Author's response to reviews

Title: Why is asymptomatic bacteriuria overtreated?: A tertiary care institutional survey of resident physicians

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Dr. Philippa Harris

The Editor, *BMC Infectious Diseases*

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‘Why is asymptomatic bacteriuria overtreated?: A tertiary care institutional survey of resident physicians’

Dear Dr. Harris

We thank the editors and reviewers of ‘*BMC Infectious Diseases*’ for reviewing our article. We have made numerous corrections and changes in the revised manuscript after considering the reviewers’ helpful comments.

We present below a point-by-point response to the comments and questions of each reviewer. We believe that we have adequately addressed all the questions and comments, but if necessary, we would be happy to provide further information or revision. We very much hope the revised manuscript will now be found suitable for publication in ‘*BMC Infectious Diseases*’. Thank you for your consideration.
Sincerely yours,

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**Editor's comment:**

"The authors should be careful about correlating the 2 aspects of the study (inappropriate antibiotic use and the survey) as the 3rd reviewer suggests. Unless the authors can demonstrate that the population surveyed are the same that made the inappropriate prescriptions, this limitation should be emphasized in the discussion or the 2 studies separated as suggested."

We acknowledge that the population surveyed is not entirely the same as the one that made the inappropriate prescriptions due to an interval of a year between the clinical data collection and the survey. However, considering that the length of the residency training is 4 years for all resident physicians who took part in the survey, the majority of survey participants would have cared for episodes of ABU in 2011; only the first year resident physicians who participated in the survey would not have made any of the inappropriate prescriptions because they were interns in 2011. As the majority of the survey population overlapped with the prescription population, we think that, with some reservations, the survey and the clinical results can still be linked. However, in response to the editor’s comment, we have added this limitation to the discussion of the revised manuscript.

**In the revised Discussion section, lines 318-322:**

Third, as we surveyed physicians in the year after the care was provided (2012), some of the residents were not the same as those who actually cared for the episodes of bacteriuria in 2011. However, we believe that the inappropriate antibiotic use data can still be reasonably linked and correlated with the survey considering that the majority of the residents surveyed
A. Responses to Reviewer #1’s comments

The authors undertook a retrospective audit of positive urine cultures over 12 months. Definitions of asymptomatic bacteriuria and urinary tract infection were in accordance with NHSN and appropriateness of antibiotic management in accordance with IDSA. This was followed by a quantitative survey of knowledge, perception and practice.

While not novel, this study adds to recent literature in the area which highlights the urgent need to target inappropriate treatment of positive urine cultures as a component of antimicrobial stewardship programme.

Appropriate literature review was cited in discussion.

No major compulsory revisions.

Minor Revisions

1. Please justify exclusion of repeat urine cultures within 7 days and those within 48 hours of admission. This is of concern as 683 cases of 1167 were excluded.

As we stated in the Methods section, the unit of analysis in our study was the individual episode of bacteriuria. We excluded repeated urine cultures within 7 days because they could involve the same episode of ABU or UTI. Thus if we counted every urine culture as a single event, the number of ABU or UTI events would probably be overestimated. In addition, we excluded urine cultures set up within 48 hours of admission which would represent episodes
of ABU or UTI that started before admission. Because it was difficult to differentiate ABU from UTI in these episodes due to a lack of information about symptoms or signs preceding admission, we only included urine cultures taken 48 hours after admission, which could be assessed as ABU or UTI according to our medical records. For clarity, we have further described the exclusion criteria in the revised manuscript, as follows:

In the Methods section, lines 116-123:

Previous: However, urine cultures done among, 1) patients in the emergency room or the outpatient department, 2) pregnant women, 3) patients who underwent invasive urologic procedures, 4) patients receiving antibiotics for concomitant infections were ineligible, and repeated tests within seven days from a previous bacteriuric event, or those performed within 48 hours of admission were also excluded.

Revised: Urine cultures made among patients in the emergency room or outpatient departments were not reviewed. Similarly excluded were urine cultures from 1) pregnant women, 2) patients undergoing invasive urologic procedures, and 3) patients with concomitant infections receiving antibiotics for infections other than UTI at the time of urine collection. Urine cultures made within seven days of a previous bacteriuric event were excluded as these were likely to involve the same episode of bacteriuria. Urine cultures performed within 48 hours of admission were also excluded as these would represent episodes of bacteriuria with onset before admission and therefore hard to assess.

2. Acknowledge that retrospective review of medical records will introduce significant bias in
assessing asymptomatic bacteriuria as documentation is rarely complete in routine clinical care outside of prospective protocol guided data collection.

We agree with the reviewer’s comment and this point has been mentioned as a limitation in the Discussion section.

**In the Discussion section, lines 312-316:**

First, there may have been some misclassification of episodes of bacteriuria because of the retrospective part of the study. However, to minimize possible biases incurred from a retrospective review, three ID specialists independently participated in the classification and evaluation of the appropriateness of antibiotic use.

3. **Define resident physicians. It may mean different things to different people. The authors are referring to junior doctors within 4 years of graduation from medical schools.**

   In Korea, the postgraduate clinical medical education program usually includes 1 year of internship, followed by 4 years of residency. The definition of ‘resident physician’ in this study is, therefore, a person who is enrolled in the official 4-year-long resident training program after finishing 1 year of internship. We have added the definition of ‘resident physician’ in the revised manuscript.

