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OPEN PEER REVIEW

Antibiotic Resistance Patterns of Uropathogenic Causes of Urinary Tract Infections in < 3-Year-Old Children: A Single-Center Cross-Sectional Study

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About this report

This open peer review (OPR) report shows the public comments made on this article during peer review, by the reviewers, the associate editor and the editor-in-chief, for every revision round, together with the authors' replies. Comments appear only with the consent of the people who wrote them. Reviewers who chose to sign their report are named; the others are shown as "Referee". Comments are edited for language only, and confidential remarks to the editors are not included.

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1 Original submission

1 comment · 20 Mar 2023

Associate Editor

ACCEPT 20 Mar 2023

Dear author
Thank you for the manuscript.

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Revision 1

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Revise letter

Dear Editor,

Thank you for your kindness, and consideration.

Reviewer 2:

There are several syntax errors and mistake in presentation, which need revision: Few examples are shown below:

ABSTRACT:

The aim of this study was to evaluate the frequencies and antibiotic resistance patterns of uropathogenic causing UTIs.

Comment: …. to investigate the frequency and AMR pattern of uropathogenic bacteria.

Author Response:

The aim of this study was to investigate the frequency and antibiotic resistance patterns of uropathogenic bacteria causing UTIs in children under 3 years of age admitted to 17th Shahrivar Hospital in Rasht, Iran.

The highest percentage of uropathogenic causing UTIs was Escherichia coli (E. coli), which accounted for 56.4% of all UTIs in children.

Comment: E. coli was the most frequent cause of UTIs in children (56.4%), followed by Klebsiella (…%), …..

Author Response:

Escherichia coli (E. coli) was the most frequent cause of UTIs in children (56.4%), followed by Klebsiella (**33.2%**),

Comment: The highest antibiotic susceptibility was observed for ciprofloxacin, nitrofurantoin, amikacin, gentamicin, imipenem, and nalidixic acid. The highest resistance was observed to cephalothin, cephalexin, ampicillin, and amoxicillin.

Comment: There is no need to present susceptibility, but please present percentages of AMR for the resistance phenotypes.

Author Response:

It was revised.

The highest resistance was observed to cephalothin (77.1 %), cephalexin (77.1 %), ampicillin (78.8 %), and **amoxicillin** (100 %)**.**

Comment: Conclusion: You should describe highlight finding of your study. What is your important clinical massage? What is your new massage in microbiological view? Is hospital responsible for UTIs in <3 years old children or they are

community acquired? Is your finding support an increasing trend of AMR for uropathogenic bacteria in your city/hospital in children?

Author Response:

It seems that using aminoglycosides as the drugs of choice, and in case of any contraindications for aminoglycosides, third generation cephalosporins should be considered for empirical treatment. If there is no response to treatment within 48 to 72 hours, ciprofloxacin should be substituted unless the antibiogram indicates a more appropriate antibacterial agent. Of course, after the age of two years old, nalidixic acid or nitrofurantoin can be used in cases suspected of cystitis. Considering the high rate of antibiotic resistance, ampicillin, amoxicillin, cotrimoxazole and even cephalosporins are not recommended as primary empirical treatment for urinary tract infections in children.

Introduction:

Comment: Please write spp. after bacterial names in correct format.

Author Response:

It was revised.

Comment: Complications of UTIs and its side effect on patients' health are greatly described in the introduction; however, the study methodology is designed basic microbiology.

Author Response:

It was revised.

Methods:

Comment: Please add standard strains if they have used for control of disc diffusion tests.

Author Response:

We did not used.

Results:

Comment: Table 1 is not necessary.

Author Response:

It was deleted.

Comment: In the case of the presentation of laboratory tests (Table 2), their correlation with culture results could be presented statistically. A p value should be presented accordingly. The difference in the etiology of UTIs and length of stay in hospital between the two age groups of patients should also be presented statistically (Table 3).

Author Response:

It was revised and showed in figure 2 and 3.

Comment: Table 4. Both number and percentages of AMR are needed. There is no need to shoe % of sensitivity, please delete related numbers.

Author Response:

It was revised.

