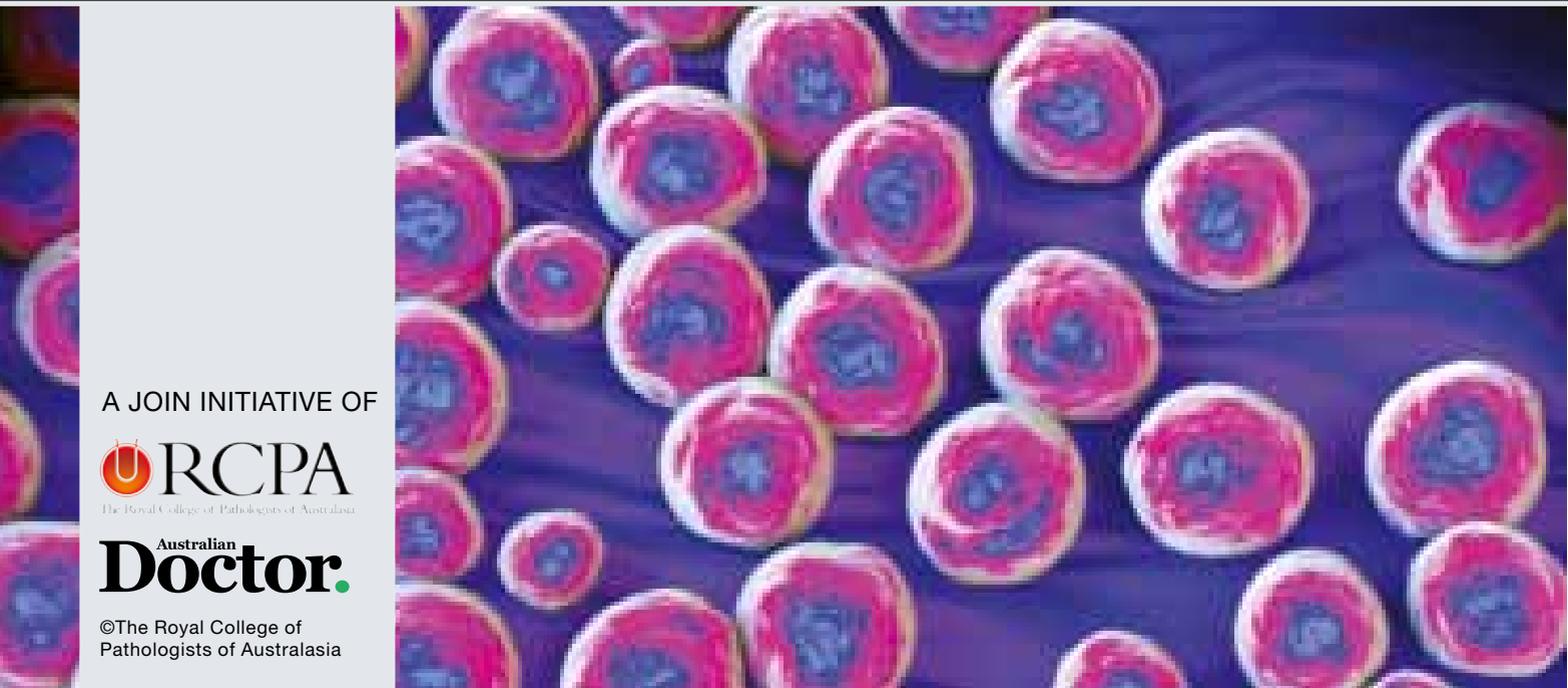


COMMON SENSE PATHOLOGY

A REGULAR CASE-BASED SERIES ON PRACTICAL PATHOLOGY FOR GPs

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Sexually Transmitted Infections



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Glossary

ELISA	enzyme linked immunosorbent assay
FPU	first pass urine
HSV1	herpes simplex virus 1
HSV2	herpes simplex virus 2
Imi	intramuscular injection
MIC	minimum inhibitory concentration
NAAT	nucleic acid amplification test
RPR	rapid plasma reagin test
TPPA	treponema pallidum particle agglutination assay
VDRL	Venereal Disease Research Laboratory test

Sexually transmitted infections are seen in all areas of medical practice, so a working knowledge of the common STIs and the appropriate diagnostic tests is important.