**In the revised Methods section, lines 156-157:**

Resident physician was defined as a person enrolled in the official 4-year-long resident
4. Explain why senior doctors were not surveyed as they are ones that often make decisions and teach junior doctors.

We surveyed resident physicians only because they are mainly in charge of issuing orders on behalf of inpatients. We partially agree with the reviewer that senior doctors have an influence on junior doctors when they make clinical decisions. However, in our hospital, rather than taking part in every minor decision, senior doctors usually guide the more critical decisions involving patient care. Since our purpose was to investigate factors which cause the doctors who primarily care for inpatients to overtreat ABU, which includes ‘pressure from the senior doctors to use antibiotics discordant with their own opinion, we did not survey senior doctors. For clarity, we have revised the manuscript to clarify this point as follows.

In the revised Methods section, lines 157-160:

Although senior doctors often influence junior doctors when the latter are making clinical decisions, they were not surveyed because we targeted those physicians who were primarily in charge of issuing orders for and managing inpatients.

5. 1167 unique episodes of positive urine cultures over a year in a 900-bed tertiary hospital appeared to be an underestimation. How did the authors obtain their data?

In the study hospital, only urine cultures growing $\geq 10^5$ cfu/mL of bacteria/fungi are
reported unless there is a special request for reporting the results for low-count bacteriuria/funguria. For data collection, we reviewed all of the reported urine culture results (mostly $\geq 10^5$ cfu/mL of bacteria/fungi and some requested culture results with $< 10^5$ cfu/mL of microorganisms) done at the study hospital in 2011. From them we excluded the cultures of $< 10^5$ cfu/mL and those done in outpatient care, the emergency room, and pediatric wards. Thus the 1167 episodes of positive urine culture only include those with a bacterial/fungal density $\geq 10^5$ cfu/mL among hospitalized adult patients. We have clarified this case selection criterion in the revised Methods section as follows.

In the Methods section, lines 110-125:

Previous: In all adult inpatients, we retrospectively reviewed all the positive urine cultures, defined as the presence of more than 105 colony-forming units/mL of bacteria or yeast, identified from January to December in 2011, at a 900-bed university-affiliated, tertiary care hospital in Korea. Since the unit of analysis in our study was an episode of bacteriuria, repeated bacteriuria examinations of a single patient were counted as separate events. However, urine cultures done among, 1) patients in the emergency room or the outpatient department, 2) pregnant women, 3) patients who underwent invasive urologic procedures, 4) patients receiving antibiotics for concomitant infections were ineligible, and repeated tests within seven days from a previous bacteriuric event, or those performed within 48 hours of admission were also excluded.

Revised:

We retrospectively reviewed all the positive urine cultures obtained from the adult inpatients,
from January to December in 2011, in a 900-bed university-affiliated tertiary care hospital in Korea. Positive urine cultures were defined as the presence of bacteria or yeast $\geq 10^5$ cfu/mL, because only cultures yielding $\geq 10^5$ cfu/mL of microorganisms are routinely reported in the hospital unless there is a request for reporting low-count bacteriuria. Since the unit of analysis in our study was a single episode of bacteriuria, repeated bacteriuria examinations of a single patient were counted as separate events. Urine cultures made among patients in the emergency room or outpatient departments were not reviewed. Similarly excluded were urine cultures from 1) pregnant women, 2) patients undergoing invasive urologic procedures, and 3) patients with concomitant infections receiving antibiotics for infections other than UTI at the time of urine collection. Urine cultures made within seven days of a previous bacteriuric event were excluded as these were likely to involve the same episode of bacteriuria. Urine cultures performed within 48 hours of admission were also excluded as these would represent episodes of bacteriuria with onset before admission and therefore hard to assess. However, since we did not try to distinguish between catheter-associated bacteriuria and non-catheter-associated, patients with urine catheters were included.

6. Clarify if polymicrobial positive urine cultures were included, and if patients with urine catheterization were included.

We did not restrict UTI or ABU to bacteriuria involving no more than 2 species, as provided in the guidelines, because the distinction between true bacteriuria and contamination was not important in our context. Therefore, positive polymicrobial urine cultures were included. In addition, we were not concerned to distinguish between catheter-associated bacteriuria and bacteriuria unrelated to a urinary catheter; therefore patients with urine catheters were included.
catheterization were also included as shown in Table 1 (variables of urinary catheterization). We have included this point in the revised Methods section as follows.

**In the revised Methods section, lines 123-125:**

However, since we did not try to distinguish between catheter-associated bacteriuria and non-catheter-associated, patients with urine catheters were included.

**In the revised Methods section, lines 133-135:**

We did not confine ABU or UTI to bacteriuria involving no more than 2 species of microorganisms, as we were not concerned to distinguish between true bacteriuria and contamination.

