Author’s response to reviews

Title: External validation study of a clinical decision aid to reduce unnecessary antibiotic prescriptions in women with acute cystitis

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Thomas Frese, Editor

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Response letter addressing reviewer’s comments regarding study “External validation study of a clinical decision aid to reduce unnecessary antibiotic prescriptions in women with acute cystitis (FAMP-D-00105).

Dear Dr Frese,

Below are the point-by-point responses to the reviewers concerns raised in their review of the above manuscript, and where changes have been made in the revised manuscript.

A. Response to Comments by Reviewer 1, Dr. Ai Theong Cheong:

We thank Dr Cheong for having reviewed the paper. We agree the application of and validity of the decision aid in a developing country will need further evaluation. A comment has been added on pg. 11, line 265-66.
B. Response to Comments by Reviewer 2, Dr. Nick Francis - we greatly appreciate Dr. Francis’ review and comments. Below are our responses.

1. “Suggest including the cut point for positivity (> 102 CFU/ml) used in the study in the abstract” - the following has been included in Line 30-31 of the abstract on page 2 - “... compared to a gold standard positive urine culture (defined as >102 cfu/ml).” – we have also included the SI units (CFU/L) as well as in the Methods section.

2. Introduction:

“make it clear that you previously developed a rule (2002 paper), which was then validated and modified (2007 paper), and it this this modified rule that you are now validating” – additional explanation has been added to clarify the process of developing and modifying the rule on page 4, lines 80-83, and 90-92.

“suggest you indicate a range of culture positivity rates that have been shown in previous studies, with an explanation some of the variation relates to the difference in cut points, rather than just the one from your own study’ - while we agree with the reviewer that different positive culture rates have been reported in some general practice settings, it was unclear what points in the introduction the reviewer was referring to. It was unclear if by cut points, he met the microbiologic cut-points for determining a positive culture or some other aspect. We had included a comment in the submitted manuscript under limitations in the Discussion on page 11, (former) lines 259-261 regarding the impact of differing prevalences of positive cultures on the decision aid performance, as for all decision aids. We also included the rationale for choosing our cut-point in terms as the guideline recommend microbiologic cut point endorsed by both North American and European microbiologic societies (reference 1). As this comment was somewhat unclear as to what was being requested, we have not included a change in the Introduction section regarding this point. However, we have added further comments in the Discussion, pg.12, lines 277-282 to address the reviewer’s point below regarding differing thresholds used for determining a positive urine culture in some studies.

“Suggest describing the decision aid component in the introduction rather than the methods’ - the decision aid components includes both a set of clinical criteria components criteria for assessment and a set of recommended actions that a physician should take based on the criteria. The paragraph from the Methods sections describing both components has been moved (former pg 6, lines 129-135) to the introduction as suggested, on page 4, lines 83-88.

3. Methods:

“”I would suggest moving the description of the decision aid to the intro section” – this has been addressed as noted above.
“why was blood/erythrocytes not recorded when this has been shown to be a helpful predictor (if combined with leukocytes) in another study?” - the rationale for the final decision aid model was described in the original 2002 model development paper, and was not revisited here as the objective was the validation of a previously derived decision aid. Briefly, in the model development process a broad range of potential clinical and urine dip predictor variables, including hematuria which did demonstrate a univariate association with having a positive culture, were collected on each woman and through a process of forward and backwards stepwise logistic regression modeling, different variables were gradually removed and reintroduced into the model to determine if useful additional discrimination for predicting a positive urine culture was added by retaining a given variable. Hematuria was not found to add additional predictive power beyond the other clinical and urine variables in multivariate modeling. It is important to realize that our decision aid includes both clinical and urine variables combined, whereas the study by Little et al (Br J Gen Pract 2010, now reference 20) for instance, that included hematuria, provided separate decision aid models for just clinical or just urine variables. As physicians use both pieces of information in clinical practice, we have chosen to combine all the clinical and urine variables in a decision aid model. This difference may explain why hematuria did not remain in our multivariate association although it did demonstrate a univariate association. Had we limited the aid to just urine predictors as in the study by Little et al, hematuria may have remained as well.

