Clinical review

Recent advances

Sexually transmitted infections

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See also Editorial by Catchpole

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Rates of sexually transmitted diseases are increasing, particularly in people aged between 15 and 25. How best to tackle this increase is unresolved, although several tests have recently been developed that are providing new opportunities for screening, early detection, and prevention of sexually transmitted infections and their complications, particularly for *Chlamydia trachomatis*, herpes simplex virus, and human papillomavirus. Already these tests are being used in research studies, but their introduction into clinical practice raises complex issues. This articles describes the tests that are now available for the major sexually transmitted infections and discusses the important issues they raise in the management of those diseases.

Methods

We selected topics for inclusion by reviewing specialist journals and conference abstracts from 1998 to 2000. We chose areas that were the subject of most research reports and that are having a direct impact on patient care. We performed a search of Medline for the same period, based on keywords related to these topics. Earlier references were among those quoted in the publications retrieved by the systematic search. We have not considered advances in HIV disease and its management.

Surveillance data

In the United Kingdom most cases of sexually transmitted infections are treated at genitourinary medicine clinics. Surveillance data from these clinics show that their workload is steadily increasing (fig 1). There has been a noticeable increase in the number of cases of bacterial infections, particularly chlamydia and gonorrhoea since 1995.[1]

Chlamydia

Chlamydia trachomatis is the most commonly diagnosed bacterial sexually transmitted infection in the developed world and a leading cause of pelvic inflammatory disease.[2] In 1999, 56 855 patients with uncomplicated chlamydial infection were seen at UK clinics dealing with genitourinary medicine, an increase of 61% since 1996.[1] Given the potential for morbidity from ectopic pregnancy and tubal infertility the case for screening for chlamydia among those most at risk is strong.

Recent advances

Cervical cancer is almost always associated with human papillomavirus type 16; whether screening for high risk virus types will contribute to cancer prevention is still being evaluated and vaccines are in development

Sexually transmitted infections in young people are common and more needs to be done to control them at the same time as reducing the rate of teenage pregnancy

The numbers of reported cases of chlamydial infection are increasing, and strategies for widespread screening of those at risk are being evaluated

Treatment algorithms for countries with poor resources are valuable, and UK national guidelines for the management of sexually transmitted diseases are now available and should improve the consistency and quality of care

Enzyme immunoassays for detecting chlamydial antigen and direct nucleic acid probe assays are the most widely used tests and can evaluate large numbers of samples. Their use for screening in community settings is limited, however, because their positive predictive value is low in populations with a low prevalence of infection. Nucleic acid amplification tests for chlamydia, including polymerase chain reaction, ligase chain reaction, and transcription mediated amplification assays, are more sensitive and highly specific.

Although there is no absolute "gold standard" for chlamydia tests, amplification assays have a sensitivity of at least 90% compared with 60-70% for culture and 60% for antigen assays.[3] Samples not requiring genital examination can also be used. The sensitivity of nucleic acid amplification tests on urine samples from males is high and may even be higher than a urethral swab, perhaps because of the limitations on taking an adequate urethral swab sample. In women the sensitivity of urine testing is lower, and a vaginal swab is a better alternative. Urine samples are more time consuming to process, and a cold chain to the laboratory is recommended.

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Figures showing the UK rates of chlamydia and gonorrhoea by age group appear on the BMJ's website

In 1998, proposals were published to extend chlamydia testing in the United Kingdom to include all patients attending clinics, with or without symptoms, and all women seeking termination of pregnancy.[4] It was also recommended that sexually active people under 25 and those over 25 with a new sexual partner in the past year should be screened. How this would be implemented is problematic. A pilot study is underway to determine whether opportunistic screening of those in the age groups at highest risk can be undertaken in a variety of primary care settings and how patients should be managed.[5] This pilot used nucleic acid amplification tests, but other studies are looking at which tests and clinical samples can be used.