7. *The statement from lines 307-309 appeared to be referring to a separate study but no reference was cited.*

We are sorry that our statement was confusing. The statement from lines 307-309 (previous manuscript) does not refer to a separate study, but to the findings from the bacteriuria review in this study. We sought to point out that many urine cultures had been ordered for which we could not find any written indications in our retrospective chart review; therefore we assume that many of the urine culture were being ordered regardless of the probability of UTI. We have revised the Discussion section to make this clearer:

**In the Discussion section, lines 284-287:**
Previous: We revealed that urine cultures were often ordered regardless of the probability of UTI for various reasons mostly associated with misperception of bacteriuria. This practice was also reflected in a retrospective chart review suggesting that the indications of urine culture were often not clarified on the medical record.

Revised: From the survey, we could see that urine cultures were often ordered regardless of the probability of UTI for various reasons mostly associated with misunderstanding of bacteriuria. This effect was also evident in our review of bacteriuria cases, as the indications for urine culture were often not clarified on the medical records.

B. Responses to Reviewer #2’s comments

The information presented in this manuscript is not new, as overtreatment of ASB (asymptomatic bacteriuria) and lack of knowledge about ASB are both well-documented. However, this is, to my knowledge, the first such study from Korea and thus adds to our appreciation of these problems on a global scale. Furthermore, the inclusion of surgery residents in the survey population is also novel. My comments are intended to strengthen the manuscript, primarily in terms of ensuring that the case classification process was rigorous and transparent to the reader.

Weaknesses include the scant information on how ASB and CAUTI were defined, lack of clarity about how cases were classified, inadequate information about the survey questions, choice of a new survey instrument when others exist that address this topic, and the conclusions about education as an intervention in itself. I will address these topics below in the categories of revisions.
Major Compulsory Revisions

1) Methods: episodes of bacteriuria were classified as ASB or UTI using the 2008 NHSN surveillance criteria for UTI. These criteria have since been updated several times, and they are also intended for use in reporting UTI’s, not helping with the clinical decision to prescribe antibiotics. The literature in this filed is weakened by the subjective nature of case classification (UTI versus ASB), so the manuscript needs more clarity on the points below:

   a) Please justify the choice of this outdated surveillance criteria. I am aware that subsequent NHSN criteria dropped ASB as a condition, so why did the authors not use the IDSA definitions for both ASB and UTI?

   We agree with the reviewer that the criteria used might seem awkward. We were aware that the 2012 CDC/NHSN surveillance definition of HAI dropped ASB as a specific infection type. Our criteria for ASB and UTI were adapted and modified by us from the 2008 CDC/NHSN surveillance definitions and IDSA guidelines. We regret the brief description which caused this misunderstanding. Accordingly, we have revised the Methods section to be more explicit about our case definitions:

In the Methods section, lines 126-135:

Previous: Two infectious disease (ID) specialists independently reviewed the medical records of patients with positive urine cultures and classified each episode of bacteriuria as ABU or
UTI according to the Centers for Disease Control and Prevention surveillance criteria and evaluated the appropriateness of antimicrobial use for ABU.

**Revised:** We applied standardized criteria for diagnosing ABU and UTI, modified from the Centers for Disease Control and Prevention surveillance criteria as well as the 2005 Infectious Disease Society of America (IDSA) guidelines [10, 17]. UTI was defined as the presence of bacteriuria or funguria $\geq 10^5$ cfu/mL along with at least one of the following symptoms and signs with no other recognized cause: fever (temperature $\geq 37.8^\circ$C), dysuria, urgency, frequency, suprapubic tenderness, and costovertebral angle pain or tenderness. ABU was defined as bacteriuria or funguria $\geq 10^5$ cfu/mL, without any symptoms or signs suggesting UTI. We did not confine ABU or UTI to bacteriuria involving no more than 2 species of microorganisms, as we were not concerned to distinguish between true bacteriuria and contamination.

*b) List the defining criteria of UTI – what symptoms were included?*

We defined UTI according to the following criteria: presence of bacteriuria or funguria $\geq 10^5$ cfu/mL with at least one of the following symptoms and signs with no other recognized cause: fever (temperature $\geq 37.8^\circ$C), dysuria, urgency, frequency, suprapubic tenderness, costovertebral angle pain or tenderness.

**In the revised Methods section, lines 128-131:**

UTI was defined as the presence of bacteriuria or funguria $\geq 10^5$ cfu/mL along with at least
one of the following symptoms and signs with no other recognized cause: fever (temperature ≥ 37.8 °C), dysuria, urgency, frequency, suprapubic tenderness, and costovertebral angle pain or tenderness.

c) What were the criteria used to determine if antibiotic use was appropriate or inappropriate? The team must have applied some set rules. The guidelines themselves are not directly applicable to individual cases without some interpretation.

We agree with the reviewer that the decision about the appropriateness of the antibiotic used is challenging. As we have mentioned in the Methods section, we determined the appropriateness of antibiotic use for ABU based upon the IDSA guidelines for asymptomatic bacteriuria. Therefore, antibiotic use for ABU was regarded as appropriate when it was for pregnant patients and patients undergoing transurethral prostate resection or traumatic genitourinary procedures during which mucosal bleeding was anticipated. However, some ambiguous cases were reviewed by other researchers in our team and, after discussion, the appropriateness of antibiotic use in individual cases was determined by the majority rule. We have revised the Methods section as follows.

