

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Long-term antibiotics for prevention of recurrent urinary tract infection in older adults: systematic review and meta-analysis of randomised trials
AUTHORS	Ahmed, Haroon; Davies, Freya; Francis, Nick A.; Farewell, Daniel; Butler, Christopher; Paranjothy, Shantini

VERSION 1 - REVIEW

REVIEWER	Michael Moore University of Southampton UK
REVIEW RETURNED	24-Nov-2016

GENERAL COMMENTS	<p>This is a well conducted and relevant review given international concerns regarding antibiotic resistance and the high level of prophylactic use of antibiotics particularly in the care home population. The protocol was lodged in advance on the PROSPERO database. There does appear to be one minor inconsistency between the protocol and the review in that for two studies with women of mixed ages the authors requested data on postmenopausal women or those over 65 whereas in the protocol the preference for data was reversed with those over 65 appearing to take precedence. The standard of reporting for confirmed UTI was different in the studies than that specified in the protocol although I do not regard this as critical since all three studies used the same standard and hence were comparable. The review is limited to English language studies and this may preclude additional studies. This limitation is mentioned in the discussion, given the paucity of data additional studies would be helpful. Did the authors attempt to assess whether the inclusion of non english studies could usefully add to the review?</p> <p>Given the reported frequency of antibiotic use for prophylaxis in care home settings then it is disappointing that there was no evidence to support this practice. The authors mention this in the final sentence of the abstract as well as in the discussions of the strengths and weaknesses of the study but it does not feature in the concluding paragraph of the discussion. I suspect this is a simple oversight as older men are mentioned.</p>
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REVIEWER	Xiaoqiang.Ding 1,Nephrology Department, Zhongshan Hospital,Fudan University, Shanghai, People's Republic of China 2,Shanghai Key Laboratory of Kidney Disease and Blood Purification, Shanghai, People's Republic of China 3,Shanghai Institution of Kidney Disease and Dialysis,Shanghai, People's Republic of China
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REVIEW RETURNED	15-Dec-2016
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GENERAL COMMENTS	<p>This systemic review and meta analysis including 534 postmenopausal female aging 65 and above from 3 randomized controlled trials compared the long term antibiotics with non-antibiotics therapy including vaginal estrogen, oral lactobacilli and mannose powder in the efficacy and safety in preventing recurrent urinary tract infection. The conclusion that the long term prophylaxis therapy with antibiotics reduced the risk of RUTI by 24% without significant increase in adverse events could be referred to when making clinical decisions.</p> <p>The limitations of the article were the relatively few numbers of the enrolled papers and the existence of selection bias. As the target population was older and frail female, the clinical information about the factors that are proved to be related to recurrent urinary tract infection other than catheterization and urinary tract structural abnormality such as the impaired renal function, comorbidity with diabetes, compromised immune state were not mentioned in this article.</p>
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REVIEWER	Isabel E. Allen UCSF, US
REVIEW RETURNED	12-Jan-2017

GENERAL COMMENTS	<p>This is a well written very small systematic review of 3 trials in recurrent urinary tract infection. I am not sure that it warrants publication as a journal article given the paucity of data. However, given that it is well done, I have 2 suggestions: Rewrite and publish as a research note rather than journal article or include the non-RCTs that were excluded from the synthesis to increase the number of patients/studies included in the analyses. It isn't clear if these excluded studies had appropriate age and control groups but meta-analyzing only 3 studies seems weak, at best.</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Michael Moore

Institution and Country: University of Southampton, UK Competing Interests: None declared

This is a well conducted and relevant review given international concerns regarding antibiotic resistance and the high level of prophylactic use of antibiotics particularly in the care home population.

Thank you for taking the time to review our research article and for your positive comments.

The protocol was lodged in advance on the PROSPERO database. There does appear to be one minor inconsistency between the protocol and the review in that for two studies with women of mixed ages the authors requested data on postmenopausal women or those over 65 whereas in the protocol the preference for data was reversed with those over 65 appearing to take precedence.

Thank you for highlighting this inconsistency. We requested data from authors of two RCTs. One did not respond. The other provided data for post-menopausal women. The reason for requesting data on post-menopausal women in preference to women over 65, was the age-range (29-58 years) reported in the published paper.

The standard of reporting for confirmed UTI was different in the studies than that specified in the protocol although I do not regard this as critical since all three studies used the same standard and hence were comparable. The review is limited to English language studies and this may preclude additional studies. This limitation is mentioned in the discussion, given the paucity of data additional

studies would be helpful. Did the authors attempt to assess whether the inclusion of non english studies could usefully add to the review?

Removing English language limits from our search strategies identified only one further relevant RCT: Xu R, Wu Y, Hu Y. *[Prevention and treatment of recurrent urinary system infection with estrogen cream in postmenopausal women]. [Chinese]. Chung Hua Fu Chan Ko Tsa Chih [Chinese Journal of Obstetrics & Gynecology] 2001;36:531-533.*

This trial was reported in mandarin and compared intra-vaginal oestrogen cream (N=30) with an oral antibiotic (N=15) in post-menopausal women. Due to resource constraints, we were unable to appraise this trial further. The small sample suggests it is unlikely to have any important impact on the overall risk estimates.

