Author's response to reviews

Title: Management of non-gonococcal urethritis

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Version: 7  Date: 13 July 2015

Author's response to reviews: see over
Dear dr. Hilary Logan,

Article: Management of non-gonococcal urethritis

These were the requests:

Referee 1:
http://www.biomedcentral/imedia/1595138425177264_comment.pdf

Referee 2 (you have responded to, I include this for reference):
http://www.biomedcentral/imedia/7816071821776231_comment.pdf

Additional Editorial requests
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1) Please provide the email addresses of all of the authors on the title page
2) Please provide an Abstract - a short, unstructured, single paragraph summary, no more than 350 words, of the major points raised, making evident the key work highlighted in the article. (I note you have done this, but you have added it as a file to the end of your manuscript. Please could you add it to the main manuscript itself).
3) Please provide three to ten keywords representing the main content of the article.
4) Please move the "Declaration of Interest" to before the References and rename it "Competing Interests".
5) Please provide an Author contributions statement (sorry, I have to ask for this even for reviews, for example you can just say HM, KB and PJH performed research and wrote the paper).

Please could you perform these revisions as requested and add them to your manuscript and to your point-by-point reply to the second reviewer?

Please also ensure that your revised manuscript conforms to the journal style (http://www.biomedcentral/info/ifora/medicine_journals). It is important that your files are correctly formatted.

Comments referee 1:

Major compulsory revision:
- Treatment – on page 4 the authors make the dogmatic statement that “Doxycycline …should be used as first line treatment.” This is despite the fact that in the same section they say that two recent RCTs from the US showed no difference in the clinical response rate of Doxycycline and Azithromycin, and that there are no randomised studies comparing different regimens of Azithromycin in men with acute NGU. In the face of this shortage of evidence I think they need to substantiate this dogmatic statement about using Doxycycline first line more
It is correct that there is a lack of randomized controlled studies, and that the clinical response rate of Doxycycline and Azithromycin is almost the same.

However, it has been shown that the rate of macrolide resistant strains of *M. genitalium* is increasing in some countries. An obvious reason is that using azithromycin as first line treatment without TOC for *M. genitalium*, azithromycin will induce resistance in some cases, and already macrolide resistant strains of MG will not be cured. Most of them are asymptomatic after azithromycin, probably because the bacterial load is reduced after Azithromycin treatment, but with a risk of recurrence. Jørgen Skov Jensen and Lars Falk has shown in a submitted paper that those converting to macrolide resistance during azithromycin treatment, often have negative NAAT direct after treatment, but are positive at 3-4 week TOC. Without TOC, the patients will think they are cured, and spread the macrolide resistant strains. Using azithromycin as first line NGU treatment will cure the susceptible strains, but select the macrolide resistant strains, which will increase in the population when not detected by TOC and subsequent treated with moxifloxacin. Doxy as first line treatment will eradicate almost all chlamydia, 1/3 mycoplasma without inducing resistance, and most ureaplasma and BV associated infections. Using a lot of azithromycin as first line treatment without testing for M genitalium will possibly end up with a 100% macrolide resistance like in Greenland, because the macrolide susceptible strains will be eradicated and the resistant left and spread.

If already macrolide resistant, single dose or 5 days do not matter. But it is possible, but not definitely proven, that single dose will convert some more wildtype strains to resistant strains.

We have substantiated the dogmatic statement in the article about using Doxycycline first line as follows:

Doxycycline has a somewhat higher cure rate in *C. trachomatis* than azithromycin [49-50], cures 20 - 40% of *M. genitalium* without inducing macrolide resistance, and should be used as first line treatment.

Azithromycin 1 gram stat is widely used as first line treatment for NGU, has a comparable efficacy against chlamydia as doxycycline, and will cure 60-80% of *M. genitalium*. However, azithromycin, especially the single 1 gram regimen, will induce macrolide resistance in some *M. genitalium* strains [52], and will cure only the macrolide susceptible strains. Thus, without a test of cure (TOC) for *M. genitalium* and subsequent moxifloxacin treatment of treatment failures, the macrolide resistant strains will be selected and further spread. As a consequence, the proportion of macrolide resistant strains in the population will increase. The extensive use of azithromycin 1 gram for treatment of NGU without a TOC for *M. genitalium* may explain the declining cure rates [49]. In Greenland, with a small population of 55,000 inhabitants, a very high incidence of NGU and extensive use of single dose azithromycin, the macrolide resistance rate of *M. genitalium* has been shown to be 100% [53], with a high and comparable incidence of chlamydia and *M. genitalium*.