In Methods section, lines 135-141:

Previous: Two infectious disease (ID) specialists independently reviewed the medical records of patients with positive urine cultures and classified each episode of bacteriuria as ABU or UTI according to the Centers for Disease Control and Prevention surveillance criteria and evaluated the appropriateness of antimicrobial use for ABU [17]. If the two opinions differed,
that of another ID specialist was obtained. The final decision was made by a majority. The appropriateness of antibiotic use for ABU was assessed using the 2005 Infectious Disease Society of America guidelines for the diagnosis and treatment of asymptomatic bacteriuria in adults [10].

**Revised:** Antibiotic use for ABU, except for pregnant patients and those undergoing traumatic urologic procedures in which mucosal bleeding is anticipated, was regarded as inappropriate based on the IDSA guidelines [10]. Two infectious diseases (ID) specialists independently reviewed the medical records of patients with positive urine cultures and classified each bacteriuric episode as ABU or UTI and assessed the appropriateness of management. If the two opinions differed, another ID specialist was consulted and the final decision was made by majority.

d) Information was collected on underlying diseases: which diseases, and how were these defined?

We investigated patient’s underlying diseases including diabetes mellitus (DM), chronic kidney disease (CKD), spinal cord injury, and solid tumor (cancer), as we supposed these comorbidities might lead physicians to treat the ABU. However, as underlying disease was not critical for our study, we did not review extensively whether the diagnosis of each patient’s alleged comorbidity was correct or not. We basically collected data using the ICD-10 diagnosis code for each patient, through review of medication, medical records, and diagnosis by related specialists.

We have modified the referring sentence as below:
In Methods section, lines 142-146:

**Previous:** In order to find out the patients’ clinical factors associated with antibiotics use for ABU, data on patient demographics, the admitting department, underlying diseases, the existence of an indwelling urinary catheter, organisms found in urine culture, urinalysis and other laboratory findings, body temperature and antibiotic use were collected.

**Revised:** In order to identify clinical factors associated with antibiotic use for ABU, we collected data on patient demographics, the admitting department, underlying disease including diabetes mellitus, chronic kidney disease, spinal cord injury and solid tumor, as well as indwelling urinary catheter, organisms found in urine culture, urinalysis and other laboratory findings, body temperature and antibiotic use.

2) **Abstract and conclusions:** Education in itself is a very weak intervention. The authors can comment that education needs to be a part of a larger implementation program that addresses both the knowledge gap but also the barriers to following the guidelines. The results highlight that even when respondents knew an episode was ASB, they still felt a need to prescribe antibiotics. Thus, education alone will not be sufficient.

We agree with the reviewer that simple education may be insufficient, and have revised the Abstract and the Conclusions section:

In the Abstract, lines 72-75:
Previous: Lack of knowledge and discrepancy between knowledge and practice contributed to antimicrobial overuse for ABU, which highlight the importance of further educational interventions.

Revised: Lack of knowledge and discrepancies between knowledge and practice, contributed to antimicrobial overuse for ABU. Our findings highlight the importance of developing interventions, including education, audit and feedback, to tackle the problem of inappropriate treatment of ABU.

In the Discussion section, lines 308-309:

Previous: To overcome this gap, educational efforts and practice-based audit and feedback, encouraging guideline adherent management, are of critical importance.

Revised: Practice-based audit, and feedback to help physician detect the errors of their practices, as well as fundamental educational efforts are of critical importance in overcoming this gap.

In the Conclusions section, lines 328-330:

Previous: Therefore, an antimicrobial stewardship program including the education for indication and interpretation of urine culture and clinical intervention on antimicrobial prescription is required to promote appropriate antimicrobial use for bacteriuria.

Revised: Therefore, interventions addressing both education to improve knowledge, and audit and feedback to overcome the barriers to following guidelines, are warranted.
Minor Essential Revisions

1) Methods: $\geq 10^5 \text{ or } >10^5$? Clarify and justify. IDSA definitions use $\geq$.

We defined positive urine cultures as $\geq 10^5 \text{ cfu/mL}$ of bacteria or yeast for the case selection, and also used ‘$\geq 10^5$ mL of bacteria for the clinical vignettes in the survey. The inequality sign was mistakenly written as $>$ in the manuscript, and we have corrected the error throughout the revised manuscript.

In the Abstract, lines 55-58:

We reviewed all the urine cultures $\geq 10^5 \text{ cfu/mL}$ bacteria among inpatients in a 900-bed hospital in 2011.

ABU was defined as a positive urine culture ($\geq 10^5 \text{ cfu/mL}$) without symptoms or signs suggesting UTI.

In the Methods section, lines 112-114:

Positive urine cultures were defined as the presence of bacteria or yeast $\geq 10^5 \text{ cfu/mL}$ in urine, because only cultures yielding $\geq 10^5 \text{ cfu/mL}$ of microorganisms are routinely reported in the study hospital unless there is a request for reporting low-count bacteriuria.
In the Methods section, lines 128-130:

UTI was defined as the presence of bacteriuria or funguria $\geq 10^5$ cfu/mL along with at least one of the following symptoms and signs with no other recognized cause.

In the Methods section, lines 131-133:

ABU was defined as bacteriuria or funguria $\geq 10^5$ cfu/mL, without any symptoms or signs suggesting UTI.