A syndromic approach to diagnosis of STIs is recommended. The WHO lists five main STI syndromes:

- Urethral discharge in men
- Testicular pain in men
- Vaginal discharge in women
- Low abdominal pain in women
- Genital ulcer

Other syndromes that should also be borne in mind include:

- Anorectal syndromes (“lumps”, “bumps”, ulcers and sores, pain)
- Skin rash (generalised eg, syphilis)
- Arthritis and tenosynovitis with or without rash (disseminated gonococcal infection)
- Reiters syndrome (post-chlamydia infection)

A user-friendly reference for healthcare practitioners can be found at www.sti.guidelines.org.au (Australian STI Management Guidelines). The same website

should be consulted for information about: screening of asymptomatic individuals for STIs; information on rarer STIs; more detailed information on treatment and management of patients and the public health aspects of STIs. It also has clear guidelines concerning specimen collection, which can be done by the healthcare professional or the patient. Specimen collection in asymptomatic patients can be done by the patient, if so desired, in most cases with appropriate information and guidance, but the healthcare professional should always collect the specimens in patients with symptoms and/or signs. In pathology, the quality of the specimen is paramount. Incorrect sampling is more likely to yield an unreliable result.

CASE 1

Michael is a 25-year-old man who presents with profuse yellow urethral discharge and dysuria of two days' duration. Sexual history reveals he is single, his partners are female, he had unprotected mutual oral sex, and engaged in protected penetrative vaginal sex with a female he met in a bar in Bali one week previously.

Examination reveals an otherwise well man with obvious urethral discharge, normal pharynx and no ano-genital lesions. Urethral swab is collected and testing is requested for chlamydia and gonococcus. This is accompanied by a throat swab, even though the throat looks normal on examination and the patient has no throat symptoms.

The most common cause of urethritis in males in Australia is chlamydia, so chlamydia treatment should be administered while awaiting results. Other causes include gonorrhoea, *Mycoplasma genitalium*, trichomonas and ureaplasma species, herpes simplex virus and adenovirus. When tests for chlamydia and gonorrhoea are negative and urethritis is persistent, it is good policy to obtain specialist advice. Some large centres offer PCR testing for *M. genitalium*, which may

be appropriate, as could HSV PCR in some situations. Confirmation of gonorrhoea in males with urethritis is usually simple, even in resource-poor healthcare settings. A Gram stain on urethral discharge or a urethral swab has high sensitivity and specificity. For females, Gram stain on an endocervical swab has lower sensitivity and specificity because of the presence of normal flora and from sampling error. Culture and especially PCR of the aforementioned swabs enables a better detection rate, especially in females, and for swabs collected from other sites such as throat and rectum.

The most common specimen used to diagnose gonorrhoea in both males and females is a first-pass urine specimen that is tested for both chlamydia and gonococcus by nucleic acid amplification tests (NAATs, such as PCR). The FPU is collected into the standard sterile urine pot to fill about one-third of the container. It is not necessary to collect the first (morning) urine specimen. Note that a mid-stream urine is not the appropriate specimen. The patient can collect the first part of the urine stream while being seen in the clinic or office.

A urethral swab is collected if the patient has obvious discharge. The swab does not have to be inserted into the urethra. The discharge can be expressed from the urethra onto the swab. If there is urethral discharge, then the swab result is accurate, irrespective of the last voided urine result. While the FPU is simple to collect and PCR tests have high sensitivity and specificity, it is important that specimens are still collected for gonococcal culture, wherever possible. For other specimens/sites follow the below instructions:

- Rectal swabs: insert swab into the anal canal to a depth of 2-4cm and then move the swab gently from side to side for 10-20 seconds.
- Pharyngeal swabs: swab the tonsils and oropharynx.
- High vaginal swab (HVS): insert swab into the vagina in the same manner as inserting a tampon; make a smear from the swab onto a glass slide (if able) before replacing swab into the provided transport medium. An endocervical swab collected

under direct vision is preferred, but because the NAATs are so sensitive now, the HVS may be adequate.

Michael's results were: PCR on the FPU was positive for *Neisseria gonorrhoeae* and the urethral swab yielded *N. gonorrhoeae* on culture. Throat swab was negative for *N. gonorrhoeae* PCR. The isolate was susceptible to ceftriaxone, but resistant to all other agents tested. Chlamydia PCR was negative. Serology was negative for syphilis (ELISA) and HIV. He had immunity to hepatitis B from previous vaccination.

