Author’s response to reviews

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

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Reviewer's report - 1

Reviewer: Ritu Banerjee

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.

→ Although the number of cases in the ESBL group in the present study was small, other recent studies also reported a favourable effect of non-carbapenem antibiotics on ESBL-producing strains. We added the following sentences in the “Discussion” section (line 251-255).

“Although therapeutic effect of non-carbapenems in UTIs due to ESBL-producing strains may change as the number of these cases is increasing, other recent studies also showed a favourable therapeutic effect of non-carbapenems in UTIs caused by ESBL-producing strains [11,12,17-21]. However, further studies including a large number of cases should be necessary to exactly define the effectiveness of non-carbapenems in UTIs due to ESBL-producing strains.”
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.

The following paragraph in the “Discussion” section was revised to emphasize the importance of aminoglycosides rather than cephalosporins (line 214-219).

“Although there were only two episodes, cefotaxime monotherapy in the ESBL group achieved defervescence and urinary sterilization in the present study. In addition, although 50.0% of the ESBL group received third generation, oral cephalosporins, there was no recurrent UTI during oral antibiotic therapy administered after discharge from the hospital. However, no controlled studies on the clinical efficacy of third generation cephalosporins in UTIs caused by ESBL-producing strains have been conducted and the use of third generation cephalosporins is significantly associated with the development of ESBL-producing strains [13,16,23].”

→ “Cefotaxime monotherapy in the ESBL group helped achieve defervescence and urinary sterilisation in the present study, but there were only two such cases. Although 50.0% of the ESBL group received third-generation oral cephalosporins after discharge from hospital and there was no re-emergence of fever or urological symptoms during oral antibiotic therapy, most children of the ESBL group had received a median of 6.0 days of aminoglycoside therapy during their hospitalisation. Prolonged antibiotic effect of aminoglycosides should be considered. In addition, no controlled studies on the clinical efficacy of third-generation cephalosporins in UTIs caused by ESBL-producing strains have been conducted and the use of third-generation cephalosporins is significantly associated with the development of ESBL-producing strains [13,16,23].”

Minor Essential Revisions

1. Abstract – should mention time period.

→ The study period, between 2010 and 2014, was additionally commented in the “Abstract” (line 34-35).

2. Methods –

a. It is not clear if all patients were admitted to the hospital, or were some treated as outpatients?

→ This study included all children treated for UTIs in the inpatient and outpatient clinics, and this comment was added in the “Methods” section (line 66-68). In addition, the comment that 11 episodes were treated solely at the outpatient clinic was added in the “Results” section (line 120).
b. Were bacteremic patients excluded? Please clarify.

→ Bacteremia accompanied eight episodes, however, intensive care was not given at all. This comment was added in the “Results” section (line 124-125).

c. Define empirical therapy.

→ The following sentence was added in the “Methods” section (line 96-97).

“Antibiotics that were initially administered to febrile children before the identification of the urinary pathogen and its antibiotic susceptibility were defined as empirical antibiotics.”

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?

→ The administration of empirical aminoglycosides was discontinued during hospitalisation for 16 (9.6%) episodes based on the antibiotic susceptibility results, and it was continued during the entire period of hospitalisation in the remaining episodes. This comment was added in the “Results” section (line 141-143).

Empirically administered amoxicillin/clavulanate and cefotaxime were non-susceptible to identified pathogens in 16 (76.2%) of the 21 episodes for which susceptibilities to administered antibiotics were evaluated in the ESBL group. Nevertheless, the non-susceptible amoxicillin/clavulanate and cefotaxime had been administered until discharge from hospital in all of the 16 episodes based on favourable clinical responses in the ESBL group. This comment was added in the “Results” section (line 161-164).

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

→ Most of the enrolled children have re-visited our outpatient clinic for several months or years, however, most of return visits were due to other medical causes rather than UTIs. Therefore, we could not exactly determine recurrent UTI episodes based on retrospective review of medical records.