In the Results section, line 190-191:

Among these we identified 1,167 episodes of positive urine cultures that grew $\geq 10^5$ cfu/mL, and another 362 episodes with lower counts.

In Table 2:

In all the clinical vignettes, ‘UC grew with $> 10^5$/ml …’ has been changed to ‘UC grew $\geq 10^5$/ml…’.

2) Background: since this study is not unique, more rationale must be provided – did the authors want to study these issues in a new setting? From a new angle? With different emphasis?
We are aware that there have already been studies of this issue. However, as mentioned in the reviewer’s general comments, this is the first study performed in Korea, which has a different medical environment from Western countries where most other studies have been carried out. Therefore our findings represent data in a novel setting. In addition, we performed this study from a new angle by linking ABU management in real practice to physicians’ knowledge and perceptions of it. We have emphasized the significance of our study in the revised Background section:

**In the Background section, lines 100-105:**

**Previous:** Therefore, we performed this study to assess the appropriateness of ABU management and to evaluate clinical and physician-related factors including knowledge, perception and practice regarding ABU.

**Revised:** However, the issues of bacteriuria management and its associated factors in Korea have not been investigated. Therefore, we performed this study to assess the appropriateness of ABU management and to evaluate clinical and physician-related factors including knowledge, perception, and practice regarding ABU. This information should be valuable for designing further interventions to enhance the proper management of bacteriuria.

3) **Methods:** *patients with concomitant infections were excluded. This statement is not clear – did they exclude patients suspected to have another infection (such as a febrile patients who might have either pneumonia or UTI?)*

We defined ‘patients with concomitant infections’ as patients who were being prescribed
antibiotics for infections other than UTI (e.g. pneumonia, intra-abdominal infections…) at the time of urine collection. We excluded them because it was hard to judge whether it was the ABU / UTI that was being treated with antibiotics. We have revised the manuscript to add clarity:

**In the Methods section, lines 117-120:**

**Previous:** However, urine cultures done among, 1) patients in the emergency room or the outpatient department, 2) pregnant women, 3) patients who underwent invasive urologic procedures, 4) patients receiving antibiotics for concomitant infections were ineligible, and repeated tests within seven days from a previous bacteriuric event, or those performed within 48 hours of admission were also excluded.

**Revised:** Similarly excluded were urine cultures from 1) pregnant women, 2) patients undergoing invasive urologic procedures, and 3) patients with concomitant infections receiving antibiotics for infections other than UTI at the time of urine collection.

4) **Methods:** without the survey questions to refer to, it is somewhat difficult to follow the description provided in methods and again hard to understand the results. Perhaps include all survey questions as a table.

We agree with the reviewer that the methodology and results are difficult to understand without the original survey questions. However, as our aim was to assess the overuse of antibiotics in ABU based on the survey, we propose to present the questionnaire as Supplementary Data, rather than in the main body of the manuscript.
5) Results: Mean correct responses was 37.3% (line 225)-was this the mean correction response per person, or averaged across all vignettes?

We intended to address the mean correct response rate to the seven clinical vignettes per participant. We have changed the sentence to add more clarity.

In the Results section, lines 212-215:

Previous: The mean proportion (± SD) of correct response to seven clinical vignettes was 37.3% (± 26.7%) with a significant difference between the specialties in training; 44.0% (± 30.0%) for medical departments, 29.8% (± 20.4%) for surgical departments (P=0.008).

Revised: The mean frequency (± SD) of correct responses to the seven clinical vignettes was 37.3% (± 26.7%), and there was a significant difference between the specialties that were being followed; 44.0% (± 30.0%) for those in medical departments, 29.8% (± 20.4%) for those in surgical departments (P=0.008).

6) Results, lines 229-230: without knowing the survey questions, these results are hard to interpret.

The statement in lines 229-230 refers to the responses to the clinical vignettes in the survey which are presented in Table 2. As we mention in Methods (lines 168-171 of the revised manuscript), we examined the resident physicians’ knowledge regarding ABU by means of the clinical vignettes. ‘Poor recognition of ABU among the respondents (33.7%)’
refers to the low mean percentage of correct diagnoses in clinical vignettes #1-6 (ABU cases) and ‘restricted understanding of… (20.0%)’ refers to the mean percentage of both correct diagnoses and proposed treatments in clinical vignettes #5-6 (ABU for which antibiotics are indicated). To make things clearer, we have changed the sentence as follows.

In the Results section, lines 216-218:

Previous: In general, respondents showed poor recognition of ABU (33.7%) and also had restricted understanding of the indications of antibiotic use for ABU (20.0%).

Revised: In general, the respondents showed poor recognition of ABU (33.7%) and also had a limited understanding of the indications for antibiotic use (20.0%), judging from the responses to the clinical vignettes involving ABU (Table 2).

7) Results, lines 245-247: could the authors analyze whether the concerns about postoperative infections were higher in surgical residents than in non-surgical residents? The information about initiating antibiotics despite knowing that the patient had ASB is one of the most novel aspects of this manuscript and could thus be developed further.

We would like to thank the reviewer for this advice. We have analyzed this matter and have added the result in the revised Results section.