Given the reported frequency of antibiotic use for prophylaxis in care home settings then it is disappointing that there was no evidence to support this practice. The authors mention this in the final sentence of the abstract as well as in the discussions of the strengths and weaknesses of the study but it does not feature in the concluding

paragraph of the discussion. I suspect this is a simple oversight as older men are mentioned. Thank you for highlighting this. We have amended the “strengths and weaknesses” section after the abstract, the 7th paragraph in the discussion, and the conclusion paragraph, to include this important point.

Reviewer: 2

Reviewer Name: Xiaoqiang.Ding

Institution and Country: 1,Nephrology Department, Zhongshan Hospital,Fudan University, Shanghai, People's Republic of China; 2,Shanghai Key Laboratory of Kidney Disease and Blood Purification, Shanghai, People's Republic of China; 3,Shanghai Institution of Kidney Disease and Dialysis,Shanghai, People's Republic of China Competing Interests: None declared

This systemic review and meta analysis including 534 postmenopausal female aging 65 and above from 3 randomized controlled trials compared the long term antibiotics with non-antibiotics therapy including vaginal estrogen, oral lactobacilli and mannose powder in the efficacy and safety in preventing recurrent urinary tract infection. The conclusion that the long term prophylaxis therapy with antibiotics reduced the risk of RUTI by 24% without significant increase in adverse events could be referred to when making clinical decisions.

Thank you for taking the time to review our research article. Our over-arching aim was to provide estimates of effectiveness and safety to better inform clinicians and patients considering the use of long-term antibiotics for prevention of recurrent UTI.

The limitations of the article were the relatively few numbers of the enrolled papers and the existence of selection bias.

We agree. Our systematic searches identified few RCTs investigating the effect of long-term antibiotics on recurrence of UTI. However, the lack of RCT evidence is an important finding and needs disseminating amongst clinicians and patients to allow informed and shared decision making. This finding also warrants wider dissemination across researchers and research-funders to prompt further high quality research to address the on-going uncertainties in this common and clinically important condition.

As the target population was older and frail female, the clinical information about the factors that are proved to be related to recurrent urinary tract infection other than catheterization and urinary tract structural abnormality such as the impaired renal function, comorbidity with diabetes, compromised immune state were not mentioned in this article.

Thank you. The included trials reported little data on associated morbidities. Of the three included trials:

- Raz et al excluded those with diabetes or renal impairment
- Beerepoot et al excluded those with renal impairment but included those with diabetes (9% of participants in the antibiotic group and 11% of participants in the lactobacilli group)
- Kranjcec et al excluded those with diabetes and did not report details of renal function.

We have added information to paragraph 1 of the “trial characteristics” section.

Reviewer: 3

Reviewer Name: Isabel E. Allen

Institution and Country: UCSF, US

Competing Interests: None declared

This is a well written very small systematic review of 3 trials in recurrent urinary tract infection. I am not sure that it warrants publication as a journal article given the paucity of data. However, given that it is well done, I have 2 suggestions: Rewrite and publish as a research note rather than journal article or include the non-RCTs that were excluded from the synthesis to increase the number of patients/studies included in the analyses. It isn't clear if these excluded studies had appropriate age and control groups but meta-analyzing only 3 studies seems weak, at best.

Thank you for taking the time to review our research article. Our over-arching aim was to provide estimates of effectiveness and safety for clinicians and patients considering the use of long-term antibiotics for prevention of recurrent UTI. As pre-defined in our review protocol (http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015016628), we only included data from randomised controlled trials to protect against confounding and biases associated with observational studies. Although our study identified few RCTs investigating the effect of long-term antibiotics on recurrence of UTI, the lack of RCT evidence is an important finding in itself. This finding warrants dissemination amongst clinicians and patients to allow informed and shared decision making and raise awareness of the uncertainties around this important clinical decision. This finding also

warrants wider dissemination across researchers and research-funders to prompt high quality research to address the on-going uncertainties in this common and clinically important condition.

VERSION 2 – REVIEW

REVIEWER	Xiaoqiang.Ding 1,Nephrology Department, Zhongshan Hospital,Fudan University, Shanghai, People's Republic of China; 2,Shanghai Key Laboratory of Kidney Disease and Blood Purification, Shanghai, People's Republic of China; 3,Shanghai Institution of Kidney Disease and ialysis,Shanghai, People's Republic of China
REVIEW RETURNED	18-Feb-2017

GENERAL COMMENTS	Thanks for author's reply. As the renal function were not reported in detail in Kranjcec's article, it might be improper to express the words like the author amended in "trial characteristics".
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REVIEWER	Isabel Allen UCSF
REVIEW RETURNED	02-Feb-2017

GENERAL COMMENTS	Good revision - answered my questions regarding clinical importance and guidance provided with such a small group of studies.
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