Treating index cases without treating their sexual partners results in a high rate of reinfection, so that notification of partners and contact treatment are essential. Whether this is best done by referring the patient to a clinic needs to be established, and local policies will have to be agreed and implemented if management is to be effective. Whether, or how, men should be included in the screening process remains uncertain, but their exclusion has been criticised.[6]

Failure to treat partners may be the commonest cause of "treatment failure" of chlamydia infection, but treatment compliance is also an issue. A single dose of azithromycin 1 g has been shown to be effective in treating chlamydia and other causes of non-gonococcal urethritis but at a much greater cost than a 7 day course of doxycycline.[7] Single dose treatment may be cost effective because of improved compliance, however even with poor compliance the cure rate with doxycycline is still high, typically 95%.[8] This is consistent with evidence that the effective dose and possibly the duration of doxycycline treatment is less than that recommended.[9] Even if such treatment is cost effective, whether clinical services with limited resources will be funded to take advantage of this is uncertain. One solution may be to use single dose treatment for cases where compliance is less likely.

Herpes simplex virus

Genital herpes (fig 2) can be caused by either herpes simplex virus type 1 or herpes simplex virus type 2. In 1999 in the United Kingdom, where genital herpes is the commonest infectious cause of genital ulceration, 17 456 people were diagnosed with a first episode of genital herpes and 14 329 with recurrent herpes. In the United States, comparable surveillance data are not available, but it has been estimated that about 500 000 people visited a doctor for genital herpes in 1999.[10]

Studies using improved type specific serological tests have shown wide variation in the seroprevalence of infection with herpes simplex virus type 2. For example, a birth cohort from New Zealand tested at age 21 showed a seroprevalence of 3.4% whereas in rural Tanzania the seroprevalence in males aged 25 and over was 60% and in females 75%.[11 12] Studies have confirmed that the risk factors for the acquisition of herpes simplex virus type 2 include age (infection is uncommon in children, with the highest rate of acquisition between 15 and 40), sex (women have higher rates than men), increased numbers of sexual partners in a lifetime, earlier age at first sexual intercourse, history of other sexually transmitted infection, level of education, and involvement in the commercial sex industry.[11–14]

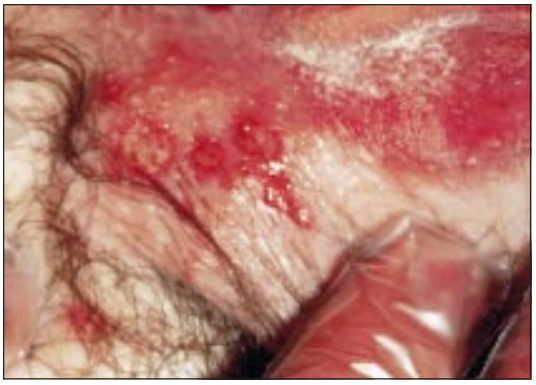

Fig 2 Herpes simplex infection of vulva

Although the utility of type specific serology for herpes simplex virus in epidemiological studies is undisputed, the use of these tests for diagnostic purposes remains more contentious. Possible uses include assessment of asymptomatic sexual partners of patients with genital herpes, diagnosis of genital ulcers where viral culture repeatedly gives negative results, exclusion of herpes in pregnancy, and routine testing as part of a screen for sexually transmitted diseases.[15] There are several limitations: the test usually does not give positive results until about six weeks after exposure; a positive test result indicates previous exposure but does not prove that particular clinical signs or symptoms are due to herpes; and the sensitivity and specificity of the tests range from 95% to 99% (in populations with a low prevalence most positive test results will be false positives).

Increasing evidence shows that many herpes infections are asymptomatic.[16] The rate of viral shedding from the genital tract of asymptomatic and seropositive people is similar to that of those with a history of symptomatic infection (3% and 2.7%, respectively).[17] In people with symptoms, much of the viral shedding occurs close to the time when the symptoms occur. This has stimulated discussion about how transmission can be reduced.[18] Consistent use of condoms may help to reduce the risk by covering exposed or susceptible

