Archives of Pediatric Infectious Diseases
Volume 10 · Issue 4 · e118809

OPEN PEER REVIEW

Incidence, Clinicomicrobiological Characteristics, Risk Factors, and Treatment Outcomes of Bacterial Infections Following Liver Transplantation in Pediatrics: A Retrospective Cohort Study

Afsaneh Vazin, Reza Shahriarirad, Nazanin Azadeh, Nahid Parandavar, Kourosh Kazemi, mojtaba shafiekhani

SUBMITTED	REVISED	ACCEPTED	DOI
3 Sep 2021	29 Mar 2022	7 Apr 2022	10.5812/pedinfect-118809

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.

More about open peer review: brieflands.com/knowledgebase/opr

Contents

1 Original submission Associate Editor 2
2 Revision 1 3
Authors' reply to reviewers 4
Reviewer and editor comments 12
3 Revision 2 13
Authors' reply to reviewers 14
Reviewer and editor comments 16

1 Original submission

1 comment · 5 Nov 2021

Associate Editor

MINOR REVISION 5 Nov 2021

Dear author
Please specify the follow-up time for patients to measure the outcome in the "Methods" section.
Regards

2

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.

Dear Editor and Reviewers,

Thanks for reaching out to us regarding the manuscript entitled "The incidence, clinicomicrobiological characteristics, risk factors, and treatment outcome of bacterial infections complicating liver transplants in children, A retrospective comparative study from Shiraz Organ Transplant Center, Iran" (previously entitled: "Bacterial Infections after Pediatric Liver Transplantation"). We believe that these comments have helped us enhance the quality of the manuscript. We also have done our best to revise as well as improve the paper according to the comments. Herewith, we provided the authors' response to each comment right after each statement. Also, all the changes have been addressed in the manuscript through track changes.

- ***Reviewer 1:***

1. Abstract: Please give the total number of cases and statistic results in the result part.

Authors response: This information has been added as requested.

2. Introduction:in this sentence:" Since there are significant differences among pediatric and adult patients regarding their susceptibility to various organisms and infection courses" please give the reference.

Authors response: Related reference has been added as requested.

3. Fluconazole dose is very high. It is 12 mg/kg/day in medscape.

Authors response: The dose has been corrected to 3 to 5 mg/kg/day

4. Discussion: Please check all the important variables and discuss the literature with you results accordingly.

Authors response: In the discussion section, the prevalence of bacterial infections, the distribution pattern of gram-positive and negative pathogens, the risk factors for bacterial infections, as well as

the clinical outcome are discussed based on the results of our study and other studies. However, according to the journal instructions (5000 words for the original article) if a matter is specifically intended by the esteemed referee, please mention it for further discussion.

5. In this sentence" Bacterial infections constituted the majority of documented infections. Interestingly, in the , a reduced size or split donor liver was associated with increased risk of developing bacterial infections" a part of sentence is omitted plz correct it.

Authors response: Thank you for pointing out this short coming. The mentioned section has been completed.

6. Since many variables are studied in this article please check to discuss the variables with significant statistical results, for example death in infected group was not discussed in the discussion part

Authors response: Details and data related to mortality and bacterial infections based on the results of our study and similar studies were added to the discussion section as suggested.

- ***Reviewer 2***

1. Methods: Antibiotic Prophylaxis: The authors stated: "For the first 6 months following LT, all patients were treated with trimethoprim/sulfamethoxazole (TMP/SMX) (23 mg/kg/day) for Pneumocystis jiroveci prevention. Ganciclovir (10 mg/kg/day) and fluconazole (35 mg/kg/day) or valganciclovir (13 mg/kg/day) were used for fungal and viral (Cytomegalovirus) prophylaxis, respectively." Kindly re-check the dose of fluconazole.

Authors response: Fluconazole dose has been corrected to 3 to 5 mg/kg/day

2. Also, it is suggested to write the dose of trimethoprim/sulfamethoxazole based on the trimethoprim or sulfamethoxazole.

Authors response: All patients received trimethoprim/sulfamethoxazole (TMP/SMX) prophylaxis with 2-3 mg per kilogram TMP for Pneumocystis jiroveci prevention.

3. Microbiological Evaluation: Did the authors perform MIC? Did they use E-test for detecting vancomycin resistance? Kindly add more details to this part.

