

SCREENING

Screening asymptomatic men for non-specific urethritis

J C D Ross

For a clinical guideline to be of use, it needs to make clear recommendations for practice based on the available evidence. But what should be recommended when the evidence is finely balanced, limited and/or contradictory? An example of this is whether or not men without symptoms should be screened for non-specific urethritis (NSU)—a decision faced by virtually all clinicians working in sexually transmitted infection (STI) clinics every day. In many countries this practice was abandoned many years ago, but in others, particularly in the UK, it remains common.

If robust clinical trials are not available, then expert opinion forms the next level in the evidence hierarchy. The papers presented here provide an analysis of the

data on screening asymptomatic men for NSU, interpreted by experts who are familiar with the data and have considerable clinical experience. As you will see, they reach different conclusions. The purpose of presenting the arguments for and against in this forum are threefold. First, it draws together the available evidence and allows individual clinicians to make an informed choice about their own practice. Second, it clarifies the process that informed the decision not to recommend screening asymptomatic men for NSU in the recently published *UK national screening and testing guidelines for STIs*.¹ In this case the group commissioning the guidelines (clinical effectiveness group of the British Association for Sexual Health and HIV (BASHH))

reviewed the expert opinions and made a recommendation based on them. Third, it highlights the obvious gaps in our knowledge and indicates the need for further research. The main focus here needs to be on further defining the aetiology and pathogenesis of NSU, and on determining its long-term morbidity, especially regarding any effect on fertility in women.

The arguments for and against screening asymptomatic men for NSU are not clear-cut, but when an asymptomatic man walks into a clinic, clinicians have to make a decision, and not changing current practice is as active a choice as altering practice. The national guidelines and the information below should allow you to make the best choice for your patients based on what is currently known.

Sex Transm Infect 2007;**83**:79.
doi: 10.1136/sti.2007.025130

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Accepted 5 February 2007

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- Ross JD, Ison CA. UK national screening and testing guidelines for STIs. *Sex Transm Infect* 2006;**82**(Suppl IV):iv1–iv5.

Chlamydia trachomatis, is it still useful to perform urethral microscopy in all men attending STI clinics even when symptoms are absent? We believe not and present our argument below in the form of answers to the questions that reflective clinicians will ask themselves when confronted with this issue.

WILL IMPORTANT PATHOLOGY BE MISSED IN THE MEN?

There is no evidence that cases of *C trachomatis* infection would be missed. Although the sensitivity of chlamydia assays is not 100%, more modern NAATs such as the Aptima assay from Gen-Probe Inc (San Diego, California, USA) shows very high sensitivities for detecting chlamydia in men via either urethral swabs or urine specimens (97.5% and 96.2%, respectively).¹⁴ So the question becomes that of whether there are any serious causes of NGU once infection with *C trachomatis* has been excluded. Currently the only microorganism that is a candidate for this role is *Mycoplasma genitalium*. The evidence that this causes NGU in men is extremely strong,¹⁵ but NGU itself in men is a nuisance condition, not a serious disease. By analogy with chlamydia, the important question is

Urethral smear in asymptomatic men

Is the urethral smear necessary in asymptomatic men attending a genitourinary medicine clinic?

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Available evidence does not support the performance of urethral smears in asymptomatic men

Urethral microscopy has long been an integral part of screening for non-gonococcal urethritis (NGU) in men.¹ This made sense when reliable tests were not available for chlamydia, although it has long been recognised that the urethral smear is a poor investigation, having high rates of both inter-observer² and intra-observer²⁻³ error (hardly surprising when one pauses to consider how the test is carried out). Another important observation, made by Swartz and Kraus,¹ is that more than one half of cases of asymptomatic urethritis resolve after 1

week without any treatment. Although a number of microorganisms are associated with NGU, no pathogen is isolated in the majority of patients (table 1), particularly in asymptomatic men.⁴⁻¹² Moreover, there is no evidence that pathogen-negative NGU is a sexually transmitted infection (STI).¹³ Hence many patients are unnecessarily labelled as having an STI with all the associated implications for themselves and their partners. Now that accurate tests (nucleic acid amplification tests (NAATs)) are routinely available for the important pathogenic agent known to cause NGU,

