapted from *Therapeutic guidelines: antibiotic.*[8]

Human papillomavirus infection

Infection with one of the 30 human papillomavirus (HPV) types that infect the genital epithelium is very common, although the vast majority of these infections are asymptomatic.[17] A study of women attending a United States university found that the proportion with HPV detected by PCR was 30% in the first year after initiation of sexual intercourse and 80% after 56 months.[18] The most common virus type was HPV 16, followed by 6 and 11.

5: Treatment of sexually transmitted infections (2)*

Genital warts

Clinic-based therapy
Cryotherapy, cautery/laser ablation, podophyllin solution (25%) *or* trichloroacetic acid.

Self-administered therapy
Podophyllotoxin paint (0.5%) (applied twice daily) for 3 consecutive days per week until warts resolve
or imiquimod cream (5%) applied on alternate days for up to 3 months.

Herpes simplex types 1 and 2

Initial infection
Famciclovir (125 mg) *or* valaciclovir (500 mg) (both orally, 12-hourly) for 5–10 days or until symptoms resolve
or aciclovir (200 mg orally, 5 times daily, or 400 mg 8-hourly) for 5 days or until symptoms resolve.

Episodic therapy
Famciclovir (125 mg) *or* valaciclovir (500 mg) (both orally, 12-hourly) for 5–10 days or until symptoms resolve
or aciclovir (400 mg orally, 3 times daily) for 5 days or until symptoms resolve.

Suppressive therapy
Famciclovir (250 mg orally, 12-hourly) *or* valaciclovir (500 mg orally daily [if < 10 recurrences per year] or 1 g daily [if ⩾ 10 recurrences per year])
or aciclovir (200 mg orally 8-hourly or 400 mg orally 12-hourly) for up to 6 months.

Syphilis

Primary, secondary or latent disease (up to two years' duration)
Procaine penicillin (1.0 g intramuscularly, daily for 10 days)
or benzathine penicillin (1.8 g intramuscularly, as a single dose).

Late latent syphilis (asymptomatic disease over two years' duration)
Procaine penicillin (1.0 g intramuscularly, daily for 15 days)
or benzathine penicillin (1.8 g intramuscularly, once-weekly for three doses).

Pregnant patients should be treated with penicillin in the dosage schedule recommended for non-pregnant patients at a similar stage of disease.

Donovanosis

Azithromycin (1 g orally once-weekly for 4 weeks *or* 500 mg orally once-daily for 7 days).

*Adapted from *Therapeutic guidelines: antibiotic*.[8]

The most usual manifestation of HPV infection, when one occurs, is genital warts. Indeed, genital warts are the most common symptomatic STI. They are usually caused by HPV types 6 and 11 and develop in about half the women infected with these types.

Infection with "oncogenic" strains of HPV has been identified as one of the main risk factors for developing cervical and other anogenital cancers.[19] HPV types 16 and 18 account for about 80% of the "high-risk" types, with the remainder being 31, 33, 35, 45, 51, 52, 58 and 59.[19]

Laboratory diagnosis and management

Diagnosis of external genital warts is almost always clinical. They can be treated by several practitioner-applied therapies (Box 5), which produce similar initial responses (50% to 70%), but relapse may be less common with the more expensive imiquimod (Box 6).[18] This new immune-response modifier has a good safety profile and high efficacy and can also be self-administered. Only cryotherapy is definitely safe in pregnancy. Condoms reduce but do not eliminate the risk of HPV transmission.

A single HPV typing assay is commercially available in Australia and can detect the most common HPV types and classify them as high- or low-risk. This test is currently used in some specialist centres to assist management of pre-cancerous lesions. Acceptable samples include cervical samples taken with the Digene cervical sampler and the Thin Prep or Autocyte thin-layer Pap preparations. However, the role of HPV detection in general practice has not been clearly defined, and the Pap smear remains the cornerstone of screening for cervical precancerous lesions.

Vaccines for HPV are in development, but their role in clinical practice is yet to be determined.