Authors response: Due to the fact that it is not possible to perform MIC measurement through ETEST in our center, so all resistance / sensitivity data is based on the results of disk diffusion results , which is why this issue was added to the limitation section as a limitation of this study.

4. Results: Kindly categorize the infections according to a defined time table for example during first month, between 1 to 6 months after transplantation and 6 -12 month after transplantation. Then reanalyze the data and determine which infections and which microorganisms were the most prevalent in each group.

Authors response: We thank the reviewer for this valuable comment. The requested changes and reanalysis were made and detail added to table 3.

5. Which viral agents were detected in this study? For example, “CMV infection” in the Table 1 is not clearly explained. Was CMV infection occurred after transplantation? Were the patients symptomatic? What was the viral load? What was the time of infection? before or after transplantation and if it was in the post transplantation time, when was it occurred? during the first month? Between 1 to 6 months after transplantation? Was there any relationship between previous CMV infection and bacterial infection?

Authors response: Due to the fact that the focus of this study is on bacterial infections after transplantation, so information related to viral or fungal infections have not been collected.

However, CMV infection refers to CMV infection within one year after liver transplantation. Diagnosis was based on a positive CMV PCR blood test or Based on the opinion of a pediatric infectious disease specialist, they were eligible to receive a therapeutic dose of ganciclovir or valganciclovir.

As shown in Table 1, no significant association was observed in terms of CMV infection between pediatrics with bacterial and other infections. Therefore, in our study, no significant relationship was observed between CMV infection and bacterial infection, which is contradicting to reports from a number of studies. This may be due to the low sample size and one-year follow-up duration of our patients.

Ref: [van den Berg AP, Klompmaker IJ, Haagsma EB, Peeters PM, Meerman L, Verwer R, The TH, Slooff MJ. Evidence for an increased rate of bacterial infections in liver transplant patients with cytomegalovirus infection. Clin Transplant. 1996 Apr;10(2):224-31. PMID: 8664524.] [Nichols WG, Corey L, Gooley T, Davis C, Boeckh M. High risk of death due to bacterial and fungal infection among cytomegalovirus (CMV)-seronegative recipients of stem cell transplants from seropositive donors: evidence for indirect effects of primary CMV infection. J Infect Dis. 2002 Feb 1;185(3):273-82. doi: 10.1086/338624. Epub 2002 Jan 17. PMID: 11807708.]

6. Table 1 contains several data. However, the reader does not understand the importance and relationships. What was the importance of “Type of Surgery “in this study?

   Authors response: We provided these data to demonstrate an overview of the clinical features of the patients in our study, along with the therapeutic and surgical measures applied for them. Furthermore, we wanted to demonstrate that some variables such as type of surgery had no effect on the infectious outcome of the patients.

Specifically about two variables Type of Anastomoses and type of surgery,Due to the fact that in each method the type of anastomosis are different and in one of the methods anastomosis to the jejunum is used to drain the bile (Roux-en-Y Choledochojejunostomy), so the possibility of bacterial translocation increases and in some Studies have cited it as a risk factor for infection after liver transplantation:

[Bacterial translocation during liver transplantation: A randomized trial comparing conventional with venovenous bypass vs. piggyback methods]

7. Kindly explain the importance of Re-transplantation in the occurrence of infection. There was no data about donors in the results and discussion.

Authors response: In re-transplantation patients, the risk of infection may naturally increase due to re-transplantation surgery with all its risks as well as the promotion of immunosuppressive drugs after the second transplant to prevent rejection as a result. Due to the fact that only three patients were re-transplanted, it was practically impossible to study this variable [Ref: “Herden U, Ganschow R, Grabhorn E, Briem-Richter A, Nashan B, Fischer L. Outcome of liver re-transplantation in children--impact and special analysis of early re-transplantation. Pediatr Transplant. 2014 Jun;18(4):377-84. doi: 10.1111/petr.12264. PMID: 24802344.”]

Donor type information was added to Table 1, but the Honorable Referee's opinion on the absence of donor-related infectious information is correct. Although one of the imperative criteria for donor selection is the absence of any active infection at the time of organ donation, but information about colonization with resistant pathogens in the donor due to the retrospective nature of this study is impossible. We have added these notes in the limitation of our study.

8. Discussion: Please compare very briefly the results of this study with the type and rate of infection in adult transplanted cases and other solid organ transplantations in children in Iran.