Table 1 Pathogens isolated from urethra of men with urethritis in more recent studies (as percentage)

| Study | Population studied | <i>Chlamydia trachomatis</i> | <i>Mycoplasma genitalium</i> | <i>Trichomonas vaginalis</i> | Other | No pathogen |
|-------------------------------------|--------------------|------------------------------|------------------------------|------------------------------|-------|-------------|
| Bradshaw <i>et al</i> ⁶ | Only symptomatic | 20 | 9 | 1 | 7 | 63 |
| Falk <i>et al</i> ⁵ | >10 PMN/hpf | 22.5 | 12.5 | | | 65 |
| Anagnrius <i>et al</i> ⁴ | All attendees | 7.4 | 7.7 | | | 84.9 |
| Geisler <i>et al</i> ²⁰ | All attendees | 27 | Not done | | | 73 |
| Marrazzo <i>et al</i> ⁷ | All attendees | 17 | Not done | | | 83 |

PMN, polymorphonuclear leucocytes; hpf, high power field.

whether *M genitalium* is an important cause of pelvic inflammatory disease (PID) and its serious sequelae (such as tubal infertility) in women. This has yet to be proven.¹⁵ Although *M genitalium* is associated with inflammation of the female genital tract,¹⁶ it must be remembered that the demonstration of an association does not by itself establish causation; other proofs need to be provided, in particular natural history and intervention studies, which have yet to be carried out in the case of *M genitalium* and PID. Moreover, most cases of *M genitalium* are symptomatic⁵ and the organism is found in only 5–6% of asymptomatic men,^{4, 5, 8, 10} over 90% of whom will have negative microscopy and hence would not be picked up by a urethral smear.^{5, 7} In addition, there are no studies that show that a Gram-stained urethral smear will detect cases of chlamydial infection in asymptomatic men that have been missed by NAAT. Indeed, it is likely that the rare cases of NAAT-negative chlamydia will be in those men with a low chlamydial load and a correspondingly low inflammatory response, which will therefore not lead to an abnormal urethral smear.^{12, 17, 18}

Complications other than PID do occur, for example epididymo-orchitis. The most important known cause of this is *C trachomatis* for which of course a sensitive

test in the form of a NAAT is now routinely available. There is no evidence that adding a urethral smear to such a test in asymptomatic men will prevent any additional cases of epididymo-orchitis. In addition, this condition does not in any case result in any serious consequences comparable to PID in women (especially infertility).

Several other microorganisms have been shown to be associated with NGU, namely *Trichomonas vaginalis*, herpes simplex virus and adenoviruses, but studies show them to be rarely present (0.4–4% of cases^{7, 19, 20}), and, as they are also not responsible for serious sequelae in men or their partners, it is not important to detect asymptomatic cases.

MIGHT SOME OTHER SIGNIFICANT, AS YET UNDISCOVERED, PATHOGEN BE MISSED?

It is of course impossible to answer this because by definition the answer is currently unknown. However, it is hardly an argument for using this technique to say that such a pathogen might at some point be discovered, and that the Gram-stained urethral smear will be the best means of detecting it. If new evidence becomes available in the future on this point, then of course guidelines should be changed appropriately.

Table 2 Consequences of omitting a urethral smear in asymptomatic men attending a clinic for sexually transmitted infections

| Study | Diagnosis of <i>C trachomatis</i> delayed* | Diagnosis of <i>M genitalium</i> missed† | No pathogen present‡ | Urethritis on microscopy¶ but no pathogen present | Reference |
|-------------------------------|--|--|----------------------|---|-----------|
| Anagnrius <i>et al</i> , 2005 | 2.9 | 2.9 | 94 | 39 | 4 |
| Falk <i>et al</i> , 2004 | 8.2 | 1.6 | 89 | 35 | 5 |
| Leung <i>et al</i> , 2006 | N/A | 1.8 | 83 | N/A | 8 |
| Marrazzo <i>et al</i> , 2001 | 3.4 | N/A | N/A | N/A | 9 |

Values are percentages. N/A, data not contained in study report.

*Positive microscopic result in men who tested positive for *C trachomatis*.

†But not proven that this is of any clinical significance in asymptomatic men (see text).

‡Absence of both *C trachomatis* and *M genitalium*.

¶>4 polymorphonuclear leucocytes per high power field.

WILL IMPORTANT PATHOLOGY BE MISSED IN THE FEMALE PARTNERS?

