

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*<sup>9</sup> 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.<sup>13</sup> 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pathogen known to be a cause of NGU, and time to stop producing “urethral cripples” on the basis of an unreliable and outdated investigation that has already been abandoned in many countries.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,<sup>1</sup> there is as yet no definitive answer. Men with asymptomatic

**Authors’ affiliations**

**M Shahmanesh, K W Radcliffe**, Department of Genitourinary Medicine, Whittall Street Clinic, Whittall Street, Birmingham, UK

Correspondence to: Dr K W Radcliffe, Whittall Street Clinic, Whittall Street, Birmingham B4 6DH, UK; Keith.W.Radcliffe@hobtpct.nhs.uk

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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 ongoing transmission in the community.<sup>2,3</sup> 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*.<sup>2,4-6</sup>
- For men at high risk of HIV, it is a potential marker for increased HIV susceptibility and infectivity.<sup>2</sup>

**Table 1** Estimated risk of having *Chlamydia trachomatis* and/or *Mycoplasma genitalium* in high risk young men with and without urethritis (Gram-stained urethral smear with or without first passed urine Gram-stained thread<sup>17</sup>), and their partners, depending on clinical findings

Clinical findings of index male attending Department of Genitourinary Medicine			Risk of <i>C trachomatis</i> and/or <i>M genitalium</i>	
Discharge* and/or dysuria	Penile irritation	Urethritis	Index male	Partner(s)†
Yes	+/-	Yes	45–55% <sup>5 9 10</sup>	High <sup>5 6</sup>
No	Yes	Yes	15–25%‡ <sup>1 7 13 20</sup>	Moderate†
No	No	Yes	10–20%‡ <sup>1 2 5 7 8 16 28</sup>	Moderate to low† <sup>4 6 8 28</sup>
Yes	+/-	No	10% <sup>1 5 7</sup>	Unknown
No	Yes	No	<10%	Low
No	No	No	3% <sup>1 5 7 16</sup>	Low

\*Either as a symptom or clinical sign.

†High, 40–50%; moderate, 15–25%; low, <10%. Assumes that the partner of a man with urethritis who has tested positive for *C trachomatis* and/or *M genitalium* has a 66% risk of also testing positive,<sup>5 29 30</sup> and the partner of a man who has tested negative has a 5–25% risk.<sup>4 6 8 28</sup>

‡Exact risk difficult to quantify because of variation in definition of “asymptomatic” in clinical studies; see text.

- High negative predictive value (NPV) (>97%) for *C trachomatis* and/or *M genitalium* in those without urethritis.<sup>5 7</sup>

### ANALYSIS OF CURRENT LITERATURE ON URETHRITIS WITH A UNIFYING HYPOTHESIS ON THE AETIOLOGY

The literature on urethritis is full of contradictory findings, which make interpretation difficult. I believe that we need to be able to explain these conflicting observations, in order to understand the true value of testing for urethritis in clinical practice. For example (1) Angarius *et al* detected *C trachomatis* and/or *M genitalium* in only 26% of men with acute urethritis, whereas Falk *et al*, Totten *et al* and Horner *et al* observed >45%.<sup>3 8–10</sup> (2) Why do some studies show that urethritis identifies >80% of people with *C trachomatis* (and *M genitalium*)<sup>5 7 8 11</sup> but others do not?<sup>12 13</sup>

### Possible explanations for conflicting observations

- (1) In some studies the urethral smear was more representative of the urethral inflammatory response than others. This will be related to both the technique of obtaining and preparing the urethral smear and probably how long patients have held their urine (given the long-standing clinical practice of undertaking an early morning smear in symptomatic patients who initially test negative for urethritis). There is no internationally recognised standardised technique for testing for urethritis. There are at least five different methodologies in the literature for diagnosing urethritis,<sup>1 5 7 9 13</sup> and in one recent study

patients only had to be symptomatic to be defined as having urethritis!<sup>12</sup> In addition, inter-observer and intra-observer error, especially in samples with low-grade inflammation (5–20 polymorphonuclear leucocytes/ high power field), may also play a role.<sup>13–15</sup>

