Reviewer's report

Title: Aminoglycoside combination therapy for childhood urinary tract infection due to extended-spectrum beta-lactamase-producing Escherichia coli or Klebsiella pneumoniae

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Reviewer: Ritu Banerjee

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The manuscript by Han et al describes characteristics and outcomes of children with febrile UTIs who were treated with non-carbapenem therapy at a single institution in South Korea. The study addresses an important question. As the rates of ESBL-producing Gram negative pathogens increase, clinicians are being forced to use carbapenem antibiotics (traditionally last resort agents) as empiric therapy, which selects for carbapenem-resistance. For patients with UTIs caused by ESBL-producing strains, can non-carbapenem empiric antibiotics be used?

Overall, the manuscript is well written. After excluding children with HAIs and comorbidities, the authors identified 205 unique patients with febrile UTI; only 22 (10%) had ESBL strains. They found no differences in baseline characteristics or outcomes between ESBL and non-ESBL groups. The vast majority of all subjects in both groups received combination therapy with an aminoglycoside and beta-lactam antibiotic. The authors conclude that combination aminoglycoside/betalactam therapy is an alternative to carbapenem therapy for empiric treatment of febrile UTIs in children.

Major compulsory revisions

The main concern regarding this study is that the small number of patients with ESBL strains limits power to detect differences in clinical outcomes between those with ESBL vs. non-ESBL strains. This needs to be clearly stated in the Discussion and conclusions. Also, the majority of patients received a third generation cephalosporin and aminoglycoside combination. It is likely that the aminoglycoside rather than the 3rd generation cephalosporin, or the combination of the 2 agents, was effective against the ESBL strains. This needs to be stated more clearly in the discussion.

Minor Essential Revisions

1. Abstract – should mention time period.

2. Methods –
   a. It is not clear if all patients were admitted to the hospital, or were some treated as outpatients?
   b. Were bacteremic patients excluded? Please clarify.
   c. Define empirical therapy.
d. Was combination therapy continued for the duration of IV antibiotic therapy in all patients? Or was it deescalated to a single agent in the non ESBL group? Was the beta-lactam antibiotic discontinued for the ESBL group?

e. Clarify how long after hospital discharge patients were followed for UTI recurrence?

f. How did they prevent clinicians from prescribing carbapenems for the patients with ESBLs? Is that standard practice at their institution, or are carbapenems restricted antibiotics?

3. Results – were there any antibiotic-associated adverse events such as nephrotoxicity?

4. Discussion

a. Should include a paragraph discussing limitations of the study including small # of ESBL strains, lack of comparator group of children with ESBL UTI who received carbapenem therapy, DMSA and VCUG were not done in all patients, catheterized urine specimens were not obtained, etc…

b. Their patients were largely infants, and about 2/3 in each group were males. This is different from the female predominance seen in many centers, and thus their results may not be generalizable to other patient populations.

c. Please comment on why oral cephalosporins were given to many of the patients with ESBL isolates upon hospital discharge? That seems inappropriate since they have ESBL isolates that are by definition, resistant to extended spectrum cephalosporins.

d. Comment on the broader implications of their finding. It appears that most patients in both ESBL and nonESBL groups received empiric combination antibiotic therapy. If ESBLs cause febrile UTIs in only 10% of their population, is empiric combination therapy warranted for all children admitted to the hospital with this condition? You will be overtreating 90% of patients with this strategy. Might it be possible to risk stratify and give combination therapy to only children at high risk for ESBL?

e. Clarify why in lines 211 and 212, the authors state that aminoglycosides in combination with BL or BL/BLIs are appropriate for treatment of ESBL UTI. Do they have any evidence that aminoglycoside monotherapy would not have been equally effective? Again, I am not sure the BL or BL/BLI agent is needed for treatment of ESBLs, although I understand the rationale for including these agents in the empiric regimen, before antimicrobial susceptibility results are available.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests:

I declare that I have no competing interests.