Reviewer's report

Title: Management of non-gonococcal urethritis

Version: 5  
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Reviewer: Lisa E Manhart

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Overview: This paper summarizes the published evidence on the aetiology of nongonococcal urethritis and diagnostic methods, and provides recommendations for clinical management. The information is presented in the same manner in which clinical guidelines are presented.

Major Compulsory Revisions

1. There is a striking similarity between this paper and the recently published 2015 UK National Guideline on the management of non-gonococcal urethritis (Int J STD AIDS 2015 May 22, Epub ahead of print), yet the published paper is not referenced. Given the similarities, the 2015 UK National Guideline should be referenced.

2. There are a number of broad declaratory statements that are supported by only one or two references and this does not always reflect the breadth of the literature that exists. Ideally, a broader spectrum of supporting literature would be cited (where applicable).

3. In the first paragraph under the heading “Investigations”, the second sentence indicates that “…if available, specific tests for M. genitalium, Trichomonas vaginalis, adenovirus and HSV should be taken…” Since T vaginalis is of relatively low prevalence in most settings, and adenovirus and HSV typically account for no more than ~2% of cases of urethritis, it is surprising that routine testing for these organisms is recommended (where diagnostics are available). Could the authors expand on the rationale for this recommendation?

Minor Essential Revisions

1. In the first paragraph under the heading “Clinical features and signs”, only mucopurulent discharge is listed as characteristic of NGU, yet cases of NGU can also have cloudy or clear discharge and cloudy/clear discharge is often characteristic of chlamydial infections. This also arises under the “Treatment” section where the recommendation is to only treat when the patient has “…purulent or mucopurulent discharge…”. This would suggest that a man with a cloudy or clear discharge (with or without elevated PMNs) would not be treated, yet this clinical presentation may characterize chlamydial infection.

2. Under the heading “Complications” there are two incomplete sentences and no additional text. Could the authors expand, perhaps indicating how commonly these complications of NGU occur?
3. It appears that the 5 day azithromycin regimen with an initial dose of 1g is being recommended, yet this is unfamiliar. Has the use of this variation on the extended regimen been reported in the literature? Could the authors articulate the reason for recommending this over the standard extended dose that begins with an initial dose of 500mg?

Discretionary Revisions
1. Not all would agree with the recommendation that doxycycline should be used as first line treatment for NGU. Could the authors include some mention of the fact that there is not universal agreement about this?

Minor Issues not for Publication
1. On p. 1, at the end of the first paragraph under the heading “Aetiology”, the reference supporting the last sentence is Sena et al, JID 2012 (ref #11), yet this paper describes treatment failures. The statement would be better supported by studies that assessed primary cases of pathogen-negative NGU.

2. At the bottom of p. 1, the second to last sentence states “… and therefore detection of this microorganism is not recommended as a screening test” is unclear. Was the goal to note that testing men with NGU for U. urealyticum is not recommended?

3. The last reference in the 3rd paragraph under the heading “Clinical features and signs”, the Rietmeijer STD 2012 (ref #37) does not appear to correspond to the statement about patient preferences for sampling urethral discharge. Is there an alternate reference for this statement?

4. Under the heading “Treatment”, the word ‘is’ should be changed to ‘are’. Additionally, the reference (#44) refers to a paper on M. genitalium and does not support the statement that stained urethral smears are recommended for the detection of Neisseria gonorrhoeae.

5. In the third paragraph under the heading “Treatment”, the statement that single dose azithromycin is thought to induce macrolide resistance in M. genitalium to a higher extent than the five day regimen is not r

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I have received test kits and reagents from Gen-Probe/Hologic, and have served on scientific advisory boards for Qiagen, Inc. and Hologic, Inc.