In the revised Results section, lines 234-236:

Concern about postoperative infection was higher among surgical residents than non-surgical
Discretionary Revisions

1) Table 2, case 4: whether or not to treat ASB before hip arthroplasty is still controversial. The authors might acknowledge this in the text or comment on specific policies at their hospital.

We agree with the reviewer’s comment and have revised our manuscript accordingly. At the study hospital, it is generally not recommended to treat ABU before hip arthroplasty.

In the revised Discussion section, lines 293-294:

Although this remains controversial, we generally do not recommend treating ABU before hip arthroplasty in the study hospital

C. Response to Reviewer #3’s comments

Overall comments

An interesting manuscript describing 2 issues: an assessment of the amount of inappropriate ABU treatment occurring, and patient/provider factors associated with such use, and a survey of resident knowledge/attitudes regarding the management of ABU. Importantly, the survey was performed approximately a year after the assessment of ABU treatment, making any correlation between the two of questionable value. In some sections of the discussion it
seems that correlations are being drawn between the two, which is not appropriate. I would consider reporting the two aspects of this study in separate reports – each is interesting in its own right, but they really are separate studies of the same general issue.

We have dealt with the main issue raised here in our response to the editor’s comment. Please see that response. In addition, as the reviewer points out, each of the issues would be interesting in itself; however as shown by the title of our manuscript, our purpose was to identify the factors influencing physicians’ management of bacteriuria in order to develop further interventions. Therefore we believe that it is more appropriate to link the assessment of ABU treatment with the survey of physicians.

**Major revisions**

1. Lines 267-71: Linking the survey answers to the level of appropriate or inappropriate treatment of ABU is not appropriate—although it may be that some of the providers answering the survey provided some of the care, this is not certain. The fact that the survey was a year or more after the care provided, with some of the residents likely having left this hospital, makes such assumptions highly dubious. I would consider reporting the 2 components of this study in separate reports: one regarding the level of inappropriate ABU treatment and the factors associated with it, and the other on the results of a survey of ABU in a hospital with a documented high level of inappropriate treatment of ABU.

Please see our response to the editor’s comment and our response to this reviewer’s previous comment.
Minor revisions:

1 - Need to define ABU in abstract

We have added the definition of ABU to the abstract, as the reviewer recommends.

In the revised Abstract, lines 57-58:

ABU was defined as a positive urine culture (≥10^5 cfu/mL) without symptoms or signs suggesting UTI.

2 - Line 175: Any validation of the survey questionnaire should be mentioned (piloted on X number of patients, developed by Y number of ID specialists, adapted from previous surveys, etc).

We have added comments on the validation of the survey questionnaire as follows.

In the revised Methods section, lines 163-164:

The questionnaire was based upon prior research, and revised after review by infectious diseases physicians and professionals in our institution.

3 - Line 203: From the figure, it appears that only cultures with 100,000 cfu/mL are accounted for. Can the authors provide a number for how many total urine cultures were performed in
this period, and how many had some (but not high-count) bacteriuria/funguria?

In total, 25,704 urine cultures were performed at the study hospital in 2011. Among them, 6,269 urine cultures were performed for adult hospitalized patients, and 1,529 of these grew some bacteria/fungi. The number of urine cultures which grew less than $10^5$ cfu/mL was 362, and 1,167 grew $\geq 10^5$ cfu/mL. We have added these details in the revised Results section.

**In the Results section, lines 189-191:**

**Previous:** We identified a total of 1167 episodes of bacteriuria during the study period.

**Revised:** A total of 6,269 urine cultures were performed among adult inpatients during the study period, of which 1,529 grew microorganisms. Among these we identified 1,167 episodes of positive urine cultures that grew $\geq 10^5$ cfu/mL, and another 362 episodes with lower counts.

**Discretionary revisions:**

1-Abstract: Although seems intuitive that further education would help with ABU management, this has not been shown. Suggest change “importance of further education” to “importance of developing solutions to the problem of inappropriate treatment of ABU.”

We have done as the reviewer suggests.

**In the Abstract, lines 72-75:**
Previous: Lack of knowledge and discrepancy between knowledge and practice contributed to antimicrobial overuse for ABU, which highlight the importance of further educational interventions.

Revised: Lack of knowledge, and discrepancies between knowledge and practice, contributed to antimicrobial overuse for ABU. Our findings highlight the importance of developing interventions, including education, audit and feedback, to tackle the problem of inappropriate treatment of ABU.

2- Line 111: Suggest different wording than “profitable”—implies that stewardship programs are making money on this. “High-yield” might be a better term. Another reason to focus on ABU that might be highlighted is the preponderance of Gram-negatives found in urine cultures, and the lack of new agents active against these organisms.

We have revised the manuscript as suggested.

In the Background section, lines 94-96:

Previous: Reducing unnecessary antibiotic use for ABU is one of the profitable areas in the antibiotic stewardship program, considering the large amount of antibiotics used for UTI of hospitalized patients and the frequent misdiagnosis of ABU as UTI

Revised: Reducing unnecessary antibiotic use for ABU is a high-yield area in the antibiotic stewardship program, considering the large amounts of antibiotics used for UTI in hospitalized patients and the frequent misdiagnosis of ABU as UTI [14].
3-Line 140: Limiting the cultures to those with 100,000 cfu/mL likely captures most episodes of ABU that are inappropriately treated, but low-count bacteriuria can both cause clinical infections and can also be found asymptptomatically (even though it may not meet the surveillance definition for ABU, which requires isolation of the same organism at high count x2 with an interval of 1 week—a rather useless clinical definition). Focusing on only high-count bacteriuria likely understates the magnitude of this problem by some degree.

