PART 2A

Gonorrhoea

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The organism *Neisseria gonorrhoeae* is a highly infectious, bacterial sexually transmitted pathogen that is frequently identified and treated in genitourinary medicine (GUM) clinics in the United Kingdom. In heterosexuals, its prevalence is associated with age (<25 years), black ethnicity, and socioeconomic deprivation. Population prevalence estimates from the Health Protection Agency suggest that it may be more prevalent in men who have sex with men (MSM) than in heterosexual men. Infection is frequently asymptomatic at the endocervix and urethra in women, and usually (>90%) asymptomatic in the rectum and oropharynx in both men and women.[1] It is associated with significant morbidity. Testing for *N gonorrhoeae* is a core component of screening for sexually transmitted infection (STI) within GUM clinics.

TESTS

Microscopy for intracellular Gram negative diplococci

Microscopic examination of Gram stained smears of urethral discharge in men or endocervical discharge can be used as a near patient test to provide an immediate presumptive diagnosis of gonorrhoea (evidence level II, recommendation grade B). In men, microscopy of urethral smears has a sensitivity of >95% in symptomatic patients, lower in asymptomatic patients (50–75%).[1–4] Microscopy of endocervical smears in women has a sensitivity of between 30–50%. Specificity is high when screened by trained personnel, >99%.[2–4] Microscopy is not suitable for pharyngeal or rectal specimens where many other bacteria are present, including Gram negative cocci belonging to other genera.[4 5]

Isolation of *N gonorrhoeae*

Specimens collected from an appropriate site should be cultured onto an enriched medium, usually GC agar base or Columbia agar, supplemented with lysed or chocolatised horse blood or a non-blood based supplement such as IsoVitaleX (Becton-Dickinson) or Vitox (Oxoid) (evidence level II, recommendation grade B). If a single medium is used this should contain antimicrobial agents as selective agents to suppress the normal flora and allow the growth of *N gonorrhoeae* (GC audit)[6] (evidence level II, recommendation grade B). Antibiotic cocktails, available commercially, contain vancomycin or linomycin (to inhibit Gram positive organisms), colistin and trimethoprim (to inhibit other Gram negative organisms), and nystatin or amphotericin (to inhibit *Candida* spp). Lincomycin is sometimes preferred to vancomycin because *env* mutants with increased susceptibility to vancomycin do not grow. However, lincomycin is less inhibitory than vancomycin and overgrowth of normal flora can occur, particularly with rectal or pharyngeal specimens. Trimethoprim sensitive strains can also occur. Choice of selective agents is dependent on the sites being screened. If resources are available culture on a non-selective medium in addition is ideal (recommendation grade C). The primary isolation medium should be incubated in a carbon dioxide enriched environment for 48 hours before being discarded as negative.

Direct plating of the specimen and use of transport swabs both give acceptable results[4 6] (evidence level IV). Culture plates inoculated directly should be kept at 37℃, in the presence of 5–7% carbon dioxide if possible, before and after transfer to the laboratory. Transport swabs should be stored in the refrigerator at +4℃ and transported to the laboratory as soon as possible, preferably within 48 hours (evidence level IV).

All colonies isolated on specialised media for *Neisseria* that are oxidase positive Gram negative cocci should be further identified using biochemical or immunological tests (recommendation grade C). With confirmation, culture has a specificity of 100% and positive predictive value (PPV) of 100%.

Culture for *N gonorrhoeae* can be used with specimens from all sites and provides a viable organism for antimicrobial susceptibility testing. Culture has been reported to have a sensitivity for urethral and endocervical infection between 85–95% where conditions for culture are optimal. However, in settings where optimisation of culture is difficult the sensitivity of culture may be lower, particularly in comparison with nucleic amplification methods.[7–13] Methods for confirmation of *N gonorrhoeae* vary greatly.