Herpes simplex

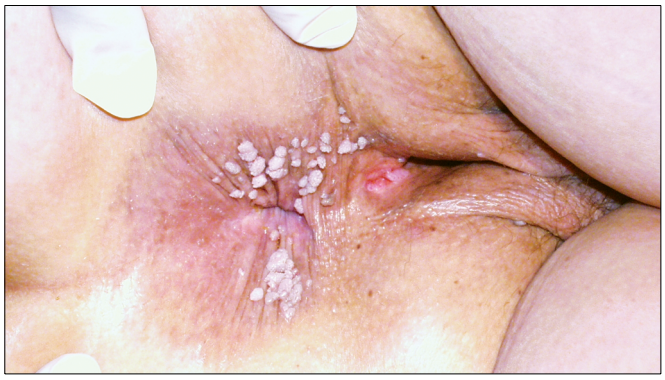
Genital herpes may be caused by herpes simplex viruses 1 or 2 (HSV-1 or HSV-2) and may be recurrent in up to 20% of those infected. Serological surveys in Australia indicate that about 15% of women attending antenatal clinics and up to 55% of those attending STI clinics have been infected with HSV-2.[20] Genital herpes caused by HSV-1 is often transmitted by oral sex, but tends to be milder than that caused by HSV-2 and recurs uncommonly. Some people with evidence of past HSV-2 infection recall no symptoms.[20] HSV transmission may uncommonly occur in the absence of genital lesions (risk, about 10% per year). The risk of acquiring genital HSV-2 from a regular partner is greater for women with no previous HSV-1 infection (20% per year) and least for men with previous HSV-1 exposure (5% per year).[20]

Laboratory diagnosis

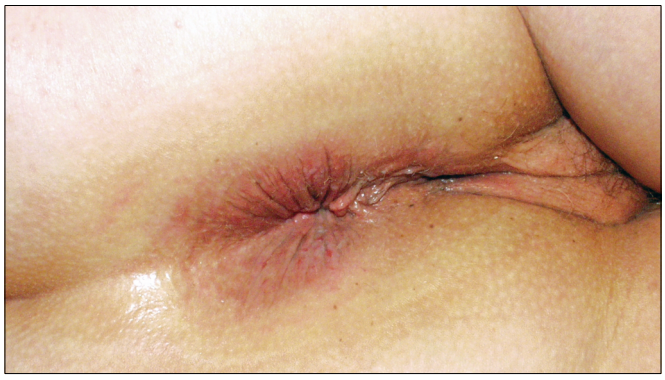
Viral culture and direct immunofluorescence are the definitive tests for HSV diagnosis, but sensitivity depends on proper specimen collection (fluid and cells from a "fresh" vesicle is best), transport conditions and local laboratory expertise. Confirmation of the diagnosis often requires the patient to return in the first one or two days of a recurrence. HSV PCR assays that are highly sensitive and specific are available but not widely used as yet.

The value of HSV antibody testing in clinical practice is not clearly defined and these tests have, until recently, lacked specificity. The western blot is the recognised gold standard, but is technically demanding, expensive, and not readily available in routine diagnostic laboratories. The sensitivity and specificity of EIA has been improved by use of recombinant viral peptides from HSV-1 and HSV-2, but false positives and false negatives remain a problem with these newer tests, which still do not perform as well as western blots.[21] Routine antibody testing is not usually recommended in clinical practice, but when a patient has

6: Genital warts



Extensive perianal warts in a 50-year-old woman who had recently begun a new sexual relationship.



The patient six weeks after beginning a course of topical imiquimod cream (5%), a new immune-response modifier.

clinical HSV-2 infection it is useful to know if his or her partner is already infected with HSV-2, as precautions against transmission are then unnecessary.

Management

Aciclovir, valaciclovir and famciclovir are all effective for the treatment of primary and recurrent episodes and for suppression[20] (Box 5). The least expensive option is aciclovir (now available in a generic formulation). Primary episodes should be treated regardless of duration of symptoms. On the other hand, symptoms of a recurrence are ameliorated and duration shortened by one to two days if treatment begins within 72 hours of symptom onset. Suppressive therapy prevents at least 75% of attacks and substantially reduces asymptomatic shedding. If recurrent attacks are mild and infrequent then long term suppressive therapy may not be warranted.

Syphilis

Presentations of syphilis include genital ulceration (primary disease) and disseminated rash and glandular fever-like illness (secondary disease), but clinically evident syphilis is very uncommon in Australia. Most detected disease is latent infection. Tertiary syphilis (which includes cardiovascular syphilis and neurosyphilis) is exceptionally rare.

Laboratory diagnosis

The diagnostic approach to syphilis has changed considerably in the past five years. Traditional screening strategies use an initial non-treponemal test (eg, rapid plasma reagin [RPR] or Venereal Disease Research Laboratory [VDRL]), and follow-up positive results with a specific treponemal test (eg, *Treponema pallidum* particle agglutination or haemagglutination assay, or fluorescent treponemal antibody absorption). However, many laboratories now screen with an automated EIA, which detects treponemal IgG and is therefore equivalent to the specific treponemal tests. EIAs appear to be as sensitive and specific as the traditional tests.[22]

Unless treatment is instituted in the very early stages of infection, the EIA usually remains positive for life (as does the *T. pallidum* haemagglutination assay), unlike the non-treponemal tests, which show falling levels (or may become non-reactive) after treatment or spontaneously over time. This means that a small group of people who have been successfully treated for syphilis in the past and have previously had negative RPR results will now test positive on the new screening assays. Conversely, people with untreated syphilis whose RPR has fallen spontaneously to unreactive will now be routinely detected (this group includes up to 25% of patients with neurosyphilis). The cost benefit of the EIA will be less in populations with a high background prevalence of prior syphilis,[23] as a significant proportion of people will have a positive EIA result and require further assessment, including an RPR.