Comment: Table 5. There is no need to present AMR for all microbial agents, while details about each bacterial genus are shown in Table 4. Recommendation about appropriate medication for UTIs in this population could be described in the discussion section.

Author Response:

It was revised.

Comment: Please add frequency of MDR phenotype in your isolates according to the characterized resistance phenotypes.

Author Response:

It was revised.

Discussion:

Comment: Please prevent redundant sentences like “The most common cause of UTIs in our study was E. coli which showed good susceptibility to ciprofloxacin, nitrofurantoin, amikacin, gentamicin, and nalidixic acid.” This sentence was presented three times in discussion.

Author Response:

It was revised.

Comment: Please italicize name of bacteria throughout your text.

Author Response:

It was revised.

Comment: In your conclusion, please add correlations between the lab findings and your variables (length of hospital stay, age groups, medications, …) after their analysis. This correlation could be compared with the finding by other researchers

Author Response:

It was revised.

It seems that using aminoglycosides as the drugs of choice, and in case of any contraindications for aminoglycosides, third generation cephalosporins should be considered for empirical treatment. If there is no response to treatment within 48 to

72 hours, ciprofloxacin should be substituted unless the antibiogram indicates a more appropriate antibacterial agent. Of course, after the age of two years old, nalidixic acid or nitrofurantoin can be used in cases suspected of cystitis. Considering the high rate of antibiotic resistance, ampicillin, amoxicillin, cotrimoxazole and even cephalosporins are not recommended as primary empirical treatment for urinary tract infections in children.

2 Revision 1

1 comment · 10 Jun 2023

Associate Editor

MINOR REVISION 10 Jun 2023

Dear Editor-in-Chief of APID,
The revised version of the manuscript “Antibiotic resistance patterns of uropathogenic causing urinary tract infections in children under 3 years; A single center cross-sectional study” was reviewed. Most of the reviewers’ comments were considered in the new version. The following points are suggested:
1. spp. should not be presented in italics. Please also use the correct names of bacteria; there are incorrectly presented names, like E. Coli in Table 4.
2. Table 4 presents only the numbers of isolates. Please also add the percentages, since the frequency of AMR is presented in this table.

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Revision 2

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Minor Revise letter

Dear Editor,

Thank you for your kindness, and consideration.

Comment: spp. should not be presented in italic. Please also use correct name of bacteria; there are mis-presentations, like E. Coli in Table 4.

Response: They were corrected.

Comment: Table 4 presented just number of the isolates. Please add also the percentages, since frequency of AMR is presenting in this table.

Response: We were added the percentages of AMR to the table.

3 Revision 2

1 comment · 14 Jul 2023

Associate Editor

MINOR REVISION 14 Jul 2023

Dear Editor-in-Chief of APID,
The manuscript has been revised based on the comments, and its presentation has improved. However, the following need to be corrected before a final decision.
1. In Table 4, the headings are confusing (Total of Cases (n), No Number of AMR Percent, Percentage of AMR (%), Frequency of AMR (%)). The AMR% is related to the bacterial isolates; please correct the word "cases". What is the necessity of presenting the frequency of AMR (for example: resistance to ciprofloxacin [13]/total bacteria that are resistant to different classes of antibiotics [714])? If this column is not necessary, please delete it and describe "total number of bacteria" in the table legend.
2. In table 3, the antibiotics are referred to as cases in some instances and as items in others. Please correct this. An antibiogram is an in vitro test related to bacterial isolates, not cases or patients. Please add the percentage alongside the frequency (e.g., ciprofloxacin, [6 resistant strains of Klebsiella/total No. of Klebsiella isolates]*100).
3. What is the importance of laboratory findings like ESR, CRP, etc., that are presented in Table 1? Do the authors want to measure a correlation between multidrug-resistant UTI and, for example, elevated levels of CRP, ESR, etc.? If yes, such a measurement should be done; if not, the authors should describe the reason for their presentation in the introduction and discussion.
4. Combination therapy could be suggested in regions where the prevalence of MDR uropathogens is high. Since AMR resistance is presented based on detected bacteria in the study, conclusions about empirical therapy could be drawn on an agent-by-agent basis. For example, which antibiotic(s) is/are recommended for P. aeruginosa, Enterobacteriacea, and Staphylococci?