In the present study, we evaluated the recurrence of UTI between the discharge from hospital and the first revisit to the outpatient clinic. Among the 200 hospitalised cases, return visits to the outpatient clinic were made for 193 (96.5%) of the episodes within a median of 7.0 days (IQR: 5.0-8.0) after discharge from hospital, and there were no re-emerging fever or urological symptoms during the period. This results was additionally commented in the “Results” section (line 152-155).

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?

→ Prescribing carbapenems has been restricted and allowed only with the permission of the infectious disease (ID) physicians in our hospital. Because attending physicians discussed with ID physicians whether to administer carbapenems or not to their patients, and ID physicians decide based on the patient’s response to empirically administered antibiotics, no children received carbapenems in our study. This comment was added in the “Discussion” section (line 187-191).

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

→ Most of enrolled children in the present study were younger than one year of age, and therefore, subjective hearing impairment due to aminoglycosides could not be evaluated. Nephrotoxicity was evaluated using serum creatinine levels, and the following results was additionally commented in the “Results” section (line 143-145).

“Serum creatinine levels were re-checked during aminoglycoside therapy in 81 episodes (72 in the non-ESBL group, nine in the ESBL group), but, none showed a rising serum creatinine level that was more than twice that of baseline.”

In the “Discussion” section, the following sentence was commented as a limitation of this study (line 264-267).

“Although definite nephrotoxicity was not observed in the present study, ototoxicity was not evaluated and serum creatinine levels were not repeatedly tested during aminoglycoside therapy in half of the episodes. Therefore, further studies determining the appropriate duration of aminoglycoside therapy, which guarantees both efficacy and safety should be performed.”

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…

→ Following paragraph was additionally commented as limitations of this study (line 248-257).

“Because we could not control the administered antibiotics and none received carbapenem therapy, treatment outcomes between carbapenems and non-carbapenems could not be compared. Risk factors for UTIs due to ESBL-producing strains could not be appropriately evaluated in the present study because of the small number of cases in the ESBL group. Although therapeutic effect of non-carbapenems in UTIs due to ESBL-producing strains may change as the number of these cases is increasing, other recent studies also showed a favourable
therapeutic effect of non-carbapenems in UTIs caused by ESBL-producing strains [11,12,17-21]. However, further studies including a large number of cases should be necessary to exactly define the effectiveness of non-carbapenems in UTIs due to ESBL-producing strains. The frequencies of APN and VUR may be inaccurate because the DMSA scan and VCUG were not performed universally, but in accordance with the attending physicians’ decisions.”

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.

→ The Nelson Textbook of Pediatrics described the male:female ratio in infants with UTIs as 2.8-5.4:1 and in children older than 1 to 2 years of age with UTIs as 1:10 (Elder JS. Urinary tract infections. In: Kliegman RM, Stanton BF, St. Geme JW, Schor NF, editors, Nelson Textbook of Pediatrics. 20th ed. Philadelphia: Elsevier, 2015;2556-62). In the present study, 188 (89.1%) of the 211 episodes occurred in children aged 1 year or younger, and the male:female ratio was 1.94:1 (124:64) among them. In children older than 1 year, the male:female ratio was 1:4.8 (4:19).

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.

→ Authors also thought such practices unreasonable. In our hospital, many UTI cases were treated by pediatricians not specializing infectious diseases, and the attending physicians might think that administered intravenous cephalosporins were effective to ESBL-producing strains based on the patient’s clinical and microbiological responses and did not ask ID physicians about oral antibiotic therapy after discharge from hospital for children diagnosed with UTIs caused by ESBL-producing strains. This might lead the doctors prescribing third-generation oral cephalosporins.

d. Comment on the broader implications of their finding. It appears that most patients in both ESBL and non-ESBL 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?

→ Please see the response to the next advice.
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.