Nucleic acid hybridisation or amplification tests

Tests that probe or amplify specific nucleic acid sequences have the ability to detect small amounts of nucleic acid and can detect non-viable organisms. These tests can be used with non-invasive samples such as urine or self taken swabs. Although nucleic acid amplification tests (NAATs) offer high sensitivity (95%) for endocervical and urethral samples they are currently not recommended for screening in GUM clinics where samples are directly taken from mucosal surfaces because they do not provide a viable organism for susceptibility testing and PPV is <100%[14] (recommendation grade C). No molecular test to detect all known mechanisms of antibiotic resistance currently exists.

The nucleic acid hybridisation tests available are Gen-Probe, Pace 2 and Pace 2C, which have a sensitivity comparable to culture estimated to be 92.1% for endocervical and 96.4% for urethral specimens.[15] The specificity of Pace 2 appears to be 99% using discrepant analysis.[15]

Three NAATs are commercially available, Cobas Amplicor (Roche), BD ProbeTec-SDA (Becton Dickinson), and Gen-Probe Aptima Combo 2 (Biomerieux). The sensitivity of these tests is high (>90%) in comparison with culture (50–60%) for all specimens (endocervical swabs, self taken vaginal swabs, tampons, urethral swabs, and male urines), except for female urines, where the sensitivity has been found to be lower (30–60%).[10–15] The absolute values in the comparison of the sensitivities, between NAATs and culture, differ between studies and reflect inconsistencies in the definition used for a

Abbreviations: GUM, genitourinary medicine; HPA, Health Protection Agency; MSM, men who have sex with men; NAATs, nucleic acid amplification tests; PPV, positive predictive value; STI, sexually transmitted infections

true positive and differences in collection and transport of specimens which may reduce the sensitivity of culture.

All positive nucleic acid tests should be considered presumptive evidence of infection within a GUM clinic setting. Where the prevalence of gonorrhoea is low, PPV may be <80% and culture confirmation of a positive NAAT result is recommended[9 14] (recommendation grade C).

Nucleic acid tests have had limited evaluation on rectal and oropharyngeal samples[16–18] but may have increased sensitivity (>90%) compared to cultures(<60%) taken from these sites. They are not currently licensed or recommended for testing at these sites (recommendation grade C).

RECOMMENDATION

Factors determining the choice of screening test for *N gonorrhoeae* include test sensitivity, ability to assess antimicrobial susceptibility, ease of specimen collection, cost, biological site tested, tolerance of possible non-culture false positive results, specimen transport and laboratory capability. Within GUM clinics, culture remains the preferred test for routine use on invasively collected samples (recommendation grade C). NAATs are the recommended tests for urine and non-invasively collected samples (evidence level II, recommendation grade B). The use of NAATs on endocervical and urethral specimens may offer advantages in terms of sensitivity and specimen transport but denies the opportunity for continuing surveillance of antimicrobial resistance.

SITES FOR TESTING

All mucosal sites associated with symptoms (discharge and/or pain) should be tested for *N gonorrhoeae* (recommendation grade C).

There is little evidence to guide testing protocols with respect to which sites to test when screening asymptomatic individuals. In women, the sensitivity of a single endocervical culture is 85–95% in detecting infection with *N gonorrhoeae*. The urethra is the only site of infection in 6% of infected women.[1 19 20] There has been no recent evaluation of the additional contribution of routinely taking rectal and pharyngeal specimens when screening women, although these sites should be sampled when there is a history of direct exposure[1] (recommendation grade C).

Microscopy of Gram stained endocervical and urethral smears has low (40–60%) sensitivity in screening asymptomatic patients.[1 19] It is time consuming and has considerable resource implications for a clinic. It is relevant in patients with symptoms or signs and when screening high risk individuals who are unlikely to reattend for follow up. Its routine utility in screening asymptomatic individuals warrants further evaluation.[19]

Samples may be taken by loop or cotton tipped swab for culture. Samples for nucleic acid tests should be taken and transported as specified by the manufacturer of the test used.