- (2) The populations studied varied in degree of risk (behaviour and age) for having a sexually transmitted infection (*C trachomatis* detection is associated with a younger age<sup>16</sup>).
- (3) Some studies do not distinguish men with penile irritation/discomfort from those with dysuria or discharge, as the former are at decreased risk of asexually transmitted infection (STI).<sup>1 7 13</sup>
- (4) There is confusion about the term “asymptomatic” which is often assumed to mean that the person does not have a urethral discharge. About 10% of men will have a discharge on examination which is not reported as a symptom.<sup>7</sup> *M genitalium* is associated with urethral discharge.<sup>5 7</sup>

### Other causes of urethritis

Partner studies, although limited, suggest that up to 25% of patients with microorganism-negative acute urethritis may have a partner infected with either *C trachomatis* or *M genitalium*.<sup>2 4–6</sup> Although ureaplasmas can cause urethritis, their exact role remains unclear and probably only account for ~5–15% of acute urethritis.<sup>17 18</sup> The importance of *Trichomonas vaginalis* probably depends on the prevalence in the local population.<sup>17</sup> Herpes, adenovirus and urinary tract infections probably account for <5% each.<sup>17 19</sup> What causes the remainder is not known. It

remains to be shown whether another major pathogen will be identified.

### Unifying hypothesis

My group's work suggests that the risk of an STI increases as the degree of inflammation increases and that the symptoms, discharge, dysuria and/or an observable discharge, are surrogate markers for the degree of inflammation.<sup>20</sup> Or looked at the other way round, it implies that urethritis can have non-pathogenic causes—for example, bacterial vaginosis<sup>2 21</sup>—and this is more likely in men with low-grade urethritis. This challenges the idea of having a simple cut-off and labelling all those with <5 polymorphonuclear cells per high power field as at low risk of having a *C trachomatis* and/or *M genitalium* infection, and all those with ≥5 polymorphonuclear cells per high power field as at high risk. Thus men with asymptomatic urethritis are more likely to have a low-grade urethritis with a lower risk of being caused by an STI than if they were symptomatic, but at increased risk compared with asymptomatic men without urethritis. This reduced risk also probably applies to their partner(s) testing positive for an STI even if they test microorganism negative, although the evidence is conflicting.<sup>4 6</sup>

To fully assess a patient's risk (and that of their partner(s)) of having either infection, one needs to consider, age, sexual behaviour, clinical presentation, and the results of testing for urethritis. Table 1 details the estimated risks according to clinical findings based on published evidence currently available.

### IS THE GRAM-STAINED URETHRAL SMEAR THE BEST METHOD FOR DETECTING URETHRITIS?

As hypothesised in (1) above, it is likely that a Gram-stained urethral smear is more reliable in some centres than others in detecting urethritis. The technique described by Wiggins *et al*,<sup>20</sup> although too complex for routine clinical practice, offers the opportunity of investigating how best to obtain, and evaluate, a specimen that is representative of the urethral inflammatory response. This would provide an objective evidence base for not only helping to interpret studies but also to develop an international standard for future research which can then be translated into clinical practice.

### Potential role of leucocyte esterase testing in asymptomatic men

Given the variability of a Gram-stained urethral smear in detecting urethritis (see above), especially at low grades,<sup>15</sup> are there other ways of testing for urethritis? Although the leucocyte esterase test has

insufficient sensitivity to detect urethritis,<sup>17</sup> Marrazzo *et al*<sup>16</sup> observed in a study of over 1500 asymptomatic men using a nucleic acid amplification technique (NAAT) that the leucocyte esterase test had a positive predictive value (PPV) of 13% and an NPV of 97.7% for the detection of *C trachomatis* compared with 20% and 97.8% for the Gram-stained urethral smear. Horner and Taylor-Robinson<sup>22</sup> have recently argued that the leucocyte esterase test, which is both inexpensive and non-invasive, offers an interim, evidence-based, solution to the issue of whether asymptomatic men attending departments of genitourinary medicine should be screened for the presence of urethral inflammation.