In-house PCR tests for syphilis are available in a number of laboratories, but their role in routine diagnosis has not been validated against standard assays. A commercial multiplex PCR test for genital ulcer disease (which tests for *T. pallidum*, *H. ducreyi* and HSV) has shown promise in field testing but is yet to be released.[24]

Management

Penicillin remains the treatment of choice for all stages of syphilis (Box 5). Despite over 50 years of exposure of *T. pallidum* to this antibiotic, antibiotic resistance does not seem to be a clinical problem.

Patients with penicillin allergy should be desensitised if this can be performed quickly and safely. Ceftriaxone has been used in penicillin-allergic patients, but must be avoided if there is a history of immediate hypersensitivity to penicillin. Although not currently recommended, oral azithromycin has been shown to be effective, and may become more important for syphilis treatment in time.[25]

Donovanosis

Donovanosis is a genito-ulcerative disease caused by a gram-negative organism, *Klebsiella granulomatis* (formerly *Calymmatobacterium granulomatis*). It is principally confined to indigenous populations in the tropics,[26] and is becoming increasingly rare in Australia since the introduction of azithromycin. The standard diagnostic technique is the identification of Donovan bodies in histological or cytological specimens from lesions. A PCR test has also been developed which is sensitive and specific but is not commercially available.[27]

Management

Two Australian studies have demonstrated the utility of azithromycin.[28,29] The agent is highly effective and can be used in pregnancy and in children. Primary cure rates are high, and relapse appears rare.

Conclusions

With the increasing availability of new diagnostic technologies, we are on the verge of a major change in the approach to STI control in Australia. An effective control strategy is based on an accessible and well-trained healthcare workforce, suitable infrastructure, partner notification, disease surveillance, health promotion and outbreak investigation. Primary care physicians will continue to play a central role to ensure the success of such an important program.

Evidence-based recommendations

- For treatment of uncomplicated genital chlamydial infection, azithromycin (1 g orally as a single dose) has been shown to be as effective as doxycycline (100 mg orally 12-hourly for 7 days)[5] (E2).
- Azithromycin (1 g orally once weekly for 4 weeks or 500 mg orally once daily for 7 days) is highly effective treatment for donovanosis and minimises compliance problems[28] (E2).
- Treatment of asymptomatic trichomoniasis with metronidazole in pregnancy is associated with an increased risk of premature labour.[30] Therefore, preventing trichomoniasis in women of childbearing age remains a priority (E2).
- Minimally invasive testing is acceptable for diagnosis of sexually transmitted infections in women living in remote and rural areas[4] (E2).