Endocervix

Samples taken from the endocervix during speculum examination are suitable for microscopy, culture and nucleic acid tests. Vaginal lubricants should be avoided since some gels are toxic to *N gonorrhoeae*[21] (evidence level II, recommendation grade B).

Urethra

Samples directly taken from the urethra are suitable for microscopy, culture, and nucleic acid tests. As with microscopy, NAATs are less sensitive using urethral specimens in men with asymptomatic infection than with symptomatic infection.[22 23] For sampling, a loop or cotton tipped swab is introduced 1–2 cm into the urethral orifice. A higher sensitivity for microscopy is reported for urethral samples taken with a plastic loop compared to those taken with a cotton tipped swab[19] (evidence level III).

Rectum

Rectal samples are suitable for culture (sensitivity not well defined). However the sensitivity of microscopy is low[20] because of the large numbers of other bacteria present in the rectum and is not recommended on anorectal swabs (recommendation grade C), although it may be useful if smears are obtained following insertion of a proctoscope in symptomatic patients[1 24] (evidence level III, recommendation grade C). Nucleic acid tests are susceptible to false positive reactions because of contamination/cross reaction and are not well evaluated at this site. Anorectal samples from patients without symptoms may be obtained by blindly passing a moist swab 2–4 cm into the anal canal, using lateral pressure to try to avoid any faecal mass[1 25] (evidence level III, recommendation grade B). Swabs with heavy faecal contamination should be discarded. In symptomatic patients, anorectal specimens should be obtained under direct vision following insertion of a proctoscope.

Oropharynx

Pharyngeal samples are suitable for culture (although sensitivity not defined). Nucleic acid tests are not well evaluated at this site and cross reactions with other species are possible.[1 26] Specimens are obtained by wiping a swab over the posterior pharynx, tonsils, and tonsillar crypts.

Urine

The first 15–30 ml of urine are collected after the patient has held urine for at least an hour. Urine samples should be tested using a NAAT. The sensitivity of testing urine using a NAAT to identify gonococcal infection in women is lower than testing an endocervical specimen[9 23] (evidence level III).

Vagina

Patient taken vaginal swabs or tampon specimens from the vagina are suitable for testing using a NAAT. Such samples offer a sensitive alternative for screening women who decline speculum examination or be would deterred from screening by the need for such an examination[8] (evidence level III).

N gonorrhoeae may infect the vaginal mucosa of prepubertal girls. Vaginal samples should be cultured in these circumstances in view of the implications of the diagnosis and to provide diagnostic certainty (recommendation grade C)

Bartholin's duct

When a Bartholin's abscess is present, purulent material expressed from the duct may be cultured and stained for microscopy.

Ophthalmic and systemic sites

Ophthalmic samples are suitable for culture. Conjunctival samples are obtained by wiping a swab over the inner lower eyelid. All patients must be referred to an ophthalmologist (recommendation grade C)

Proving infection in patients with suspected disseminated infection is sometimes difficult. Culture of blood and joint aspirate may confirm the diagnosis. Genital and pharyngeal samples should also be taken and have a higher yield in identifying the presence of *N gonorrhoeae*[1] (evidence level III).

SCREENING IN SPECIFIC PATIENT GROUPS

Infection of mucosal surfaces with *N gonorrhoeae* may be, and often is, asymptomatic. Screening procedures/protocols are influenced by sexual history. A wider number of sites may need to be tested in symptomatic compared with asympto-

matic individuals to include the symptomatic sites. A history of condom use for intercourse is generally not an indication to omit screening for gonorrhoea.

