PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Effect of point-of-care susceptibility testing in general practice on appropriate prescription of antibiotics for patients with uncomplicated urinary tract infection: a diagnostic randomized controlled trial
AUTHORS	Holm, Anne; Cordoba, Gloria; Soerensen, Tina; Jessen, Lisbeth; Frimodt-Møller, Niels; Siersma, Volkert; Bjerrum, Lars

VERSION 1 – REVIEW

REVIEWER	Wagenlehner Florian Justus Liebig University Giessen Germany
REVIEW RETURNED	07-Jun-2017

GENERAL COMMENTS	The study has been well performed. The caveat that should be considered is the fact that, although both methods compared present results earlier than usual microbiology, but it is probably not what nowadays is called point of care testing (POC), where results are seen almost immediately. Therefore the wording POC should be reconsidered. A true POC analysis of susceptibility results availabl within one or two hours would probably have had an impact on adequate antibiotic treatment. The point has been well taken, that in uncomplicated UTI resisntance levels are two low, to yield significant differences. It could be added that in som parts of the world resistance even in uncomplicated UTI might be as high as to yield significant differences with this study approach.

REVIEWER	Chris Butler University of Oxford, UK I have done research on point of care urine culture in general practice using the Flexicult system
REVIEW RETURNED	28-Jun-2017

GENERAL COMMENTS	This is an important study, and with some changes, will add to the evidence base in an important way. Uncomplicated urinary tract infection is an important, common condition, and antibiotics are often inappropriately prescribed for it in primary care. Improving the quality of antibiotic prescribing for this condition is a priority, and point of care urine culture is already in widespread use in Denmark. It could be used even more widely if supported by an appropriate evidence base. Knowing the added value of point of care susceptibility testing over and above point of care culture alone has resource and training implications for general practice. The trial reported here therefore adds very useful data to an important question.

	However, before it can be published, the manuscript needs some enhancements. Overall, the abstract does not provide enough information in my view. Here are some specific comments. 1. Line 21. I would say 'open' rather than 'open label' RCT, as the latter refers more to a drug 2. It is worth stating what the level of randomisation was here (individual patient vs clinicians vs practice) 3. Line 27: suggest ad in the number of practices 4. Mention how patients were followed up in the abstract (diary etc) 5. Line 33: 'Women' rather than 'female patients'. 6. Abstract needs to mention sample size calculation and analytic approach 7. Line 51; need to define 'appropriate' 8. 53: need to define 'clinical cure" Self-report"? reported to a clinician? 9. Results need to indicate the proportion of urine samples that were considered positive for UTI and the proportion of pathogens that were considered resistant. 10. Was there a urine sample sent to the laboratory for a reference standard? Single laboratory or many labs? How many labs? Although the protocol paper is referred to, the results paper itself should be readable on its own. So, for example, the basis for the sample size and the sample size itself needs to be included in this paper, even if in brief. I had to look up the protocol paper to make sense of this aspect, for example. Some further specific issues: 1. Page 5 line 21: Laboratory culture giving a definitive answer is very controversial as we have found sending fractions of the same sample to two labs can give a very different answer? As the authors say in their discussion, perhaps the POC gives a better answer as the urine is inoculated fresh onto the culture plate. 2. Page 6, line 7. Even if you refer to the protocol, you should summarise the main design here in a few sentences. 3. Sealed envelope randomisation: Opaque? Sequentially numbered? 4. Why the difference in patient numbers between study arms? Needs to be better considered in the discussion. 5. Why the 13 exclusions form the analysis? Consent withdrawn: consent for what: to use all data, or for further data collection? If the latter, the data you have can be analysed. 6. What is the definition of 'elderly'? >50 years? Finally, the authors need to be clearer about the study question, which is the comparative effectiveness between the two POCT approaches, rather than the effectiveness of susceptibility testing. When I first read the protocol paper, it initially seemed that it was the later question that was the focus which implied a comparison between POC susceptibility testing vs no POCT culture of any kind. The main reason for the findings is the very few cases where there was a UTI and the bug was resistant to the antibiotic prescribed (17 cases). Susceptibility testing would presumably have been hypothesised to achieve more appropriate prescribing among this group. But given the small numbers, one could never expect to see a difference within this group of patients.

	The main finding therefore is that very few cases are caused by resistant organisms so knowing the susceptibilities can't really change the overall appropriateness of prescribing. This needs to be addressed properly in the discussion. Best wishes for a successful revision and for getting these important data into the public domain.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

The authors have presented a randomized study comparing early results of culturing with and without susceptibility testing in uncomplicated UTI.

Comments:
The study has been well performed. The caveat that should be considered is the fact that, although both methods compared present results earlier than usual microbiology, but it is probably not what nowadays is called point of care testing (POC), where results are seen almost immediately. Therefore the wording POC should be reconsidered. A true POC analysis of susceptibility results availabl within one or two hours would probably have had an impact on adequate antibiotic treatment.

Response:
both the protocol of this study and another study, investigating the same test, has used the phase "point-of-care" we would like to keep this wording in our report of the final results. The definition of a POC test is actually that it is performed at the point-of-care, ie. Close to the patient, while the time-aspect is not included.

Comment:
The point has been well taken, that in uncomplicated UTI resisntance levels are two low, to yield significant differences. It could be added that in som parts of the world resistance even in uncomplicated UTI might be as high as to yield significant differences with this study approach.

Response:
I have changed the final sentence in the article to:
Based on these results, performing POC culture prior to treatment for patients with uncomplicated UTI seems rational, but adding POC susceptibility testing should be reserved for those patients at high risk of a resistant infection or complications or for geographical areas with high levels of resistance.