We agree with the reviewer’s comments. Only urine cultures yielding $\geq 10^5$ cfu/mL of microorganisms are routinely reported at the study hospital, unless there is a doctor’s request to report culture results with low counts. Therefore, we were only able to locate urine cultures with $\geq 10^5$ cfu/mL of microorganisms and limited our study to those cultures. We have explained this in the revised manuscript as follows:

In the revised Methods section, lines 112-114:

Positive urine cultures were defined as the presence of bacteria or yeast $\geq 10^5$ cfu/mL in urine, because only cultures yielding $\geq 10^5$ cfu/mL of microorganisms are routinely reported at the study hospital unless there is a request for reporting low-count bacteriuria.

4-Line 165: Note that the survey was administered to physicians in October 2012, whereas the urine clinical data was collected for calendar year 2011. Presumably many of the surveyed providers were not providing care in this hospital in 2011, and those that were may not have been caring for the episodes of ABU recorded. Linking the survey and the clinical
results is ill-advised.

Please see our response to the editor’s comment.

5- Line 307-9: Was this prospective chart review done as a portion of this study? Is so, needs mention in methods. If performed for another study, this should be specified and a reference provided, if the experience has been published.

Please see our response to comment 7 of Reviewer #1

6- Lines 322-3: the finding that so many residents report practicing contrary to their reported knowledge is striking; future surveys and/or focus-group based studies would be of interest to explore the drivers of this contradictory behavior.

We thank to the reviewer for this comment. We have added further information in the discussion of the revised manuscript:

In the revised Discussion section, lines 308-311:

Practice-based audit, and feedback to help physician detect the errors of their practices, as well as fundamental educational efforts are of critical importance in overcoming this gap. Further studies are needed to explore the drivers of physician practice that contradicts their knowledge.
7- Lines 328-30: I would caution against recommending efforts that have a modest (if any) track record at reducing ABU. In particular, I’m unaware of strong data supporting educational efforts with improved management of ABU. Audit and feedback has a better evidence base, although unfortunately an initial dose (or more) of antimicrobials are often administered before the stewardship team is able to approach the providers.

We agree with the reviewer’s comment. We did not mean to emphasize only educational efforts for reducing inappropriate ABU management. The relevant findings of our study were physician’s knowledge deficits, misperceptions, and the discordance between knowledge and practice. Based on these findings, we suggested that the antimicrobial stewardships including education for better recognition of clinical situations and antibiotic use, and audit and feedback for detecting their errors of management are needed. We have revised the manuscript in response to the reviewer’s comment:

In the Discussion section, lines 308-309:

Previous: To overcome this gap, educational efforts and practice-based audit and feedback, encouraging guideline adherent management, are of critical importance.

Revised: Practice-based audit, and feedback to help physician detect the errors of their practices, as well as fundamental educational efforts are of critical importance in overcoming this gap.

In the Conclusions section, lines 328-330:
Previous: Therefore, an antimicrobial stewardship program including the education for indication and interpretation of urine culture and clinical intervention on antimicrobial prescription is required to promote appropriate antimicrobial use for bacteriuria.

Revised: Therefore, interventions addressing both education to improve knowledge and audit and feedback to overcome the barriers to following guidelines are warranted.

8- Section on weaknesses: In addition to the weaknesses mentioned by the authors, drawing a close linkage between the 2 components of this study is a major one. Strongly consider de-linking them.

Because of the time between chart review and the resident survey, linking the two components could be considered a weakness but we believe that it is also a strength of our study looked at from a different angle. We have added a comment about this limitation to the revised manuscript as we acknowledge what this reviewer (and the others) has pointed out. As already stated we believe it is better to link them considering the purpose of the study.

In the Discussion section, lines 318-322:

Third, as we surveyed physicians in the year after the care was provided (2012), some of the residents were not the same as those who actually cared for the episodes of bacteriuria in 2011. However, we believe that the inappropriate antibiotic use data can still be reasonably linked and correlated with the survey considering that the majority of the residents surveyed did practice in 2011.
SUPPLEMENTARY DATA

Questionnaire for resident physicians

Please read the following clinical vignettes and indicate your decisions about diagnosis and treatment.

1. A 50-year-old man with hypertension was seen for his annual physical exam, and had no urinary symptoms. Routine UA showed pyuria; UC grew $\geq 10^5$/ml of *Escherichia coli*.

1) What is your diagnosis?

☐ Asymptomatic bacteriuria   ☐ Urinary tract infection   ☐ Uncertain

2) Would you prescribe antibiotics?

☐ Yes                      ☐ No                        ☐ Not sure

2. A 70-year-old woman with a history of recurrent UTI was admitted due to trauma, without urinary symptoms. UA showed pyuria; UC grew $\geq 10^5$/ml of *Escherichia coli*

1) What is your diagnosis?