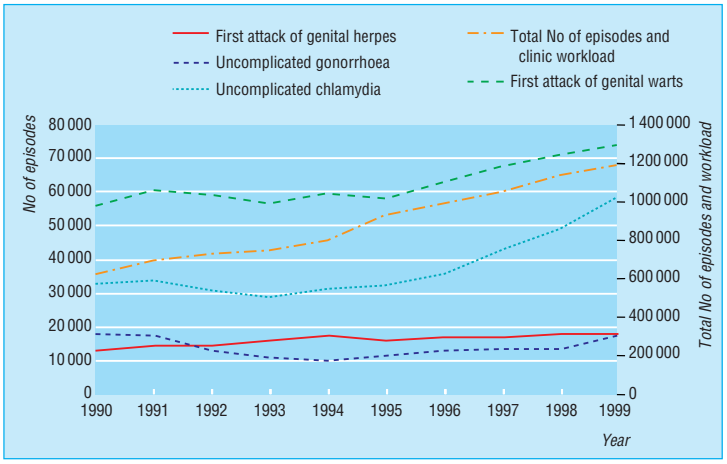

Fig 1 Annual number of new episodes of acute sexually transmitted infections seen in UK genitourinary medicine clinics, 1990-9

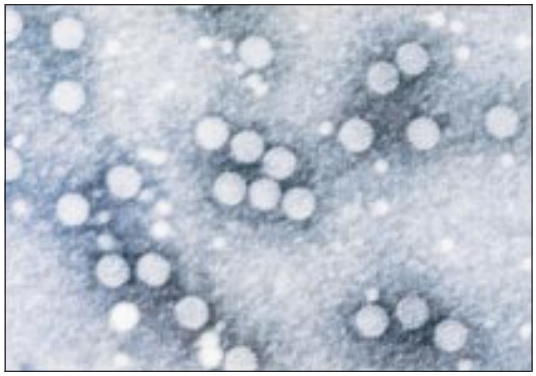

Fig 3 Electronmicrograph of human papillomavirus

mucous membranes and skin, but it has been suggested that the continuous use of antiherpes drugs would reduce the risk of transmission by decreasing the quantity of asymptomatic viral shedding. Clinical studies to assess this are under way. Considerable interest has been shown in the development of a vaccine to prevent acquisition of genital herpes, although results from early trials have been conflicting.[19 20]

Human papillomavirus

Genital warts are the most commonly diagnosed sexually transmitted diseases in UK genitourinary medicine clinics. In 1999, 72 233 cases of a first attack of genital warts were reported, an increase of 25% in men and 28% in women since 1993. About 90% of genital warts are caused by papillomavirus (fig 3) type 6 or 11, although most infected people do not have overt warts, possibly as few as 1%.

Human papillomavirus types may be categorised as high or low risk on the basis of their association with neoplasia of the genital tract, principally cervical cancer. Nearly all cases of cervical cancer are associated with high risk human papillomavirus types, mainly 16 and 18.[21] Types 6 and 11 are low risk, although coinfection with more than one virus type also occurs. The use of DNA testing to detect high risk types is being evaluated in screening for cervical cancer.[22–24] The utility of this approach depends on the sensitivity and specificity of the tests and the prevalence of high risk virus types in the population to be screened. The sensitivity of the current tests, including the Hybrid Capture II Assay (Digene, Gaithersburg, MD) is about 90%.[24 25] However, specificity is a problem, with false positive rates of 15-20%.[24] Further studies are required to establish whether screening is possible and affordable and how it can be integrated into existing screening programmes.

The understanding of the epidemiology of human papillomavirus has increased with the availability of serological tests for antibodies against the virus. Studies have shown that antibodies to virus type 16 are rare in children, more common in women with cervical cancer (51%) than in controls (16%),[26] and associated with several sexual behaviour and social factors, including the number of sexual partners in a lifetime, years of sexual activity, level of education, and previous gonorrhoea.[27]

Treatment for genital warts remains unsatisfactory, with all treatments having similar initial response rates (typically 50-75%); recurrences are common. Imiquimod, a new topical immunotherapeutic agent, has a similar clearance rate to existing treatments,[28] although the relapse rate may be lower.