Authors response: In different parts of the discussion, the comparison of our results with the study of Pouladfar et al. has been used as the only study on pediatric liver transplantation in Iran "Pouladfar G, Jafarpour Z, Malek Hosseini SA, Firoozifar M, Rasekh R, Khosravifard L. Bacterial infections in pediatric patients during early post liver transplant period: A prospective study in Iran. Transplant Infectious Disease. 2019; 21 (1): e1300"

Regarding the comparison of the results of this study with the results of adults, some items were added to the discussion

9. Please discuss the infection type according to the type of donors.

Authors response: Information related to the type of donor was added to Table 1 and was briefly discussed in the discussion section

- ***Associate Editor's Comments***

Associate Editor 1:

Please specify the follow-up time for patients to measure outcome in the "Methods" section.

Authors response: The clinical and laboratory data of the patients were evaluated and followed for one year from the time of transplantation.

- ***Editorial comments***

1. The title is not informative and should be improved. Suggested title: "The incidence, clinicomicrobiological characteristics, risk factors, and treatment outcome of bacterial infections complicating liver transplants in children, A retrospective comparative study from Shiraz Organ Transplant Center, Iran".

Authors Response: The title has been changed as requested

2. The abstract, "methods" section is not informative and should be improved.

Authors Response: Additional data have been added as requested.

3. The abstract, "results" section is not informative and should be improved.

Authors Response: Additional data have been added as requested.

4. The main manuscript, the "Methods" section should be improved. Inclusion and exclusion criteria should be added. The author investigates several variables between the case (infected) and control (non-infected) group; however, no information is provided in this regard in the method section.

Authors Response: Additional data have been added as requested.

5. Add study limitations and advantages at the end of the discussion part.

Authors Response: A paragraph regarding the limitations of our study has been added as requested.

6. Remove "Future Perspective" and "Summary Points" sections. The author could summarize and add "Future Perspective" and "Summary Points" to the end of the discussion section "without headings".

Authors Response: The requested changes have been made and the mentioned sections have been added to the discussion section.

2 Revision 1

0 comments

No public comments in this round.

3

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.

Dear Editor and Reviewers,

Thanks for reaching out to us regarding the manuscript entitled " The Incidence, Clinicomicrobiological Characteristics, Risk Factors, and Treatment Outcomes of Bacterial Infections following Liver Transplantation in pediatrics, A Retrospective Cohort Study" (previously entitled: "The incidence, clinicomicrobiological characteristics, risk factors, and treatment outcome of bacterial infections complicating liver transplants in children, A retrospective comparative study from Shiraz Organ Transplant Center, Iran"). We believe that these comments have helped us enhance the quality of the manuscript. We also have done our best to revise as well as improve the paper according to the comments. Herewith, we provided the authors' response to each comment right after each statement. Also, all the changes have been addressed in the manuscript through highlights.

- ***Associate Editor 1:***

1. Improve your title: "The Incidence, Microbiology, Risk Factors, and Outcome of Bacterial Infections Complicating Pediatric Liver Transplant, A Retrospective Study from Organ Transplant Center, Shiraz, Iran"

Authors response: The title has been changed as requested.

2. Line 43: Newly added references (10 and 11) are not relevant to this statement. Cite to the more relevant studies in the field of a liver transplant.

Authors response: The reference has been replaced with a new reference

"Yamamoto M, et al. Changes in Surgical Site Infections after Living Donor Liver Transplantation."

3. Lines 138-140: replace "Furthermore, the most isolated type of infection during the first month after LT and also first till sixth month was intra-abdominal surgical site infection, during the first till sixth month was, and during sixth to twelfth month was UTI." with, "Intra-abdominal surgical site infection was the most common type of infection which was detected during <1 month and 1-6 months period after LT, while UTI was more prevalent after 6 months of LT."

   Lines 171-172: replace "In this regard, Jafarpour et al. reported a rate of 38.6% for the first year and Shafiekhani et al. reported a rate of 25.4%." with, "In Jafarpour et al. and Shafiekhani et al. studies, the reported incidence of infections following LT was 38.6% and 25.4%, respectively".

   Line 240: "Because" should not contain a capital letter.

   Line 244, remove "is", following policy.

   Lines 268-269: it seems that "have been not reported" is correct.

Authors response: The mentioned amendments have been applied.

3 Revision 2

0 comments

No public comments in this round.