Heterosexual women

A single endocervical test (culture) will detect 85–95% of women infected with *N gonorrhoeae*.[19 20] The urethra is the sole site of infection in 6% of infected women.[19 20] There are no contempory data on how frequently the rectum and/or pharynx are the sole site of infection; historically this has been low.[20] Repeat testing gives a small increase in the diagnostic yield in women.[27] An endocervical test (culture or nucleic acid) should be regarded as a core screening test for *N gonorrhoeae* in asymptomatic women receiving a speculum examination in GUM clinics[28] (recommendation grade C). A urethral culture may be combined with a cervical culture on the same plate where direct plating is practised to increase sensitivity. Testing non-invasively collected samples (urine and vaginal or vulval samples) should currently be reserved for women not undergoing speculum examination (recommendation grade C). Non-invasive samples should be tested by a NAAT. Rectal and pharyngeal tests should be taken when directed by sexual history or symptoms (recommendation grade C).

Heterosexual men

Urethral swab or first catch urine test. Microscopy of a urethral smear may allow immediate presumptive diagnosis, but all men should receive a sensitive direct identification test (recommendation grade C).

Men who have sex with men

Tests should be taken from all sites (urethra, rectum, and oropharynx) potentially exposed to infection as directed by the sexual history (recommendation grade C). Rectal infection may be acquired by transmission from the oropharynx in the absence of penetrative anal intercourse.[29]

Women who have had a hysterectomy

Urethral swab for culture offers a better yield than high vaginal culture.[30]

''Young'' men and women

Testing in post-pubertal young men and women follows that in adults. Young people may be intimidated by the prospect of invasive tests and may prefer non-invasive options when available, notably urine testing.

Pregnancy

Screening tests as for heterosexual women.

Sex workers

Test all sites potentially exposed to infection as indicated by sexual history. Testing should generally proceed at sites apparently protected by consistent condom use (recommendation grade C).

Sexual assault

Culture is the recommended method for detecting *N gonorrhoeae* at all sites following sexual assault in adults because of 100% specificity (recommendation grade C). Tests should include all sites potentially exposed to infection.

Sexual contacts of individuals with gonococcal infection

Consider including rectal test in addition to endocervical and urethral tests in female contacts (recommendation grade C). Consider pharyngeal test in cases of oropharyngeal contact.

TEST OF CURE

Patients should be assessed after treatment. A test of cure is not routinely necessary when infection has been treated with a recommended directly observed therapy, symptoms have resolved, and there is no risk of re-infection. If the patient is symptomatic, and has received suboptimal treatment, a potentially resistant strain is identified on culture, or there is a possibility of re-infection, test of cure with culture is advised. Pregnancy does not impair treatment efficacy. Efficacy of treatment at eradicating pharyngeal infection is lower for some antimicrobials than their efficacy at anogenital sites.[31] Test of cure is recommended following treatment for pharyngeal infection (recommendation grade C).

FREQUENCY OF SCREENING IN ASYMPTOMATIC PATIENTS

Advice on frequency of screening in the absence of symptoms is dependent on individual risk for infection and is determined by pragmatism rather than prospective studies. Young people with a history of gonorrhoea may be at higher risk of repeat infection; encouragement for repeat screening may be prudent although screening intervals have not been defined.[32 33]

AUDITABLE OUTCOME MEASURES

- All men presenting with symptoms or signs suggestive of urethritis (urethral discharge/dysuria) should be tested for gonorrhoea.
- All women with symptoms suggestive of pelvic inflammation should be tested for gonorrhoea.
- All sexually active women aged $\leqslant$25 years with recent onset symptoms of vaginal discharge should be tested for gonorrhoea.
- All sexually active men and women aged $\leqslant$25 years requesting screening for STI should be offered a test for gonorrhoea.
- Test of cure should be performed in no more than 25% of patients treated for gonorrhoea in the genital tract.
- Test of cure should be offered to all patients with pharyngeal gonorrhoea.
- The sensitivity of microscopy, when performed, should exceed 90% for urethral samples in symptomatic men and exceed 40% for endocervical samples in symptomatic women.
- Patients tested for gonorrhoea should receive written information about STI and their prevention ($\geqslant$80%).

