Author's response to reviews

Title: Management of non-gonococcal urethritis

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

Thank you for the comments from professor Chen.

I have changed as follows:

Abstract:

*If doxycycline was given as first therapy, azithromycin five days plus metronidazole 4-500 mg twice daily for 5-7 days should be given. If azithromycin was prescribed as first therapy, doxycycline 100 mg x 2 for one week plus metronidazole, or moxifloxacin 400 mg orally once daily for 7-14 days should be given.*

To:

Evidence for the following recommendations is limited, and is based on clinical experience and guidelines. If doxycycline was given as first therapy, azithromycin five days plus metronidazole 4-500 mg twice daily for 5-7 days should be given. If azithromycin was prescribed as first therapy, doxycycline 100 mg x 2 for one week plus metronidazole, or moxifloxacin 400 mg orally once daily for 7-14 days should be given.

*If reinfection is unlikely at follow-up, the patient is symptomatic or an observable discharge is present or microscopic evidence of urethritis is confirmed, re-treatment should be given. If doxycycline was prescribed as first line therapy, switch to Azithromycin 500 mg or 1gram day one, then 250 mg once daily for 4 days plus metronidazole 4-500 mg twice daily for 5 days. If azithromycin was prescribed as first line therapy, doxycycline 100 mg twice daily for 7 days plus metronidazole 4-500 mg twice daily for 5-7 days should be prescribed. However, if positive for M. genitalium at TOC after azithromycin treatment without suspected re-infection, or in case of positive macrolide resistant test, Moxifloxacin 400 mg orally once daily for 7-14 days should be given.*

To:

If reinfection is unlikely at follow-up, the patient has completed the initial course of therapy, is symptomatic and an observable discharge is present or microscopic evidence of urethritis is confirmed, re-treatment should be given. Any treatment of persistent NGU should cover *M. genitalium* and *T. vaginalis* and/or bacterial vaginosis associated bacteria. However, evidence for the following recommendations is limited, and is based on clinical experience and guidelines [59], [60]. If doxycycline was prescribed as first line therapy, switch to Azithromycin 500 mg or 1gram day one, then 250 mg once daily for 4 days plus metronidazole 4-500 mg twice daily for 5 days. If azithromycin was prescribed as first line therapy, doxycycline 100 mg twice daily for 7 days plus metronidazole 4-500 mg twice daily for 5-7 days should be prescribed. However, if positive for M. genitalium at TOC after azithromycin treatment without suspected re-infection, or in case of positive macrolide resistant test, Moxifloxacin 400 mg orally once daily for 7-14 days should be given.
5-7 days should be prescribed. However, if positive for *M. genitalium* at TOC after azithromycin treatment without suspected re-infection, or in case of positive macrolide resistant test, Moxifloxacin 400 mg orally once daily for 7-14 days should be given.

*The three sentences below seem to be contradictory. Could the authors please reword as appropriate.*

Doxycycline has a somewhat higher cure rate in *C. trachomatis* than azithromycin

Azithromycin 1 gram stat is widely used as first line treatment for NGU, has a comparable efficacy against chlamydia as doxycycline

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 than 7 days doxycycline against chlamydia.

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 is widely used as first line treatment for NGU, but seems to have contributed to the increasing *M. genitalium* resistance. 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.

I have also made a small addition in the following:

*Reassure asymptomatic patients that no further test or treatment is necessary.*

**Treatment of persistent or recurrent NGU**

Moxifloxacin should be used with caution and reserved for treatment failures which are thought secondary to macrolide resistant *M. genitalium*, because of rare but serious adverse hepatic reactions. In patients having contracted *M. genitalium* infection in South-East Asia, dual resistance to both macrolides and quinolones is currently around 10%. Such infections are difficult to treat and only pristinamycin (registered in France) has proven effective on a case basis [61].

**Continuing symptoms**
There is only limited evidence on how best to manage patients who either remain symptomatic following a second course of treatment or who have frequent recurrences after treatment. Reassure asymptomatic patients that no further test or treatment is necessary.

To guide management, testing for *M. genitalium*, including macrolide resistance test, is essential. All sexual partners should be treated concurrently with the same antibiotic regimen which was effective in the index [62].

I hope the manuscript is now ready for publication.

Regards

Harald Moi