→ We agree with you. We agonized about the application of aminoglycoside monotherapy in children presumably having UTIs. However, considering the possibility of having reactive pyuria due to a bacterial infection other than a UTI and urosepsis in febrile children with abnormal urinalysis and urinary microscopic examination results, empirical monotherapy with aminoglycoside, which is not so effective on Gram positive bacteria and cannot penetrate the blood-brain barrier, may not be appropriate. Therefore, empirical administration of BLs or BL/BLIs in combination with aminoglycosides and adjustment of antibiotics based on the results of urine culture and antibiotic susceptibility of the identified pathogens seem to be more reasonable than empirical aminoglycoside monotherapy. These were commented in the “Discussion” section (line 240-246). Also, the “Conclusions” section was revised as the follows (line 275-277). “Aminoglycosides can be an alternative to carbapenems in UTIs caused by ESBL-producing strains; however, further studies regarding oral antibiotic selection as well as the appropriate duration of intravenous aminoglycoside therapy are needed.” The title was revised from “Aminoglycoside combination therapy for childhood urinary tract infection due to extended-spectrum \( \beta \)-lactamase-producing \textit{Escherichia coli} or \textit{Klebsiella pneumoniae}” to “Aminoglycoside therapy for childhood urinary tract infection due to extended-spectrum \( \beta \)-lactamase-producing \textit{Escherichia coli} or \textit{Klebsiella pneumoniae}.”
Major compulsory revisions

I think that treatment of urinary tract infection due to ESBL is an important topic, especially in child.

1) Are the aminoglycosides systematically used for UTI or only for patients with severe sepsis or septic shock.

The important use of aminoglycosides in your study may have caused interpretation biases.

→ Empirical beta-lactams in combination with aminoglycosides have been administered for several decades in our hospital, regardless of the severity of illnesses in hospitalised children. This policy was established several decades ago when Korea was underdeveloped and various bacterial infections, including S. aureus, S. pneumoniae, and enteric Gram-negative bacilli, commonly occurred in Korea, and the policy has not been changed. Therefore, there should be no difference for severity of illnesses between children receiving aminoglycoside therapy and those not receiving. In addition, there was no child experiencing septic shock or receiving intensive care in the present study.

2) Is 99m technetium dimercaptosuccinic acid (DMSA) scan systematically used in case of acute pyelonephritis or only because of the study because this exam is usually a difficult to have.

→ Although the AAP guideline for UTI does not recommend performing a DMSA scan in children with UTIs, DMSA scans are performed in children diagnosed with UTIs in our hospital if parents do not refuse doing. Almost all pregnant women in the Republic of Korea receive regular antepartum care and repeated foetal ultrasonography, and therefore, clinicians in our hospital focus on identifying APN rather than urogenital structural anomalies in children diagnosed with UTIs. DMSA scans, which are more sensitive in diagnosing APN than renal ultrasonography, are performed for most UTI episodes in our hospital for such a purpose. This comment was added in the “Methods” section (line 90-93). In the present study, APN was identified in only 28 (15.1%) of the 186 episodes where renal ultrasonography was performed (data were not shown in the manuscript), however, APN was identified in 80.4% of episodes using DMSA scan.

3) How did you define "recurrent UTI" line 120? Please explain your choice.

→ The “recurrent UTI” meant a positive history of previous UTIs at the time enrolled in this study. The sentence was revised as the follows (line 130-131).
“A previous history of UTIs was identified for 10 (4.7%) of the episodes; however, the frequency of recurrence was not significantly different between the two groups.”

**Minor compulsory revision**

1) Why immunocompromised child are not included in your study?

→ For febrile immunocompromised children, empirical antibiotics with broader antibiotic spectrum compared with third-generation cephalosporins should be given. Accordingly, most immunocompromised children have already received broader spectrum empirical antibiotics, which are effective on ESBL-producing strains, such as cefepime, carbapenems, and antipseudomonal beta-lactams in combination with aminoglycosides. Therefore, we excluded immunocompromised children from the present study.

2) I think that it would be interesting to describe the susceptibility of strains to BL/BLIs.

→ The susceptibility rates to amoxicillin/clavulanate and piperacillin/tazobactam were reported in the Table 3. The susceptibility rate to ticarcillin/clavulanate was determined in 62 episodes, however, the result was not explained in the manuscript due to its similar antibiotic effect compared with piperacillin/tazobactam.