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Revision 3

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Dear Editor,

Thank you for informing me about the review of my manuscript. I appreciate the time and effort put into evaluating my work. I am pleased to hear that the manuscript has been deemed of sufficient quality to proceed with the review process.

I understand that the editorial decision requires a "Minor Revision" for the manuscript. I am grateful for the opportunity to address the reviewers' comments and make the necessary revisions to improve the manuscript further.
I am committed to making the suggested revisions promptly and thoroughly. I appreciate your guidance and assistance throughout this process and look forward to resubmitting the revised manuscript.

Thank you once again for your consideration and valuable feedback. I am eager to work on the revisions and contribute to the enhancement of the manuscript.

Sincerely,

Dr. Alireza Jafari

1. In Table 4, the headings are confusing (Total of Cases (n), No Number of AMR Percent, Percentage of AMR (%), Frequency of AMR (%). The AMR% is related to the bacterial isolates, please correct the word "cases". What is necessity of presenting the frequency of AMR (for example: resistance to ciprofloxacin [13]/total bacteria that are resistance to different classes of antibiotics [714]). If this column is not necessary, please delete it and describe "total number of bacteria" in the table legend.

Response: It was improved.

2. In table 3, the antibiotics referred in some ones as cases, and in others as item. Please correct it. Antibiogram is an in vitro test related to bacterial isolates, but not cases or patients. Please add percentage with the frequency (e.g. ciprofloxacin, [6 resistant strains of Klebsiella/total No. of Klebsiella isolates]*100).

Response: It was improved.

3. What are the importance of laboratory findings like ESR, CRP, etc that are presented in Table 1. Are authors want to measure a correlation between Multidrug resistant UTI and for example elevated level of CRP, ESR, ... If yes, such a measurement should be done, if not you should describe reason of their presentation in the introduction and discussion.

Response: In the current study, ESR was assessed in 105 patients, and it was found to be increased in 98.1% of the cases. This suggests that the majority of the patients had elevated ESR levels, indicating the presence of inflammation or an underlying condition. The mean ESR value in the studied samples was 38.61 ± 36.79. This indicates that, on average, the ESR levels were relatively high. The wide range in the standard deviation suggests that there was considerable variability in ESR values among the patients. C-reactive protein (CRP) was tested in 211 patients, and it was found to be positive in 42.7% of the cases. A positive CRP result indicates the presence of acute inflammation or infection. The lower percentage of positive CRP results compared to the increased ESR levels suggests that CRP may be less sensitive in detecting inflammation compared to ESR in this particular study. There is evidence to suggest that elevated levels of C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) can be associated with multidrug-resistant urinary tract infections (UTIs). CRP is an acute-phase protein that is produced by the liver in response to inflammation. It is commonly used as a marker of systemic inflammation. Studies have shown that CRP levels are often elevated in patients with UTIs, and this elevation can be even more pronounced in cases of multidrug-resistant UTIs. Elevated CRP levels indicate a more severe and prolonged inflammatory response. Similarly, ESR is a non-specific marker of inflammation that measures the rate at which red blood cells settle in a tube of anticoagulated blood. Like CRP, ESR levels can be elevated in patients with UTIs, particularly in cases of multidrug resistance. However, it's important to note that ESR can be influenced by various factors other than inflammation. While elevated CRP and ESR levels can be indicative of a more severe and resistant UTI, they are not definitive diagnostic markers for multidrug resistance. The gold standard for diagnosing multidrug-resistant UTIs is through laboratory testing, specifically antimicrobial susceptibility testing of the isolated bacteria. It is important to consult with a healthcare professional for a proper evaluation and interpretation of CRP and ESR levels in the context of a suspected multidrug-resistant UTI.

4. Combination therapy could be suggested in regions, where MDR Uropathogens are high. Since AMR resistance is presented based on detected bacteria in your study, empirical therapy could be concluded in an agent base way. For example, which antibiotic/s is/are recommended for P. aeruginosa, Enterobacteriacea, and Staphylococci?