RIGOUR OF DEVELOPMENT

This guideline was obtained by searching the PubMed database from 1970 to October 2004 using the terms ''gonorrhoea'' and ''diagnosis''. All entries in the English language considered. The 2005 national guideline on the management of gonorrhoea in adults, the European guideline for the management of gonorrhoea, and the Centers for Disease Control and Prevention recommendations for screening tests to detect *Chlamydia trachomatis* and *Neisseria gonorrhoeae* infections—2002 were also consulted.

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REFERENCES

1 **Hook EW III**, Handsfield HH. Gonococcal infections in the adult. In: Holmes KK, Sparling PF, *et al*, eds. *Sexually transmitted diseases*. 3rd ed. New York: McGraw Hill, 1999:451–66.
2 **Sherrad J**, Barlow D. Gonorrhoea in men: clinical and diagnostic aspects. *Genitourin Med* 1996;**72**:422–6.
3 **Ison CA**. Laboratory methods in genitourinary medicine: methods of diagnosing gonorrhoea. *Genitourin Med* 1990;**66**:453–9.
4 **Jephcott AE**. Microbiological diagnosis of gonorrhoea. *Genitourin Med* 1997;**73**:245–52.
5 **Knapp JS**, Koumans EH. Neisseria and Branhamella. In: Murray PR, *et al*, eds. *Manual of clinical microbiology* 1999:586–603.
6 **Fitzgerald M**, Bedford C. National standards for the management of gonorrhoea. *Int J STD AIDS* 1996;**7**:298–300.
7 **Van Dyck E**, Ieven M, Pattyn S, *et al*. Detection of Chlamydia trachomatis and Neisseria gonorrhoeae by enzyme immunoassay, culture and three nucleic acid amplification tests. *J Clin Microbiol* 2001;**39**:1751–6.
8 **Knox J**, Tabrizi SN, Miller P, *et al*. Evaluation of self-collected samples for Chlamydia trachomatis, Neisseria gonorrhoeae, and Trichomonas vaginalis by polymerase chain reaction among women living in remote areas. *Sex Transm Dis* 2002;**29**:647–54.
9 **Van Doornum GJ**, Schouls LM, Pijl A, *et al*. Comparison between the LCx Probe system and the Cobas Amplicor system for the detection of Chlamydia trachomatis and Neisseria gonorrhoeae infections in patients attending a clinic for sexually transmitted diseases in Amsterdam, The Netherlands. *J Clin Microbiol* 2001;**39**:829–35.
10 **Palladino S**, Pearman JW, Kay ID, *et al*. Diagnosis of Chlamydia trachomatis and Neisseria gonorrhoeae, genitourinary infections in males by the Amplicor PCR assay of urines. *Diagn Microbiol Infect Dis* 1999;**33**:141–6.
11 **Akduman D**, Ehret JM, Messina K, *et al*. Evaluation of a strand displacement amplification (BD Probtec-SDA) for detection of Neisseria gonorrhoeae in urine specimens. *J Clin Microbiol* 2002;**40**:281–3.
12 **Moncada J**, Schachter J, Hook EW III, *et al*. The effect of urine testing in evaluations of the sensitivity of the Gen-Probe Aptima Combo 2 assay on endocervical swabs for Chalymdia trachomatis and Neisseria gonorrhoeae. *Sex Transm Dis* 2004;**31**:273–7.
13 **Golden MR**, Hughes JP, Cles LE, *et al*. Positive predictive value of Gen-Probe Aptima Combo 2 testing for Neisseria gonorrhoeae in a population of women with low prevalence of N gonorrhoeae infection. *Clin Infect Dis* 2004;**39**:1387–90.
14 **Katz AR**, Effler PV, Ohye RG, *et al*. False-positive gonorrhoea test results with a nucleic acid amplification test: the impact of low prevalence on positive predictive value. *Clin Infect Dis* 2004;**38**:814–9.
