Author's response to reviews

Title: Antibiotic resistance patterns of bacteria causing urinary tract infections in the elderly living in nursing homes versus the elderly living at home: an observational study

Authors:

Mark Fagan (marfaga@online.no)
Morten Lindbæk (morten.lindbæk@medisin.uio.no)
Nils Grude (nigrud@siv.no)
Harald Reiso (harald.reiso@medisin.uio.no)
Maria Romøren (maria.romoren@medisin.uio.no)
Dagfinn Skare (dagfinn.skaare@siv.no)
Dag Berild (dag.berild@medisin.uio.no)

Version: 6 Date: 22 July 2015

Author's response to reviews: see over
08 Apr 2015

Editor in chief
BMC Geriatrics

Dear Editor,

I am writing to resubmit our manuscript “Antibiotic resistance patterns of bacteria causing urinary tract infections in the elderly living in nursing homes versus the elderly living at home: an observational study” for consideration for publication in BMC Geriatrics. I refer to your letter indicating that “we are willing to consider your manuscript further once all the concerns have been addressed”

I have revised the manuscript after the helpful suggestions of the two referees. The following text is structured with each of the referees comments followed by our responses.

Sincerely,

Mark Fagan MD
Institute of Health and Society,
Faculty of Medicine
University of Oslo, Norway

Correspondance:
Nedre Skilsø 48
N-4818 Færvik, Norway
+47 98876344 (telephone)
+47 37088890 (fax)
markfagannor@gmail.com

Reviewer’s report

Title: Antibiotic resistance patterns of bacteria causing urinary tract infections in the elderly living in nursing homes versus the elderly living at home: an observational study

Reviewer: Alex Smithson

Reviewer’s report:

I have reviewed the article entitled “Antibiotic resistance patterns of bacteria causing urinary tract infection in the elderly living in nursing homes versus the elderly living at home: an observational study”. In this study the authors try to evaluate the existence of differences in the bacterial aetiology between urinary tract infection (UTI) in elderly living at nursing homes versus those not living in nursing homes. See below my comments:

1. The abstract is far too long. Include in the methodology type of study design and in the results the total number of patients included among other
changes.

- The abstract has been condensed. The methodology section now includes study design and the results section includes the number of patients.

2. In the introduction it would be interesting to mention the concept of healthcare UTI (HCA-UTI). Patients that acquire a UTI in the residence or in other type of long term care centers are included in the concept of HCA-UTI. There are a couple of interesting articles by Horcajada et al that could be reviewed by the authors and used in the introduction and in the discussion section. Although it’s true that these studies were performed in Spain where the antimicrobial resistance patterns are very different to those found in Norway, they provide interesting data.

- Point taken. Horcajada makes a very interesting point about the similarities between HA infections and HCA infections. I have included this in both the introduction and the discussion.

3. Regarding the methodology section.

- How many isolates were included per patient?

  - We did not exclude the second urine culture results from patients having more than one presumed UTI in the study period.

- As far as I understand urinary cultures were collected from patients with symptomatic UTI right?

  - Yes, in the NH group.

- Were there any kind of clinical data recorded?

  - There is clinical data for the NH group. There is, however, no reliable clinical data for the over 3000 community dwelling patients. This was a retrospective study of urine culture results from microbiologic lab. Clinical information in these patients is not systematically reported.

- As this is a cross-sectional study avoid using the term controls as it’s confusing.

  - Point taken, this has been changed. Patients dwelling in the community are referred to the CD group.

- Why rejecting to include hospitalized patients? I think this is a very important population to evaluate. The important thing is where was the infection acquired.

I agree with your statement that it is important to know if a patient in a NH has acquired their UVI while in the hospital. But this was beyond the scope and aim of this paper for several reasons. First, the patients included in the study group acquired their UVI while living in the NH not in the hospital. We included urines only from new episodes when antibiotic treatment was initiated in the NH. Including urine results from hospitalized patients in the community group (CG) would introduce bias by increasing the heterogeneity of this group. It should be noted that we did not (could not) exclude patients in the control group who were discharged recently from the hospital and subsequently developed a UTI.

The perspective of this study is from the nursing home where the majority of patients develop their infections at the nursing home or are
admitted from the community (2 ecosystems). This contrasts to the hospital where there is a higher rate of bactereimic patients who have developed their infections in the hospital, or can be admitted from the nursing home or the community (3 ecosystems).