Ceftriaxone, as a single intramuscular injection, has been very effective in treating gonorrhoea at all mucosal sites (urethra, rectum, cervix and throat). In recent years, in Australia, as well as globally, strains with gradually increasing minimum inhibitory concentration (MIC) to ceftriaxone have appeared and have led to ceftriaxone treatment failures especially in patients with pharyngeal gonorrhoea. Globally, multidrug-resistant clone has now emerged with high-level resistance to ceftriaxone prompting Australian, European and UK guidelines to recently increase the recommended dose of ceftriaxone from 250mg imi to 500mg imi, to possibly help prevent emergence of resistant strains. The cut-off (or breakpoint) MIC for *N. gonorrhoeae* for ceftriaxone by one method (E-test) is 0.125mg/L, with strains having an MIC of >0.125mg/L being classed as resistant. Previously, most strains had MIC levels <0.002mg/L, making them exquisitely susceptible to ceftriaxone. Strains with true high-level resistance to ceftriaxone, with their MICs to ceftriaxone being >1mg/L (and as high as 4mg/L) have been detected following ceftriaxone treatment failures in Japan, France and Spain, where alternative treatment was required and was successful (eg, with gentamicin in the French case); our treatment options are now so limited that these highly resistant strains of *N. gonorrhoeae* have been labelled as "superbugs".

For the moment, however, ceftriaxone is still the treatment of choice for gonorrhoea. It is important to give 500mg imi, and add azithromycin 1gm oral stat (this may be synergistic with the ceftriaxone). European guidelines recommend a 2g azithromycin

dose. However, gastrointestinal side effects are more likely with azithromycin 2g. This higher dose given with ceftriaxone may delay or minimise the emergence of resistant strains, although there is no current data that supports this notion. Surveillance, therefore, is very important, to restrict the spread of more resistant *N. gonorrhoeae* strains. Accordingly, doctors diagnosing gonorrhoea based on a NAAT should take a swab for culture because NAATs cannot currently be used for antibiotic susceptibility testing. It is also very important to have recent sexual partners tested and presumptively treated.

Because in Sydney most gonorrhoea occurs among men who have sex with men (MSM), it is important to take swabs from all mucosal sites at risk of infection. For MSM, this usually means additional rectal and throat swabs. While infection with gonorrhoea in the urethra nearly always causes a urethral discharge, infections of the throat and rectum are usually asymptomatic, so regular screening is the only way to detect infections. Test according to the specific guidelines on testing MSM (see <http://bit.ly/1CQcCh0>), also see discussion in Case 2 below. For convenience or for those easily embarrassed, men (and women) can take their own ano-rectal swab.

Key messages

- Always test for both gonorrhoea and chlamydia if one condition is suspected
- Always attempt to collect a specimen for gonococcal culture if a NAAT is positive
- Also test for syphilis, HIV and hepatitis B, as gonorrhoea is a marker of high-risk sexual behaviour.
 - Vaccinate for hepatitis B if non-immune
 - Test for hepatitis C if there is a history of injecting drug use, either recently or in the past.
- Do a test of cure for gonorrhoea two weeks after treatment, either by taking a swab or urine for a NAAT test
- When doing an STI screen in MSM:
 - Take a throat swab and a rectal swab to test for gonorrhoea and chlamydia, and FPU to test for

- gonorrhoea and chlamydia
- Test all sites, even if the patient reports that condoms are always used
- Test for HIV
- Test once for antibodies to hepatitis A and hepatitis B
- Vaccinate if non-immune
- Test for hepatitis C if there is a history of injecting drug use
- Ascertain if regular testing is advised

CASE 2

John is a 35-year-old man living in Sydney who went to his GP six weeks prior to his current consultation (see below) with a penile ulcer, just below the glans. It was indurated and only slightly tender. His GP could not detect any inguinal lymphadenopathy. Examination of the anal and oral areas as well as general examination did not reveal any lesions, rash or other abnormalities. Sexual history elicited that he has sex with men, and has one regular male partner. The GP diagnosed the lesion as a chancre, the primary lesion of syphilis, and confirmed the man's sexuality, which is important as most cases of syphilis in Sydney are in MSM.