Vaccines against human papillomavirus are being developed both as immunotherapeutic agents for genital warts and cervical cancer and as prophylaxis against cervical cancer. Virus-like particles produced in vitro are able to induce antibodies in vivo, but induction of cellular immunity is probably a more important target. A human papillomavirus-6 L2E7 fusion protein was shown to be safe and immunogenic,[29] but clinical trials have so far failed to show efficacy in treating genital warts. For patients with cervical cancer, interest has focused on the human papillomavirus oncoproteins, E6 and E7, with a human papillomavirus-16 E7 peptide vaccine tested recently.[30] Randomised placebo controlled trials of these vaccines are under way.

Young people

Increasing attention is being paid to sexually transmitted diseases in young people, particularly adolescents. Data from the United Kingdom show that the highest rates of gonorrhoea and chlamydia are in men aged 20-24 and women aged 16-19 (see figures on website). Although rates of gonorrhoea have fallen over the past two decades in the United States, the highest rates are in men aged 20-24 and women aged 15-19 and are about 10-fold higher in black people than white people, regardless of sex, comparable with London.[31 32] In Copenhagen the highest prevalence of chlamydia among women aged 20-29 was in the 20-22 age group.[33] Rates of repeat infection are high as well. In a study in the United States, 40% of 15-19 year olds with a sexually transmitted disease had a subsequent

Key ongoing research studies

A study in Portsmouth and the Wirral funded by the Department of Health aims to assess the feasibility and acceptability of opportunistic screening for chlamydia in both primary care and secondary care (including gynaecology, termination of pregnancy, and clinics for genitourinary medicine). The study is targeted principally at women aged 16-24. The one year pilot screening period ended in August 2000, and the data are now being analysed

Studies are addressing which are the best tests for detecting chlamydia, which specimens are to be used, and what strategies are likely to be effective for notifying partners. The studies include one funded by the NHS Research and Development Health Technology Assessment programme, based at the University of Bristol. It will include an analysis of the cost effectiveness of different strategies and is due for completion in 2003

Antiviral treatment for herpes simplex virus is being assessed as a way of reducing the rate of transmission. A multinational randomised double blind placebo controlled trial sponsored by the National Institute of Allergy and Infectious Diseases in the United States will determine whether valaciclovir 500 mg orally once daily for patients with a history of recurrent genital infection with herpes simplex virus and seropositive for herpes simplex virus type 2 antibodies will prevent transmission to their heterosexual partners who are seronegative for the virus. The treatment period is 8 months, and 1500 couples are being recruited

The value of adding testing for high risk human papillomavirus infections to current strategies for managing mild or borderline dyskaryosis is being evaluated as part of the trial of management of borderline and other low grade abnormal smears (TOMBOLA) study. The study, based in Aberdeen, Dundee, and Nottingham, is funded by the Medical Research Council and the Department of Health and will involve 10 000 women, followed for 3 years. Outcomes include the incidence of more severe disease (CIN2/3)

Additional educational resources

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Current Opinion in Infectious Diseases 14(1), Feb 2001. This issue covers HIV infection and AIDS, sexually transmitted diseases, and urinary tract infections. It contains listings of recent literature and reviews of tests for bacterial sexually transmitted diseases and human papillomavirus and strategies for improving sexual health in ethnic minorities

www.agum.org.uk and www.mssvd.org.uk. Both these sites have copies of the UK national guidelines on sexually transmitted infections as well as directories of clinics dealing with genitourinary medicine in the United Kingdom and a large number of links to other sites with relevant material

www.phls.co.uk. This site includes a section on disease facts. The section on sexually transmitted diseases includes the latest surveillance data

sexually transmitted disease within a year.[34] How best to address these issues is unresolved, but the new test methodologies described above will make wider screening practicable. Suggested approaches have included offering tests for gonorrhoea and chlamydia in school health centres, screening high risk adolescent males with urine tests offered by peers who are outreach workers, and inviting school students to collect urine or vaginal flush samples at home and to post them to a laboratory.[35–37] Screening adolescents for sexually transmitted diseases is a contentious issue, but young people do need increased access to clinical services offering appropriate sexual health promotion as well as diagnosis and treatment of their diseases and contraception.