- Were intermediate and resistant strains analyzed together?
  
  • Please also refer to the footnotes in tables 2 and 3. All S-I-R breakpoints are in accordance with EUCAST. For ampicillin; E coli, and P mirabilis intermediate (I) is classified as sensitive (S) For Trimethoprim; E faecalis intermediate (I) is classified as sensitive (S). This is because these isolates express wild-type susceptibility to the respective agents. For all other bug-drug combinations (I) is classified as (R) because such isolates have reduced susceptibility, most likely due to acquired resistance mechanisms.

- Summarize the Norwegian therapeutic recommendations for UTI as it's not fundamental for the study. What is important is to mention in the introduction whether these guidelines are different depending on place of acquisition of the UTI.
  
  • Point taken and changes made.

- Summarize outcomes
  
  • Point taken and changes made.

- Provide reference on the methodology used for calculating theoretic risk of therapy failure
  
  Point taken and reference included

4. Summarize results, include mean ages (+/- SD) and difference between both groups being compared
  
  • I have included the SD in addition to the CI for the mean ages. I have included the p value showing no statically significant difference in gender distribution between the NH and CD groups.

5. I don't understand the meaning of lines 201 and 202.
  
  • The text in 201-202: The relative frequency of bacteria isolated from NH and CD group was not significant. This means that the relative contribution of the bacteria in the NH group as a whole compared to the relative contribution of the bacteria in the CG as a whole was not significantly different. I have edited table 1 with the aim to make this point clearer

6. Provide p values in the table
  
  • This is done

7. There are very few references in the discussion. The authors do not discuss about the different aetiology of UTI depending on sex.
  
  • Point taken, several new considerations are included in the discussion

8. Conclusions should be clearly restricted to Norway.
**Point taken and rewritten**

**Level of interest:** An article of insufficient interest to warrant publication in a scientific/medical journal

**Quality of written English:** Needs some language corrections before being published

**Reviewer:** Pär-Daniel Sundvall

**Reviewer's report**

This is an interesting and overall well written manuscript. Resistance problems vary substantially through the world. Therefore, these results are important for antimicrobial stewardship and the development of guidelines for empirical treatment of UTI in Norway and countries with similar resistance rates.

**Major Compulsory Revisions:**

1. Urinary catheters are more common among male patients(1). Patients with urinary catheters are expected to have different species and resistance patterns compared to patients without catheters(2, 3). Patients with urinary catheters are prescribed substantially more UTI antibiotics, including quinolones, compared to patients without catheters. Therefore, the higher resistance rates for ciprofloxacin in *E. coli* among male patients in this study could at least partially be explained by an expected higher prevalence of catheters among men. The shortcoming of not knowing catheter status is already discussed for the comparison of nursing home patients versus patients not in nursing homes. However, this should be discussed also for the comparison of male/female patients.
   - This is a good point and has been included in the discussion with references(1)

2. Result, Male vs female, line 220-221: "For *P mirabilis* there was a significantly higher resistance rates for mecillinam for males than for females (p < 0.05) (Table 3).” Especially since not knowing urinary catheter status, it is important to notice that there were only five *P. mirabilis* resistant to mecillinam in male patients (some of which might be men with urinary catheters which might explain this difference). This ought to be discussed.
   - Point taken. This is included in the discussion along with the point 1 above.

3. Patients with complicated UTIs may have different resistance patterns compared to patients with uncomplicated UTIs, as well as there might be different resistance patterns in patients with lower and upper UTIs. As the aim of this study was to assess resistance rates in patients with UTI and relate this to recommendations for empirical therapy for UTI, it would have been valuable to take into account what kind of UTI that was evaluated when the urine specimens were obtained. The lack of urinary catheter status is already discussed in the Discussion. If not possible to know what kind of UTIs
evaluated, it should be discussed if this may have affected the results. (4)

- **Point taken.** This is an interesting dilemma. Urinary tract terminology is somewhat ambiguous in the literature. Many define all UTI in the elderly as “complicated UTI” making this a broad definition including a heterogeneous group of infections. I was unable to find a study which specifically addressed differences in bacterial etiology including resistance for lower UTI (cystitis) vs pyelonephritis in the elderly. There are several studies showing increasing resistance problems with increasing age providing indirect evidence that complicated UTI and cystitis have different bacterial etiology. This is now discussed with a reference.

