Laboratory diagnosis of sexually transmitted infections

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Abstract

The laboratory plays a central role in the accurate diagnosis of sexually transmitted infections (STIs). In countries with sufficient resources the laboratory is usually involved in providing a result to inform individual patient management. In contrast, in resource-poor countries where patients are often treated according to their presenting symptoms (syndromic management), the laboratory has a role in evaluating this approach. Molecular detection of the causative agents of STIs, such as *Neisseria gonorrhoeae*, *Chlamydia trachomatis* and herpes simplex virus (HSV), using highly sensitive and specific tests, has largely replaced classical culture techniques. The detection of the host's antibody response to the infecting agent is still the mainstay for the diagnosis of syphilis and human immunodeficiency virus (HIV). In some instances a combination of antigen and antibody detection is used. In the United Kingdom, where a unique network of open-access specialized clinics exists, some laboratory procedures are performed in a clinic laboratory setting and this is particularly useful for common causes of vaginitis that can be diagnosed using a microscope. This article describes the current methods employed for the major causes of bacterial and viral sexually transmitted infections.

Keywords Bacterial vaginosis; *Chlamydia trachomatis*; herpes simplex virus; human immunodeficiency virus; laboratory; lymphogranuloma venereum; *Neisseria gonorrhoeae*; syphilis; *Treponema pallidum*; *Trichomonas vaginalis*

Introduction

The laboratory plays a central role in the diagnosis of sexually transmitted infections (STIs) either by the direct detection of the causative organism or by detection of the host's response to the infection or a combination of these.[1] The delivery of diagnostic tests is currently changing with centralization of laboratory facilities in many areas, use of automated technology and the focus on the development of point-of-care tests (POCTs) for many STIs. However, the laboratory still plays a pivotal role either in primary or confirmatory testing and that is unlikely to change for a number of years.

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What's new?

- Fourth-generation HIV Ag/Ab tests are now standard of care, reducing the usual 'window' to detect infection to just 4 weeks
- Point-of-care testing for HIV, syphilis and, more recently, trichomoniasis has the potential to transform the role of the laboratory in the clinical service. Point-of-care molecular amplification tests are in development
- Dual nucleic acid amplification tests for the detection of *Chlamydia trachomatis* and *Neisseria gonorrhoeae* are highly sensitive and specific and are the method of choice for the laboratory diagnosis of both these infections at any affected site. Culture is an essential adjunct to maintain antibiotic resistance surveillance
- Detection of *Trichomonas vaginalis* by culture, molecular methods or a validated point-of-care test are more sensitive than microscopy and preferable where resources allow.

Neisseria gonorrhoeae

The isolation of *N. gonorrhoeae* was formerly the gold standard for the diagnosis of gonorrhoea, but the development of nucleic acid amplification tests (NAATs) with a high sensitivity and specificity has heralded a change in approach. Cultural methods that use a well-taken specimen, inoculated on a highly nutritious medium, transported from the patient to the laboratory quickly and incubated in appropriate conditions can still yield a positive result in most infected patients. However, this methodology is intolerant of delays or inadequacies in this process, and the sensitivity can be low particularly when used for patients attending clinics or settings distant from the laboratory, and for certain anatomical sites.

In contrast, NAATs are more tolerant of variable storage conditions and delays in reaching the laboratory, and their high sensitivity allows use with samples taken non-invasively, such as urine samples and self-taken vaginal swabs, although urine in women is not the optimal sample for gonorrhoea.[2] The specificity of NAATs for gonorrhoea (GC NAATs), due to cross-reactivity with other species of *Neisseria*, has been a concern but recent generations of these tests have shown a marked improvement. Compared with culture, NAATs are known to detect more cases of gonorrhoea and are becoming the method of choice for the laboratory diagnosis,[3] the technology being easily automated and combined with the detection of *Chlamydia trachomatis*. It is essential to retain the expertise for culture as a viable organism is necessary to perform susceptibility testing, for surveillance purposes and to detect emerging resistance. In many instances, NAATs and culture are performed on symptomatic patients and NAATs alone for screening asymptomatic individuals, followed

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by culture when the patient is recalled for treatment. A positive predictive value (PPV) of >90% is desirable when using this approach; this can be a challenge in low-prevalence populations and may require supplementary testing of positive tests with a NAATs with a different target for this to be achievable.[4]

Detection of *N. gonorrhoeae* in extragenital samples has always been difficult: rectal samples are contaminated with large numbers of normal flora and pharyngeal samples with commensal species of neisseria. NAATs are now recognized to be superior at these sites and give significantly more positive cases than culture. None of the GC NAATs has been approved by the FDA (Food and Drug Administration) for use on samples from extragenital sites, but there are validation data to support the use of these tests and comply with accreditation requirements.