A single dose is easier to administrate, with a possible higher compliance, but there is no evidence that single dose Azithromycin has a higher cure rate against chlamydia than 7 days doxycycline.
Reviewer's report:
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.

Answer: The 2015 UK National Guidelines and the 2015 IUSTI Europe nongonococcal guidelines have been referenced. The UK guidelines were published in May after the current article was submitted. The 2015 IUSTI Europe Guidelines are almost ready to be published, and will be available in the IUSTI website before the current article is published. The text has been rephrased and copyedited in order to eliminate the same phrases as much as possible between this article and the BASHH and IUSTI European Guidelines. However, since the two authors of the current article have been involved in writing these two guidelines, similarities will occur, and we think such similarities cannot be stated as plagiarism.

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).
Answer: We think this is an overview article with limited space. We have therefore chosen only to use one or two references, and not the breadth of the literature. Both referenced guidelines contain extended references.

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?

Answer: We agree, only NAAT for Chlamydia and M. genitalium should be taken routinely after excluding gonorrhoea. However, if suspected because of clinical or epidemiological reasons, tests for Trichomonas vaginalis, adenovirus and HSV should also be included.

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.

Answer: Under Clinical features and signs, “but may be cloudy or clear” has been added.

We do not agree that sparse cloudy or clear discharge should be treated syndromically without microscopically or aetiological confirmation. This will result in misuse of antibiotics, treating healthy men who have squeezed their urethra enough to get some mucous discharge is inappropriate.

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?
Answer: The following sentence has been added: In men younger than 40 years-of-age with acute epididymitis, C. trachomatis is a major pathogen. The prevalence of genital mycoplasmas and ureaplasmas are lower, and the role of genital mycoplasmas and ureaplasmas in the development of acute epididymitis remains to be determined.

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?

Answer: There is some evidence that a single 1 gram azithromycin regimen results in more macrolide resistance than a five days treatment. Theoretically, a 1 gram initial dosage followed by a four days 250 mg should reduce the resistance pressure. However, this is, as stated, only an expert opinion, and must be confirmed in randomized trials.

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?

Answer: We think the widely use of azithromycin as first line treatment without M. genitalium diagnostics and TOC will result in increasing M. genitalium resistance in the population. We have added:

Azithromycin 1 gram stat is widely used as first line treatment for NGU, has a comparable efficacy against chlamydia as doxycycline, and will cure 60-80% of *M. genitalium*. However, azithromycin, especially the single 1 gram regimen, will induce macrolide resistance in some *M. genitalium* strains, and will cure only the macrolide susceptible strains. Thus, without test of cure for *M. genitalium* and moxifloxacin treatment of treatment failures, the macrolide resistant strains will be selected and further spread. As a consequence, the proportion of macrolide resistant strains in the population will increase. The extensive use of azithromycin for treatment of NGU without TOC for *M. genitalium* may explain the declining cure rates [49]. In Greenland, with a small population of 55 000 inhabitants, a very high incidence of NGU and extensive use of single dose azithromycin, the macrolide resistance rate of *M. genitalium* has been shown to be 100% [52], with a high and comparable incidence of chlamydia and *M. genitalium*. 
A single dose is easier to administrate, with a possible higher compliance, but there is no evidence that single dose Azithromycin has a higher cure rate against chlamydia than 7 days doxycycline.

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?
   Answer: Agree that the sentence was unclear. We have changed to: U. urealyticum may account for 5-10% of cases of acute NGU, but is often detected without urethritis, and therefore screening and test of cure for this micro-organism is questionnable

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?
   Answer: Rietmeijer and Mettenbrink in their article about sampling urethral smear for microscopy describes that they sample the smear direct on the slide without using a swab if there is visible discharge. This technique will probably be preferred by the patients.

4. Under the heading “Treatment”, the word ‘is’ should be changed to ‘are’.
   Should is be changed to are in this sentence?
   The most important step in syndromic management of urethritis is determining whether N. gonorrhoeae is present during the initial clinic visit.

   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.

Answer: The ref has been changed to 31: Taylor SN, DiCarlo RP, Martin DH. Comparison of
methylene blue/gentian violet stain to Gram's stain for the rapid diagnosis of gonococcal urethritis
in men.

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


Observations from a Swedish STD Clinic.
PLoS ONE 2013, 8:e61481.

1) Please provide the email addresses of all of the authors on the title page
Done
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of the major points raised, making evident the key work highlighted in the article. (I note you have done
this, but you have added it as a file to the end of your manuscript. Please could you add it to the main
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example you can just say HM, KB and PJH performed research and wrote the paper).
Done

2) The reference list is corrected, et al is substituted with all names.

I hope the manuscript will now be accepted

Best regards

Harald Moi