The GP took blood for syphilis serology, and a swab of the ulcer for herpes and for syphilis PCR NAAT. The GP recalled the dark ground microscopy test for diagnosing syphilis, but was not confident that the specimen could be appropriately collected and delivered to the laboratory. While the GP thought it was syphilis, testing for herpes was also organised, because HSV ulcers are very common and, as described above, infection with multiple pathogens should always be suspected in any case of STIs. Throat and rectal swabs, and a FPU for gonorrhoea and chlamydia by NAAT, and HIV testing were also done. The results obtained were: ELISA test and TPPA confirmation test for syphilis positive; TPPA confirmation test positive;



Penile syphilis chancre. Photo courtesy of Lasion Europe.

RPR titre 1:16; lesion swab PCR for syphilis positive; HIV negative; and HSV PCR negative. He had already been vaccinated with full courses for hepatitis A and B, so there was no need to order hepatitis serology.

The patient was prescribed benzathine penicillin 1.8gm by deep intramuscular injection, but he did not attend the pharmacy and have this dispensed. The patient's partner was a nurse, who obtained some penicillin and then gave him the injection, but 1.8g of benzyl penicillin, not benzathine penicillin. Benzyl penicillin is short-acting and not sufficient to adequately treat syphilis.

The patient's chancre healed, so he thought the treatment had been effective; however, the chancre of syphilis heals naturally whether treated or not. About a month later, the patient developed a rash over his body, was feeling unwell, and came to see the same GP (current visit) who had diagnosed the syphilis. Secondary syphilis was suspected. When seen, he had reddish macules on his trunk and arms, with lesions on the palms of the hands and soles of the feet.

There were no other clinical features such as lymphadenopathy, patchy hair loss, or superficial lesions on the mucosa of his mouth, but the patient's RPR had increased to 1:32. The patient was treated with

benzathine penicillin. A repeat HIV test was negative.

With respect to follow-up, antibodies to the causative organism (*Treponema sub species pallidum*) usually persist for life, so the patient's screening ELISA test for syphilis will usually remain positive for life — being a marker of either current or past infection, treated or not. The RPR (or VDRL) titre should fall dramatically and remain low or revert to negative. John should be re-tested in six months to be sure of this. All MSM should have regular STI tests, with a minimum being annual blood tests for syphilis and HIV. All MSM should be tested for antibodies against hepatitis A and B, and vaccinated if sero-negative. Annual urine, throat and rectal swabs for gonorrhoea and chlamydia NAAT is the minimum, but, for men who have a lot of partners, more frequent testing is advisable. Men who have had instruction can take their own anal swab. It is simple to take, and just as accurate as the doctor taking the sample.

Syphilis is caused by the bacterium *Treponema pallidum pallidum*, and is one of medicine's classic chronic infections. There are several phases of the infection, as it progresses from the acute to chronic phase. The classic descriptions of primary, secondary and tertiary syphilis suggest that there are distinct stages of clinical illness, but overlap between stages is not uncommon; for example, primary and secondary syphilis manifestations may be present at the same time. Dissemination of the organism to the central nervous system occurs early in the illness, even if there is only a primary chancre present.

Over the past 10 years or so, an epidemic of syphilis has become established in Sydney (similar to Melbourne and many other major western cities) with most cases among MSM, many of whom also have HIV infection.

Blood tests are usually accurate in detecting primary syphilis, but false negatives can occur; there can be a lag between the time of infection and seroconversion. Therefore, if the initial blood test is negative, it should be repeated within the next 2-4 weeks. Seroconversion may take as long as three months. PCR for syphilis from a swab of the lesion is now available at some centres in most capital cities, avoiding the need to take a specimen for dark ground microscopy. Because genital



Lesions on the palms of a patient with secondary syphilis. Photo courtesy of the Australasian Chapter of Sexual Health Medicine.

herpes is a common cause of genital ulcer, and because multiple pathogens should be assumed, a swab for HSV should always be performed. Additionally, tests for rarer conditions such as chancroid, lymphogranuloma venereum and donovanosis may be appropriate. Specialist advice from the laboratory should be sought if such conditions are suspected, so that the appropriate specimens are collected and appropriate testing is implemented.

If the early stage of syphilis is not treated, the bacteria spread throughout the body to cause the systemic symptoms of secondary syphilis. There may be a rash over the body with reddish macules on the trunk and arms, and on the palms of the hands or soles of the feet. Typically the rash is not itchy. There may be general malaise, lymphadenopathy, hepatomegaly, patchy hair loss, or superficial lesions on the mucosa of his mouth.