“Were reviewers of the urine cultures blinded to the other variables?” – yes, the laboratory urine culture reports themselves were reviewed by the study clinical investigators, separate from the physician’s recorded clinical variables, which were on separate office recording forms that were entered separately into one database by a research assistant who was not involved in the assessment of the culture reports. A comment that the urine culture were reviewed blinded to the clinical variables has been added to the Methods section on page 6, lines 133-134

4. Results:

“Only 330/15,742(2%) of approached physicians participated. This should be discussed in the Discussion section.” - A few lines have been added acknowledging this on page 11,lines 267 to page 12, line 272.

“Urine culture only obtained in 57.2%,and final analysis on 397/752 (52.8%) of recruited women. This is discussed as a limitation” - as the reviewer acknowledges this has been discussed, No further revisions were made regarding this comment.

“Suggest moving the comparison of excluded and included women to the start of the results section” – This section (former pg. 10 lines, 218-226) has now been moved to the start of the Results section on page 8, lines 168-175. This has resulted in changing the supplementary table including these results to Supplementary Table 5 from (the previous) Supplementary Table 6.
5. Discussion:

“On page 12 you indicate that other decision aids have been proposed for acute cystitis, and that none have undergone validation. You cite studies by Dobbs from 1987 and Knotterus from 2013. You did not include the work by Little et al. I would be interested in seeing some discussion comparing your work with theirs, or at least describing why you feel it is not comparable.” - we thank Dr. Francis for pointing out this omission. We have now included the 2010 paper by Dr. Little as reference 20. A discussion and comparison of the key differences of our findings with theirs is now included on pg 12, lines 287-296 on page 13.

“One of the key differences is that they (Little et al) used a higher cut point (>103) for urine culture positivity. However, I think it is worth recognizing, and describing, the fact that there are different definitions of microbiologically confirmed UTI used around the world, and it is not entirely clear how this relates to response to antibiotic treatment. Furthermore, it is worth highlighting that some studies have suggested a benefit from antibiotics in women with negative cultures, and therefore the ‘gold standard’ of urine cultures does not necessarily equate with the need for antibiotics.” – we have now included a discussion about the differences in thresholds for positivity of cultures on page 12, lines 276-283. As noted in the text, the differing thresholds appears to have had little difference on the prevalence of positive urine cultures overall, at least in primary care, as evidenced by the similar prevalences of positive cultures in the studies by Little et al (66%)20, Knotterus (61%)19 and our current (62%) and previous studies (63%)8. As commented on, this is likely because the majority of women with symptomatic cystitis symptoms that seek medical care have higher colony counts that exceed both thresholds, and only a minority likely have the lower thresholds resulting in little impact on the overall positive culture rates. As far as women with negative culture responding to antibiotics, we have included reference 21 which is a randomized trial that reported this conclusion. As noted in our discussion (pg 12, lines 283-286), the threshold for a positive urine culture in that study was the less sensitive microbiologic definition of >105 cfu/ml. This may have resulted in some women being deemed a ‘negative’ culture that might have been bacteriologic positive by the lower 102 or 103 colony count thresholds now used. Treating all women with urine symptoms irrespective of culture results would increase overall antibiotic utilization rates at a time when strategies to reduce unnecessary antibiotic utilization to address increasing rates of microbial resistance is the norm. In addition, the study by Gagyor et al (ref 16) showed the high spontaneous resolution rate of even bacteriologic positive cystitis, although not treating all of these cases resulting in some women having acute pyelonephritis. Current international guidelines for managing cystitis (ref 1), endorsed by both North American and European societies, do not recommend treatment of all women with cystitis symptoms, or those with negative culture results.

We trust the above revisions have addressed the concerns of the reviewers and look forward to your response.
Sincerely

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Corresponding Author