### CLINICAL ROLE OF TESTING FOR URETHRITIS IN ASYMPTOMATIC MEN

The questions are therefore (1) is this of benefit to the patient and the public health and (2) could testing do more harm than good (to be addressed by Dr Shahmanesh in accompanying editorial)?

If we consider rationalising/minimising testing for asymptomatic men, there are a number of options available.

- (1) Use NAATs for *C trachomatis* and *Neisseria gonorrhoeae* on a first catch urine specimen only<sup>22</sup> with all gonococcal-positives confirmed by culture. It is well recognised that some men with *N gonorrhoeae* are asymptomatic<sup>2</sup> and would be missed if the micro-organism was not tested for, and Horner and Taylor-Robinson<sup>22</sup> advocate testing for both, but acknowledge the increased risk of false-positives not only because it is a low-prevalence population<sup>23</sup> but also because some NAATs can detect commensal *Neisseria* species.<sup>24–26</sup>
- (2) As for (1) but examine and only undertake a Gram-stained urethral smear for those with a discharge.
- (3) As for (2) but include a leucocyte esterase test on those without a discharge.

The disadvantages of option (1) are:

- Failure to identify about 10% of men who are unaware of their urethral discharge. This group and their partners are at high risk of an STI, in particular *M genitalium* (table 1)<sup>2 5 7</sup>
- May result in other pathology being missed in some men
- Misses the opportunity of the intimacy of a genital examination to help enable the patients to disclose concerns of a deeply personal nature

- A group of men and their partners(s) with 10–20% (urethritis positive) risk of *C trachomatis* and/or *M genitalium* as per table 1 will be missed

Option (2) would address the first three of these points, and option (3) all of them. Although the leucocyte esterase test has a lower PPV than a Gram-stained urethral smear (see above), it still has a high NPV (>97.5%)—that is, those with a negative leucocyte esterase test are at a substantially lower risk of having an STI.<sup>16</sup>

Option (3) was introduced in 2006 in Bristol, with the examination being optional for the patient. This strategy is likely to be most cost effective in: (1) younger men (<25 years old) with high risk behaviour in whom (a) the PPV for an STI will be highest (23% for *C trachomatis*)<sup>16</sup> and (b) the risk of transmitting an STI to a new sexual partner before microbiological results are available is greatest<sup>3 27</sup>; (2) men at increased risk of HIV, as inflammation increases both susceptibility and infectivity.<sup>2</sup> It is also likely to be preferred by patients who have had a casual relationship within a regular relationship, because of the improved NPV associated with a failure to detect urethritis.

### CONCLUSION

As genitourinary physicians, we need to decide whether it is an effective use of our resources to make a complete assessment of a man's risk of having or being recently exposed to an STI. In order to do this, I believe that we need to consider, age, sexual behaviour, clinical presentation, and the results of testing for urethritis. A complete risk assessment potentially makes the consultation more complex, but need not be significantly more time consuming during the initial assessment, if we use non-invasive testing for both *N gonorrhoeae* and *C trachomatis* and urethritis using a NAAT and leucocyte esterase test respectively.<sup>22</sup> Given the increasing pressure to achieve the government's 48-hour access target for departments of genitourinary medicine<sup>31</sup> and the fact that better utilisation of resources must be part of the solution, this would seem a reasonable evidence-based compromise in the debate about testing for urethritis in asymptomatic men.<sup>22</sup> Clearly more research, with standardised methodology, to allow rapid translation of findings into clinical practice, is urgently required on the aetiology, diagnosis, acceptability and cost effectiveness of testing for urethritis in departments of genitourinary medicine.

*Sex Transm Infect* 2007;**83**:81–84.  
doi: 10.1136/sti.2006.024414

Correspondence to: Dr Horner, the Milne Centre, Bristol Royal Infirmary, Lower Maudlin Street, Bristol BS2 8HW, UK; paddy.horner@bristol.ac.uk

Dr P J Horner would like to thank the Jefferiss Trust for its support and Dr Judith Berry for her helpful comments on the manuscript.

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