At the secondary stage, the serology tests are always positive, and the titre of the RPR test (or VDRL) is usually quite high, greater than 1:16. Treatment at this stage is the same as for primary syphilis.

If secondary syphilis is not treated, the infection progresses to a stage of latency, in which the patient appears well, without symptoms or signs of infection.

Serology remains positive, usually with a low RPR titre. The patient is usually (but not always) non-infectious. Latent syphilis can progress to tertiary syphilis with disease affecting any part of the body, but especially the central nervous system and aorta.

After successful treatment of syphilis, the syphilis serology will usually remain positive for life. However, the RPR titre should drop at least two-fold in the six months after treatment, and settle thereafter at a low titre. Apart from direct sampling of new lesions in re-infection, the only useful test thereafter is the RPR titre, which should not rise two-fold. If it does, this might indicate re-infection.

Contact tracing is extremely important, but out of the scope of this article.

Key messages

- All ano-genital ulcers/sores should be regarded as syphilis until proven otherwise
- Multiple pathogens may be present in or cause ano-genital ulcers/sores
- Any rash in a person with an STI, suspected or proven, should be evaluated for syphilis
- The RPR titre is still the best indicator of disease activity, re-infection or adequacy of therapy

CASE 3

Mrs F is 28 years old. She presents with a four-day history of worsening dysuria and pain “down there”. When she walks into your office, she appears to be uncomfortable with each step she takes. She says she think it might be another “bout of cystitis” but isn't sure. She also feels general “vaginal” pain and is vaguely generally unwell. Sexual history, taken with sensitivity, is that she is married and has had no new partners since marriage two years ago.

On examination, there are multiple shallow and very tender ulcers scattered throughout the vulva. Small tender inguinal lymph nodes are palpable bilaterally.



Primary HSV.

Given the multiple and tender ulcers, first-episode genital herpes was suspected. Speculum examination was not, and should not be, performed, as it adds nothing to the diagnosis and is typically too painful to perform.

Management of a first episode of genital herpes should be immediate and not wait until the results of tests. A swab of the ulcers should be taken for HSV NAAT. These tests are extremely sensitive and specific and are the tests of choice. Although the preferred specimen is a swab of the base of an ulcer or a de-roofed vesicle, the test may still be positive on older lesions. Prior to the wide availability of NAAT, direct immunofluorescence microscopy and viral culture were the standard tests, but these are now only done in reference centres. HSV PCR on genital specimens generates a result indicating whether the cause is HSV type 1 or HSV type 2.

Initial management should include brief information about the high prevalence of the various herpes viruses in the general community, the asymptomatic and the lifelong infection it causes together with the lack of serious sequelae for the majority of people. Detailed counselling is more timely with the results of specific testing.

More than 50% of first episodes of genital herpes in Australia are caused by HSV1. A blind swab can be gently passed intra-vaginally to test for gonorrhoea and chlamydia by NAAT (or this can be delayed to a later date). General supportive measures can include analgesia (both topical with local lignocaine gel, and oral with paracetamol and/or codeine) and bed rest.

Immediate treatment should be commenced with an oral anti-HSV agent, such as valaciclovir. Acyclovir is less commonly used because of its less convenient dosing schedule (and valaciclovir is a pro-drug of acyclovir). Sex must be avoided until all lesions have healed.

The results obtained were: screening ELISA test for syphilis negative; HIV negative; and HSV PCR test positive for HSV-2. Early serology tests could not distinguish between HSV1 and HSV2 infection. Current serology can distinguish between HSV1 and HSV2 but, as HSV1 causes as many (or more) cases of first-episode genital herpes than HSV2 in Australia, and extragenital lesions can be seen with HSV2, the value of serology is dubious at best. Additionally, testing a low prevalence population for any condition generates results with poor positive predictive value. Serology for HSV is discouraged unless there is a specific situation where it may be of use in management, for example in pregnant women where there is uncertainty about previous genital herpes. Serology should not be used to diagnose infection; direct detection of the virus should always be pursued.

Key messages

- NAATs are the preferred tests to diagnose genital herpes
- HSV1 is as least as common as HSV2 as the cause of initial genital herpes infection in Australia
- Serology has little role in the diagnosis of genital herpes and its use is discouraged except in special situations

References

Australian STI Management Guidelines
www.sti.guidelines.org.au