Response: The choice of antibiotics for the treatment of multidrug-resistant uropathogens, such as Pseudomonas aeruginosa, Enterobacteriaceae, and Staphylococci, depends on several factors including local resistance patterns, patient-specific factors, and the severity of the infection. It is important to note that treatment recommendations can vary between regions and healthcare facilities, and it is crucial to consult local guidelines and infectious disease specialists for appropriate antibiotic selection. In general, combination therapy may be considered for multidrug-resistant uropathogens to improve treatment efficacy and reduce the risk of further resistance development. The specific combination of antibiotics will depend on the identified bacteria and their susceptibility patterns. For *Pseudomonas aeruginosa*, which is

known for its multidrug resistance, combination therapy with two or more antibiotics from different classes is often recommended. Commonly used antibiotics for *Pseudomonas aeruginosa* include carbapenems (e.g., meropenem, imipenem), antipseudomonal penicillins (e.g., piperacillin-tazobactam), cephalosporins (e.g., ceftazidime, cefepime), and fluoroquinolones (e.g., ciprofloxacin, levofloxacin)(23). However, susceptibility testing should guide the choice of antibiotics. For *Enterobacteriaceae*, which includes bacteria like *Escherichia coli* and *Klebsiella pneumoniae*, the choice of antibiotics may depend on the specific resistance mechanisms detected. Carbapenems (e.g., meropenem, imipenem) are often considered the drug of choice for extended-spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae*. Other options may include newer beta-lactam/beta-lactamase inhibitor combinations (e.g., ceftazidime-avibactam) or polymyxins (e.g., colistin)(24). Again, susceptibility testing is important for guiding treatment decisions. For *Staphylococci*, including *methicillin-resistant Staphylococcus aureus* (MRSA), treatment options may include vancomycin, daptomycin, linezolid, or newer agents such as ceftaroline or tedizolid(25). Susceptibility testing should be performed to determine the most effective antibiotic. It is crucial to note that the choice of antibiotics should be based on local resistance patterns, individual patient factors, and guidance from infectious disease specialists. Regular surveillance of antimicrobial resistance patterns is important to inform empirical therapy choices and ensure optimal treatment outcomes(26).

It is indeed recognized that antibiotic resistance is a significant concern in the treatment of pediatric UTIs. Empirical treatment should be based on local prevalence and patterns of antibiotic resistance, as you mentioned. In the study you mentioned, Escherichia coli (E. coli) was the most commonly isolated pathogen in UTIs. It is important to note that E. coli susceptibility patterns can vary between regions and over time. However, based on the susceptibility results reported in the study, E. coli showed susceptibility to ciprofloxacin, nitrofurantoin, amikacin, gentamicin, and nalidixic acid. Considering the potential side effects of ciprofloxacin in children, it is reasonable to consider alternative antibiotics with suitable therapeutic effects and fewer side effects, such as aminoglycosides (e.g., amikacin and gentamicin), as mentioned in the study. These antibiotics can be effective in controlling the disease. Nitrofurantoin and nalidixic acid were also mentioned as good choices for the treatment of lower UTIs (e.g., cystitis). However, they are not recommended for the treatment of upper UTIs and pyelonephritis due to their limited tissue penetration. It is important to consider the age of the children being treated, as mentioned in the study. Different age groups may have different susceptibility patterns and require tailored treatment approaches. The study acknowledges its limitations, including the age group of the children studied and the need for a larger, multicenter study to obtain more valuable and generalizable results. Conducting multicenter studies can provide a broader perspective on regional variations in antibiotic resistance patterns and guide appropriate empirical treatment choices. In summary, the choice of empirical treatment for pediatric UTIs should be based on local prevalence and patterns of

antibiotic resistance. Regular surveillance of resistance patterns is crucial to inform treatment decisions and ensure optimal outcomes for pediatric patients.

4 Revision 3

1 comment · 25 Jul 2023

Associate Editor

ACCEPT 25 Jul 2023

Dear Editor-in-Chief of APID,
The comments have been addressed, and the corresponding changes have been made. The manuscript is acceptable for publication in your journal.