☐ Asymptomatic bacteriuria   ☐ Urinary tract infection   ☐ Uncertain

2) Would you prescribe antibiotics?

☐ Yes                      ☐ No                        ☐ Not sure

3. A 68-year-old man with an indwelling Foley catheter had cloudy urine, without urinary
symptoms or signs of infection. UA showed pyuria; UC grew $\geq 10^5$/ml of *Klebsiella pneumoniae*.

1) What is your diagnosis?

☐ Asymptomatic bacteriuria ☐ Urinary tract infection ☐ Uncertain

2) Would you prescribe antibiotics?

☐ Yes ☐ No ☐ Not sure

4. An 82-year-old woman without urinary symptoms was seen preoperatively before total knee arthroplasty. A preoperative UC grew $\geq 10^5$/ml of *Klebsiella pneumoniae*.

1) What is your diagnosis?

☐ Asymptomatic bacteriuria ☐ Urinary tract infection ☐ Uncertain

2) Would you prescribe antibiotics?

☐ Yes ☐ No ☐ Not sure

5. A pregnant woman at 12 weeks of gestation without urinary symptoms presented with pyuria, nitrite positivity on UA. UC grew $\geq 10^5$/ml of *Escherichia coli*.

1) What is your diagnosis?

☐ Asymptomatic bacteriuria ☐ Urinary tract infection ☐ Uncertain

2) Would you prescribe antibiotics?
6. A 75-year-old man was about to undergo transurethral resection of the prostate. A preoperative UC grew $\geq 10^5$/ml of *Klebsiella pneumoniae*.

1) What is your diagnosis?
- □ Asymptomatic bacteriuria
- □ Urinary tract infection
- □ Uncertain

2) Would you prescribe antibiotics?
- □ Yes
- □ No
- □ Not sure

7. A 68-year-old woman admitted to the ICU with altered mentality due to drug intoxication developed SIRS. She had an indwelling Foley catheter. UC grew $\geq 10^5$/ml of *Escherichia coli*. No other suspected infection focus was found.

1) What is your diagnosis?
- □ Asymptomatic bacteriuria
- □ Urinary tract infection
- □ Uncertain

2) Would you prescribe antibiotics?
- □ Yes
- □ No
- □ Not sure
Please read the following questions and indicate your opinion (multiple choices are allowed except for question #11).

8. What would you do next for a patient without any lower urinary tract symptoms but with pyuria and bacteriuria in his/her routine urinalysis?

☐ Ask the patient again about the existence of urinary symptoms and repeat the physical exams

☐ Repeat the urinalysis in view of the possibility of contamination or laboratory error

☐ Order urine culture immediately

☐ Check for leukocytosis or elevated inflammatory markers

☐ Prescribe empiric antibiotics for urinary tract infection

9. If you have ever ordered urine cultures for patients without urinary symptoms, what was the reason for doing so?

☐ I order urinalysis with urine culture for every patient on admission or for those who are undergoing surgery, as a routine screening

☐ I order urine culture for patients with abnormalities in routinely performed urinalysis, such as pyruia, hematuria, or positive nitrite

☐ I order urine culture as one of a routine panel of tests for patients suspected of having an infectious disease, not only when urinary tract infection is strongly suspected

☐ I order urine culture routinely before prescribing antibiotics even if it is not for urinary
tract infection

[ ] I order urine culture for patients with indwelling urinary catheter as a routine screening

10. What would you take into account in diagnosing urinary tract infection when a patient gives a positive urine culture ($\geq 10^5$ cfu/mL of microorganism)?

[ ] Patient’s urinary symptoms or signs including dysuria, urgency, frequency, suprapubic pain or tenderness or fever

[ ] Blood test results including peripheral white blood cell counts, erythrocyte sedimentation rate, or level of C-reactive protein (CRP)

[ ] Presence of any abnormalities in the urinalysis (e.g. pyuria, hematuria, positive nitrite)

[ ] Existence of an indwelling urinary catheter

11. Have you ever prescribed an antimicrobial agent to a patient with asymptomatic bacteriuria despite being aware that it is not indicated?

[ ] Yes  [ ] No

12. If you answered ‘yes’ to question #11, please indicate the reason of prescribing the antimicrobial agent.

[ ] Because of the patient’s abnormal urinalysis

[ ] Because of the patients’ laboratory findings with elevated CRP or leukocytosis
In order to prevent surgical complications for a patient undergoing surgery

In order to prevent asymptomatic bacteriuria from developing into symptomatic urinary tract infection

Because of the patient’s past history of urinary tract infection

Because the patient was immunocompromised

Because of a senior doctor’s pressure to prescribe antibiotics against my judgment

Please answer the following questions regarding your demographic status

13. What is your gender? □ Male □ Female

14. What is your age? ( ) years old

15. What is your specialty in training?

□ Internal medicine □ Neurology □ Rehabilitation medicine

□ Psychiatrics □ General surgery □ Neurosurgery

□ Orthopedic surgery □ Plastic surgery □ Thoracic surgery

□ Urology □ Otorhinolaryngology □ Obstetrics and Gynecology

□ Ophthalmology
16. What is your level of residency?

- □ 1st year of residency
- □ 2nd year of residency
- □ 3rd year of residency
- □ 4th year of residency