Chlamydia trachomatis

Molecular detection using NAATs is the gold standard method for the detection of *C. trachomatis* infection because they are both highly sensitive and specific when testing a range of different clinical specimen types.[5] The increased sensitivity of NAATs for *C. trachomatis* (CT NAATs) over traditional methods of chlamydia detection (e.g. culture and enzyme immunoassay) allows detection of low levels of infectious agent, which means that they can be used to test non-invasive specimens such as urine and self-taken vaginal swabs, as well as standard clinician-taken genital swabs. As a consequence of this increased test sensitivity, testing in primary care or community settings is possible. As with GC NAATs, there is no commercially available CT NAAT that is approved by the FDA for use on samples from extragenital sites. However, NAATs have been shown to be very reliable for the detection of chlamydia infection in rectal swabs, which is important when testing men who have sex with men (MSM).

Commercially available CT NAATs are usually combined with GC NAATs and these dual NAATs are widely used as they offer testing for two STIs at little or no extra cost compared with the single test. There is a range of dual NAATs approved by the FDA but as with the single analyte tests for CT and GC alone, none is approved for use on samples from extragenital sites.

Lymphogranuloma venereum (LGV)

In some instances it may be clinically necessary to undertake testing for LGV.[6,7] At the present time, although all commercial CT NAATs report LGV infection as positive for chlamydia, there is no commercial test available that can detect LGV-specific DNA, or distinguish LGV serovars from non-LGV serovars of chlamydia. However, several LGV specific in-house real-time PCR assays do exist and have been extensively validated for the detection of LGV. Due to its specialist nature, LGV testing is generally confined to national or specialist reference centres.

Syphilis

The laboratory diagnosis of syphilis infection (caused by *Treponema pallidum* spp. *pallidum*) is most commonly achieved using serological tests, which can detect the presence of treponemal antibodies in a patient's serum. In order to unequivocally detect either a previous or current treponemal infection a battery of serological tests is required ('STS'). In most situations a serum specimen will be first screened using an enzyme immunoassay (EIA) or a chemiluminescent assay (CIA), which have the advantage of being both sensitive and automated. Sera giving EIA-positive results are then further examined using a more specific confirmatory assay, such as the Treponemal Particle Agglutination Assay (TPPA). Employing such a testing approach enables the differentiation of patients with a true history of treponemal infection from patients who may produce false positive results using the EIA or CIA screening test, which can lack specificity if used alone.[8] Even the most modern serological tests cannot distinguish between the causative agent of syphilis and the closely related agents that cause endemic syphilis, pinta or yaws. Thus, positive serological tests for syphilis always require careful clinical interpretation including a detailed patient history.

Patients with a past history of treponemal infection usually mount an immunological response for life, even following treatment, and this can make the differentiation between past and active infection difficult. In order to overcome this either a Rapid Plasma Reagin (RPR) or a Venereal Disease Reference Laboratory (VDRL) test can be used. The RPR and VDRL tests are often referred to as non-treponemal tests as they do not directly detect treponemal antibody in a patient's serum, but detect antibody to lipoidal antigens that are present in both treponemal and host cells. These antibodies fall in titre with time and after specific syphilis treatment, and rise again with relapse or re-infection. Active treponemal infection is suspected in patients who produce a reactive RPR/VDRL test against serum, especially with a titre of >1:16, although interpretation of lower titres should take into account clinical presentation to detect early cases.

Treponemal IgM EIA tests are also available, but they tend to be technically more complex to perform than the RPR/VDRL tests; their use is controversial but they are more commonly performed in specialist centres. Detection of treponemal IgM is most useful in congenital cases as IgM does not pass through the placenta, so its presence indicates infection in the baby rather than transfer of maternal antibody. It is also useful in early syphilitic infection, although positive results should be interpreted with caution, as treponemal IgM can persist for 1–2 years after treatment.

Genital ulcer disease

In the UK the main cause of genital ulcer disease is **herpes simplex virus** (HSV). The standard method for the diagnosis of HSV infection is detection of HSV DNA from the site of infection. NAAT tests are usually duplexed to detect HSV-1 and HSV-2. Commonly practitioners fail to send appropriate swabs for HSV detection, in spite of the implications for the patient of recurrence and transmission.

HSV type-specific serology can also be useful in some circumstances:

- when the sexual partner is known to have genital herpes
- where the patient presents with genital ulceration compatible with genital herpes, but attempts to detect HSV DNA have been unsuccessful
- testing pregnant women with a history of genital ulceration but no previous virological confirmation of infection

The laboratory diagnosis of genital ulcer disease caused by ***T.pallidum*** or ***Haemophilus ducreyi*** (the causative agent of

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