Reviewer: 2

This is an important study, and with some changes, will add to the evidence base in an important way. Uncomplicated urinary tract infection is an important, common condition, and antibiotics are often inappropriately prescribed for it in primary care. Improving the quality of antibiotic prescribing for this condition is a priority, and point of care urine culture is already in widespread use in Denmark. It could be used even more widely if supported by an appropriate evidence base. Knowing the added value of point of care susceptibility testing over and above point of care culture alone has resource and training implications for general practice. The trial reported here therefore adds very useful data to an important question.

However, before it can be published, the manuscript needs some enhancements.

Overall, the abstract does not provide enough information in my view. Here are some specific comments.
1. Line 21. I would say ‘open’ rather than ‘open label’ RCT, as the latter refers more to a drug
2. It is worth stating what the level of randomisation was here (individual patient vs clinicians vs practice)
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7. Line 51; need to define ‘appropriate’
8. 53: need to define ‘clinical cure” Self-report”? reported to a clinician?
9. Results need to indicate the proportion of urine samples that were considered positive for UTI and the proportion of pathogens that were considered resistant.
10. Was there a urine sample sent to the laboratory for a reference standard? Single laboratory or many labs? How many labs?

Response: I have revised the abstract completely. Please refer to the manuscript.

Comment: Although the protocol paper is referred to, the results paper itself should be readable on its own. So, for example, the basis for the sample size and the sample size itself needs to be included in this paper, even if in brief. I had to look up the protocol paper to make sense of this aspect, for example. Some further specific issues:

I have included a shorter version of the sample size calculation in the manuscript.

Comment: Page 5 line 21: Laboratory culture giving a definitive answer is very controversial as we have found sending fractions of the same sample to two labs can give a very different answer? As the authors say in their discussion, perhaps the POC gives a better answer as the urine is inoculated fresh onto the culture plate.

Response: The sentence says “Urine culture gives a definite answer for UTI in the symptomatic patient (12). However, sending urine to the microbiological laboratory for culture…”. We agree, urine culture is a good test, but it should be performed close to the patient.

Comment: Page 6, line 7. Even if you refer to the protocol, you should summarise the main design here in a few sentences.

Response: This section has been added:
DESIGN
This study was an open, randomized controlled trial (RCT). Patients were individually randomized to having either POC culture and susceptibility testing or POC culture-only performed. The design is described in detail in the published protocol (16).

Comment: Sealed envelope randomisation: Opaque? Sequentially numbered?

Response: Yes and yes, this has been added.

Comment: Why the difference in patient numbers between study arms? Needs to be better considered in the discussion.

Response: We believe this was random. We have added this in the discussion:
The number of patients recruited in the two groups was not the same, but if allocation concealment was insufficient leading GPs to avoid recruiting patients when the patient was intended to receive culture without susceptibility testing, we would have expected more patients with any complicating factor in the culture and susceptibility groups, but the opposite was the case. The unequal distribution of patients between the groups was more likely random due to the GPs not recruiting to number.

Comment: Why the 13 exclusions form the analysis? Consent withdrawn: consent for what: to use all data, or for further data collection? If the latter, the data you have can be analysed.

Response: Unfortunately withdrawn for everything, but as you can see in figure 1, only two patients withdrew consent. The rest were other reasons.

Comment: What is the definition of 'elderly'? >50 years?

Response: Fortunately, in Denmark you are not elderly until the age of 65. It is mentioned in table 1, but I have added it in the abstract and "recruitment of patients" section.

Comment: Finally, the authors need to be clearer about the study question, which is the comparative effectiveness between the two POCT approaches, rather than the effectiveness of susceptibility testing. When I first read the protocol paper, it initially seemed that it was the later question that was the focus which implied a comparison between POC susceptibility testing vs no POCT culture of any kind.

Response: The study question is the added effect of susceptibility testing. We chose two media, with similar ability to perform POC culture, but with susceptibility testing included in one of them. The medium for culture and susceptibility testing was the most commonly used and was natural to include to avoid the difficulties arising when introducing a completely new test.
With the changes in the abstract, we believe that our considerations about the choice of tests in order to fit the study questions are more clear.

Comment: The main reason for the findings is the very few cases where there was a UTI and the bug was resistant to the antibiotic prescribed (17 cases). Susceptibility testing would presumably have been hypothesised to achieve more appropriate prescribing among this group. But given the small numbers, one could never expect to see a difference within this group of patients. The main finding therefore is that very few cases are caused by resistant organisms so knowing the susceptibilities can't really change the overall appropriateness of prescribing. This needs to be addressed properly in the discussion.

Response: We have added this to the discussion:
The factor expected to drive the difference between the groups: choice of an antibiotic to which the infecting pathogen was resistant, happened in few cases with no difference between the groups. Resistance levels in Denmark are low and in countries with high resistance rates, the results would probably be different. It remains to be investigated if adding POC susceptibility testing in a high-resistance setting improves prescribing.

Best wishes for a successful revision and for getting these important data into the public domain.

VERSION 2 – REVIEW

REVIEWER	Chris Butler Nuffield Department of Primary Care Health Sciences University of Oxford UK I have done a trial of the effect of using the Flexicult technology in primary care, and have several publicly funded research grants res;eavt tot he management of UTI in primary care.
REVIEW RETURNED	31-Aug-2017

GENERAL COMMENTS	This is an effective revision: congratulations. One or two language slips that need attention still, such as, "ourinitially planned".