4. **Results, NH vs control, line 214-215:** “K pneumoniae and P mirabilis resistance rates for ciprofloxacin were significantly higher in the NH group (p < 0.05).”

Especially since not knowing urinary catheter status, it is doubtful whether it is possible to draw this conclusion as there were very few urine cultures from nursing homes with ciprofloxacin resistant K. Pneumonia (present in 2 of 11 urine cultures positive for K. pneumoniae), and very few urine cultures from nursing homes with ciprofloxacin resistant P mirabilis (present in 3 of 12 urine cultures positive for P. mirabilis). This ought to be discussed.

- **In the results section the resistance rates for both K pneumoniae and P mirabilis are statistically significant despite the low number of isolates.** The clinical significance of this finding is a point I have discussed: “Because K pneumoniae and P mirabilis contribute minimally to the total number of UTI they do not result in a significantly higher risk of therapy failure in the NH despite the higher rates of resistance in these bacteria.”

**Minor Essential Revisions:**

1. **Abstract, the two last paragraphs in Results:** It should be stated that the comparisons between females and males were irrespective of where patients reside.

- **Point taken**

2. **Results, NH vs control, line 204-206:** “K pneumoniae was more common in the control group (5.9%) than in the NH group (4.7%) while P mirabilis was more common in the NH group (5.2%) than in the control group (3.7%).”

P-values are missing. It is doubtful whether it is possible to draw these conclusions as there were very few urine cultures from nursing homes with these bacteria (11 residents with K. pneumoniae and 12 residents with P. mirabilis in the nursing home group).

- **Point taken.** The differences were not statistically significant. In addition the information is in table1. I have therefore removed this sentence from the text.

3. **In Sweden, resistance to fluoroquinolones was tested by nalidixic acid (screening for I+R) up to 2011, and by ciprofloxacin from 2011 and onwards.** This methodological change influences resistance rates and the two different methods are not comparable. Which method was used in Norway during the studied period in 2009-2010? If nalidixic acid was used as a screening disc for quinolone resistance, this should be stated as it is an important information for the reader.
• Point taken and the tables now include an explanatory footnote. In this time period, testing of quinolone susceptibility included both nalidixic acid and ciprofloxacin. This would result in an S for ciprofloxacin being classified as I if the microbe in question was R for nalidixic acid. This would contribute to a somewhat higher rate of ciprofloxacin resistance compared to the technique used after 2011 making comparisons over time tricky. It would not, however, affect comparison between the 2 groups in this study as the same technique was used in both groups.

4. In the control group, urine samples ordered by the visiting nurse service were excluded. There might be a good reason for this but it is not obvious to the reader, especially if not knowing the visiting nurse service responsibilities.

• This represented less than 1% of the total. Sometimes the visiting nurse service delivers urines from the nursing home to the hospital during the weekends or in the off-hours. To eliminate this uncertainty this small number of urine isolates was not included.

5. Discussion line 250: “Although there is a higher rate of ciprofloxacin resistance in E coli from nursing home patients...”. This is not congruent with Results: “The NH group showed a slightly though non-significantly higher resistance rate for ciprofloxacin than the control group”. The p-value is missing in Results.

• I have changed the wording in the discussion The resistance rate was slightly higher but not significantly higher in the NH group (p 0.423). In the tables I indicated in the footnotes which p-values were significant. I found including non-significant p-values for all the bug-drug made the table very confusing.

6. In Table 1, 148 urine cultures from nursing homes were positive for E. coli (133 female + 15 male). In Table 2, only 147 urine cultures from nursing homes were positive for E. coli. A typographical error?

• Thanks, Table 2 corrected.

Discretionary Revisions:

1. Usually there is a dot after the first letter in abbreviated bacterial names, for an example: E. coli

• There are several conventions used for abbreviating the names of bacteria, some include a period after genus some do not. We decided to use the convention not using a period.

2. Abstract line 73: “...Enterococcus faecalis (in 10%...”, and in the Discussion line 247: “...K pneumoniae and P mirabilis) isolated in urine...”. These two brackets are by mistake italic.

• Thank you

3. Result, Male vs female and Table 3: Although described in Methods – Outcomes, it would be good to also mention in Results and Table 3 that the comparisons between females and males were irrespective of where patients reside.

• Point taken and corrected