15 **Koumans EH**, Johnson RE, Knapp JS, *et al*. Laboratory testing for Neisseria gonorrhoeae by recently introduced nonculture tests: a performance review with clinical and public health considerations. *Clin Infect Dis* 1998;**27**:1171–80.
16 **Page-Shafer K**, Graves A, Kent C, *et al*. Increased sensitivity of DNA amplification testing for the detection of pharyngeal gonorrhoea in men who have sex with men. *Clin Infect Dis* 2002;**34**:173–6.
17 **Young H**, Anderson J, Moyes A, *et al*. Non-cultural detection of rectal and pharyngeal gonorrhoea by the Gen-Probe PACE-2 assay. *Genitourin Med* 1997;**73**:59–62.
18 **Young H**, Manavi K, McMillam A. Evaluation of ligase chain reaction for the non-cultural detection of rectal and pharyngeal gonorrhoea in men who have sex with men. *Sex Transm Infect* 2003;**79**:484–6.
19 **Ghanem M**, Radcliffe K, Allan P. The role of urethral samples in the diagnosis of gonorrhoea in women. *Int J STD AIDS* 2004;**15**:45–47.
20 **Barlow D**, Phillips I. Gonorrhoea in women. *Lancet* 1978;**i**:761–4.
21 **Singh B**, Cutler JC. The effect of vaginal lubricants on Neisseria gonorrhoeae. *Am J Obstet Gynecol* 1976;**126**:365–9.
22 **Martin DH**, Cammarata C, Van der Pol B, *et al*. Multicenter evaluation of Amplicor and automated Cobas Amplicor CT/NG tests for Neisseria gonorrhoeae. *J Clin Microbiol* 2000;**38**:3544–3549.
23 **Van Der Pol B**, Ferrero DV, Buck-Barrington L, *et al*. Multicenter evaluation of the BDProbeTec ET system for detection of Chlamydia trachomatis and Neisseria gonorrhoeae in urine specimens, female endocervical swabs and male urethral swabs. *J Clin Microbiol* 2001;**39**:1008–1016.
24 **Deheragoda P**. Diagnosis of rectal gonorrhoea by blind anorectal swabs compared with direct vision swabs taken via a proctoscope. *Br J Vener Dis* 1977;**53**:311–3.
25 **Kolator B**, Rodin P. Comparison of anal and rectal swabs in the diagnosis of anorectal gonorrhoea in women. *Br J Vener Dis* 1979;**55**:186–7.
26 **Palmer HM**, Mallinson H, Wood RL, *et al*. Evaluation of the specificities of five DNA amplification methods for detection of Neisseria gonorrhoeae. *J Clin Microbiol* 2003;**41**:835–7.
27 **Harry TC**, Rashid S, Saravanamuttu KM, *et al*. Is one diagnostic testing of multiple sites enough to detect gonorrhoea infection in women? *Int J STD AIDS* 1997;**8**:64–5.
28 **Center for Disease Control and Prevention**. Screening tests to detect Chlamydia trachomatis and Neisseria gonorrhoeae infections—2002. *MMWR* 2002;**51**:No RR-15.
29 **McMillan A**, Young H, Moyes A. Rectal gonorrhoea in homosexual men: source of infection. *Int J STD AIDS* 2000;**11**:284–7.
30 **Judson FN**, Ruder MA. Effect of hysterectomy on genital infections. *Br J Vener Dis* 1979;**55**:434–8.
31 **Bignell CJ**. Antibiotic treatment for gonorrhoea—clinical evidence for choice. *Genitourin Med* 1996;**72**:315–20.
32 **Fortenberry JD**, Brizendine EJ, Katz BP, *et al*. Subsequent sexually transmitted infections among adolescent women with genital infection due to Chlamydis trachomatis, Neisseria gonorrhoeae, or Trichomonas vaginalis. *Sex Transm Dis* 1999;**26**:26–32.
33 **Miller JM**, Maupin RT, Mestad RE, *et al*. Initial and repeated screening for gonorrhoea during pregnancy. *Sex Transm Dis* 2003;**30**:728–30.