Practical management

In regions with poor resources "syndromic" management has been advocated as a method of improving the treatment of patients where there are few, if any, laboratory diagnostic facilities. Treatment decisions are based on algorithms that map symptoms and signs (sometimes with the inclusion of a microscopy result) to the most likely diagnosis and hence to the treatment with the greatest prospect of effecting a cure. Such strategies are less effective for women with vaginal discharge than they are for men with urethral discharge or for patients with genital ulceration and will by definition not include asymptomatic people. Although such strategies have been in use for some time, recent rigorous evaluations of them have shown encouraging results.[38]

In industrialised countries, by contrast, treatment guidelines have been developed to increase the consistent application of best practice in specialist services treating sexually transmitted diseases. In the United States the Centers for Disease Control and Prevention have issued treatment guidelines (www.cdc.gov).[39] In the United Kingdom, guidelines for the management of all the major conditions treated in clinics dealing with genitourinary medicine have been produced recently by the Clinical Effectiveness Group of the Medical Society for the Study of Venereal Diseases and the Association for Genito-Urinary Medicine.[40] With the introduction into the NHS of clinical governance and the priority being given to consistency of care, the guidelines should form the basis for treatment protocols for local specialist clinics and primary care.

Competing interests: RG has received reimbursement for attending conferences from, and has been an investigator on a study funded by, 3M Pharmaceuticals, manufacturer of imiquimod.

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Evidence based management of hypertension

Using cardiovascular risk profiles to individualise hypertensive treatment

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This is the fourth in a series of five articles

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Individual risks must be assessed in order to for the best decision to be made as to which patients to treat and how. Assessment identifies important cardiovascular risk factors that may warrant treatment and helps to establish the absolute benefits that patients can expect from particular treatments. The benefits of treating hypertensive patients also vary, depending on each patient's competing risks of dying from other than cardiovascular causes. For example, patients with multiple serious conditions, such as end stage Alzheimer's disease, obstructive lung disease, frequent falls, gout, and urinary incontinence, have high competing risks that may minimise or negate the benefits of treating their hypertension.

Factors useful in helping patients prioritise their treatments

Establishing treatment priorities for patients with multiple cardiovascular risk factors and multiple conditions is difficult. Factors such as those given in the box deserve consideration. Knowing and weighing up multiple risk factors, conditions, and treatments is difficult. Explaining them to patients is daunting and time consuming. Some patients prefer to be told what to do rather than to have to take in the diverse, complicated information necessary to make their own or joint informed decisions; others prefer a great deal of information. We recommend informed decision making, with attention to the factors given in the box, when possible.

Table 1 Approximate reductions in relative risk associated with various treatments for hypertensive people with other cardiovascular risk factors but no known cardiovascular disease

	Approximate change (%) in relative risk (range)	
Treatment	**Death**	**Cardiovascular disease**
Angiotensin converting enzyme inhibitor (ramipril)	–15 (–25 to –5)	–20 (–30 to –15)
Antiglycaemic drugs	Not shown	Not shown
Antihypertensive drugs	10 (5 to –10)	–30 (–40 to –15)
Antilipidaemic drugs	–5 (–20 to 10)	–30 (–40 to –20)
Aspirin	–5 (–15 to 5)	–15 (–30 to –5)
Physical activity	Unclear	Unclear
Smoking cessation	Unclear; ⩾–20	Unclear; ⩽–50

Summary points

Several treatment options reduce risk of cardiovascular disease and improve outcomes in patients with hypertension

Providers should consider the expected benefits and potential adverse effects of different treatment options and discuss them with patients

The use of decision tools may help decision making about options for reducing cardiovascular risk

Factors helpful in prioritising patients' treatments

- Type, immediacy, and magnitude of expected benefits and harms
- Availability and costs of treatments
- Feasibility and likelihood of compliance
- Competing risks from various conditions
- Expected interactions with other treatments
- Patient and provider preferences and values