A number of studies have addressed this question. Some have shown that chlamydia can be isolated in some female partners attending as contacts of men in whom chlamydia was not detected by NAAT, but who did have NGU on microscopy. In a study by Manavi *et al*,²¹ chlamydia was detected in 8% of the female partners of chlamydia-negative men with asymptomatic NGU, and Tait and Hart²² found chlamydia in 5% of female contacts of men with chlamydia-negative NGU (although whether the urethritis in those male index cases was asymptomatic was not specified in that paper; clearly 5% is the maximum possible figure). However, these prevalences of chlamydia are no higher than would be expected among female attendees at STI clinics in any case. Two other studies showed higher rates, but these were based on very small numbers of positive cases: just four²³ and six.²⁴ Moreover, the latter two studies were retrospective, opening up the real possibility of a major selection bias. Overall therefore, although these are interesting observations worthy of further study, they do not represent a serious argument for recommending urethral smears in asymptomatic men as a universal approach.

WILL DIAGNOSIS AND TREATMENT OF INFECTION BE DELAYED?

From the published studies, 17–36% of men with chlamydia will have no symptoms, but will show microscopic evidence of infection.^{4, 5, 9, 22} Hence, performing the smear can lead to immediate treatment in these men, otherwise there will be a short delay pending the results of tests for chlamydia. However, this is an argument for clinics to review their protocols for informing patients of their results, and treating them in a timely manner. The results of audits indicate that very few (<1%) patients need remain untreated in practice.²⁵ This suggests that any additional spread of chlamydia in the community as a result of a short delay in treating some men with chlamydia is unlikely to be important. Certainly there is no evidence to the contrary, whereas far greater harm will be done by the over-diagnosis of an STI in the much greater number of men with asymptomatic urethritis of no clinical significance (table 2).

In the real world, 100% diagnostic accuracy is nearly always unachievable. The issue is therefore that of “doing the least harm”. To over-diagnose and over-treat these men for a condition, however one explains it to them, and to advise them that their partners should also be seen, examined and treated, must inevitably result in much unnecessary anxiety and damage to relationships. This harm must be balanced

against the benefit of avoiding slightly delayed diagnosis in a proportion of cases and potential loss to follow-up in a few.

IS THERE A ROLE FOR ROUTINE USE OF THE LEUCOCYTE ESTERASE TEST?

Marrazzo *et al*⁹ have shown that, in a population screening strategy for chlamydia, the leucocyte esterase test on urine may reduce costs because of a reasonable negative predictive value. However, the positive predictive value of this test in asymptomatic men was only 20.1%. With a sensitivity similar to that of the smear (66.7% versus 65.3%, respectively) but an inferior specificity (76.8% versus 85.5%), an approach based on the leucocyte esterase test would in fact perform even worse than one based on smears.

CONCLUSION

It is quite clear that NGU remains a condition that defies a comprehensive explanation.¹³ A urethral smear will continue to remain an integral part of the clinical examination in men presenting with symptoms of urethritis, not least because of its utility in providing an immediate diagnosis of gonorrhoea. Although further research is needed, available evidence does not favour retaining the present practice of physically examining or performing urethral smears in asymptomatic men. It is time that practice was modernised to reflect the availability of sensitive and specific tests for the only serious pathogen known to be a cause of NGU, and time to stop producing “urethral cripples” on the basis of an unreliable and outdated investigation that has already been abandoned in many countries.

Sex Transm Infect 2007;**83**:79–81.
doi: 10.1136/sti.2006.024653

Urethritis testing in asymptomatic men

Asymptomatic men: should they be tested for urethritis?

Paddy Horner

More research is needed to determine the cost effectiveness of testing for urethritis

Although more evidence has accumulated since questioning the role of testing for urethritis in asymptomatic men in 2002,¹ there is as yet no definitive answer. Men with asymptomatic

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could do more harm than good in high risk asymptomatic men.

Testing for urethritis in men attending departments of genitourinary medicine has the following purposes.

- To allow immediate treatment of men with *C trachomatis* and/or *M genitalium* with an associated reduction in on-going transmission in the community.^{2,3} Currently there is no commercial test for *M genitalium*.
- To identify partners who may be at increased risk of these infections despite the index patient testing negative for *C trachomatis* and/or *M genitalium*.^{2,4-6}
- For men at high risk of HIV, it is a potential marker for increased HIV susceptibility and infectivity.²