References

1. Communicable Diseases Network Australia — National Notifiable Diseases Surveillance System. Notifications of Chlamydial (NEC) received by State and Territory health authorities in the period of 1991 to 2001 and year-to-date notifications for 2002 by year — month. Available at <http://www.health.gov.au/pubhlth/cdi/nndss/year007.htm> Accessed Apr 2002.
2. Schacter J. Biology of *Chlamydia trachomatis*. In: Holmes KK, Sparling PF, Mardh P-A, et al, eds. Sexually transmitted diseases. 3rd ed. New York: McGraw-Hill, 1999..
3. Ostergaard L, Andersen B, Moller JK, Olesen F. Home sampling versus conventional swab sampling for screening of *Chlamydia trachomatis* in women: a cluster-randomized 1-year follow-up study. *Clin Infect Dis* 2000; 31: 951-957.
4. Tabrizi SN, Chen S, Borg AJ, et al. Patient-administered tampon-collected genital cells in the assessment of *Chlamydia trachomatis* infection using polymerase chain reaction. *Sex Transm Dis* 1996; 23: 494-497.
5. Martin DH, Mroczkowski TF, Dalu ZA, et al. A controlled trial of a single dose of azithromycin for the treatment of chlamydial urethritis and cervicitis. The Azithromycin for Chlamydial Infections Study Group. *N Engl J Med* 1992; 327: 921-925.
6. Stamm W, editor. *Chlamydia trachomatis* infections of the adult. 3rd ed. Washington: McGraw-Hill, 1999.
7. National guideline for the management of non-gonococcal urethritis. Clinical Effectiveness Group (Association of Genitourinary Medicine and the Medical Society for the Study of Venereal Diseases). *Sex Transm Infect* 1999; 75 Suppl 1: S9-S12.
8. Therapeutic Guidelines Ltd. Therapeutic guidelines: antibiotic. Version 11, 2000. Melbourne: Melbourne: Therapeutic Guidelines Ltd, 2000.
9. 1998 guidelines for treatment of sexually transmitted diseases. *MMWR Morb Mortal Wkly Rep* 1998; 47 (No. RR-1): 1-118.
10. Kani J, Adler M. Epidemiology of pelvic inflammatory disease. In: Berger GS, Westrom L, editors. Pelvic inflammatory disease. New York: Raven Press, 1992: 7.
11. Annual surveillance report: HIV/AIDS, hepatitis C and sexually transmissible infections in Australia. Darlinghurst: National Centre in HIV Epidemiology and Clinical Research, 2000.
12. Farrell DJ. Evaluation of AMPLICOR *Neisseria gonorrhoeae* PCR using cppB nested PCR and 16S rRNA PCR. *J Clin Microbiol* 1999; 37: 386-390.
13. Tapsall J. Annual report of the Australian Gonococcal Surveillance Programme, 1999. *Commun Dis Intell* 2000; 24: 113-117.
14. Bowden FJ, Paterson BA, Mein J, et al. Estimating the prevalence of *Trichomonas vaginalis*, *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, and human papillomavirus infection in indigenous women in northern Australia. *Sex Transm Infect* 1999; 75: 431-434.
15. Patel SR, Wiese W, Patel SC, et al. Systematic review of diagnostic tests for vaginal trichomoniasis. *Infect Dis Obstet Gynecol* 2000; 8: 248-257.
16. Klebanoff MA, Carey JC, Hauth JC, et al. Failure of metronidazole to prevent preterm delivery among pregnant women with asymptomatic *Trichomonas vaginalis* infection. *N Engl J Med* 2001; 345: 487-493.
17. Koutsky LA, Kiviat NB. Genital human papillomavirus. In: Holmes KK, Sparling PF, Mardh P-A, et al, editors. Sexually transmitted diseases. 3rd ed. New York: McGraw-Hill, 1999: 347-359.
18. Koutsky LA. HPV epidemiology — Gollow Lecture. Abstracts of the Australasian Sexual Health Conference – 2001…a sex odyssey; 2-5 May 2001; Sydney, NSW.
19. Munoz N. Human papillomavirus and cancer: the epidemiological evidence. *J Clin Virol* 2000; 19: 1-5.
20. Corey L, Wald A. Genital herpes. In: Holmes KK, Sparling PF, Mardh P-A, et al, editors. Sexually transmitted diseases. 3rd ed. New York: McGraw-Hill, 1999: 285-312.
21. Ashley RL, Eagleton M, Pfeiffer N. Ability of a rapid serology test to detect seroconversion to herpes simplex virus type 2 glycoprotein G soon after infection. *J Clin Microbiol* 1999; 37: 1632-1633.
22. Egglestone SI, Turner AJ. Serological diagnosis of syphilis. PHLS Syphilis Serology Working Group. *Commun Dis Public Health* 2000; 3: 158-162.
23. Bowden FJ, Bastian I, Johnston F. A community-based approach to the control of sexually transmitted disease in the Northern Territory. *Aust N Z J Public Health* 1997; 21: 519-523.
24. Beyrer C, Jitwatcharanan K, Natpratan C, et al. Molecular methods for the diagnosis of genital ulcer disease in a sexually transmitted disease clinic population in northern Thailand: predominance of herpes simplex virus infection. *J Infect Dis* 1998; 178: 243-246.
25. Gruber F, Kastelan M, Cabrijan L, et al. Treatment of early syphilis with azithromycin. *J Chemother* 2000; 12: 240-243.
26. Richens J. The diagnosis and treatment of donovanosis (granuloma inguinale). *Genitourin Med* 1991; 67: 441-452.
27. Carter J, Bowden FJ, Sriprakash KS, et al. Diagnostic polymerase chain reaction for donovanosis. *Clin Infect Dis* 1999; 28: 1168-1169.
28. Bowden FJ, Mein J, Plunkett C, Bastian I. Pilot study of azithromycin in the treatment of genital donovanosis. *Genitourin Med* 1996; 72: 17-19.
29. Skov SJ, Tait P, Kaldor J, Bowden FJ. A field trial of azithromycin in the treatment of donovanosis. A step towards eradication? *Venereology* 1997; 11: 11-14.
30. Carey JC, Klebanoff MA, Hauth JC, et al. Metronidazole to prevent preterm delivery in pregnant women with asymptomatic bacterial vaginosis. National Institute of Child Health and Human Development Network of Maternal-Fetal Medicine Units. *N Engl J Med* 2000; 342: 534-540. ❑