

Manuscript 6744: Comments to author:

Overall comments: Well written and well researched review article. Length needs to be shortened and avoid redundancy. Suggested minor modifications as follows:

1. Abstract: Lines 4-5: suggested change: Bacterial infections are predominant during the first two months post transplantation and affect patient and graft survival.

- Changed as suggested
2. Abstract: Line 9-10: "Some factors.....or other factors remain vigilant" -Would change the language and explain it to make the point clear. Unclear to me what the author wishes to convey.

- Deleted the sentence
3. Abstract: Line 15: Use another word for "status" such as data or antibiogram

- Changed to "data"
4. Introduction: Lines 11-15: The Net State of Immunosuppression is an important concept described by Fishman and Rubin in their 1998 NEJM article. It is a complex interaction between multiple factors as described by author and is of utmost importance from infectious disease perspective. I would like to see more credit given to Fishman and Rubin such as " The Net State of Immunosuppression as described by Fishman and Rubin is a complex interaction among multiple factors such as immunosuppressive drugs.....(as described by author). This is the most crucial determinant of infections in an organ transplant recipient.

- Totally agree with reviewer's opinion and changed as recommended.
5. Introduction: Lines 16-18: Again the concept of timeline of infection post transplantation was first conceptualized by Fishman and Rubin 1998, 2007 and hence recommend adding relevant references to their articles.

- added references
6. Introduction: Lines 25-27: Most of the infections during this time period are caused by nosocomial organisms or patient's normal flora, however infection can

also be transmitted from the donor. High degree of vigilance should be maintained in order to prevent and treat donor derived infections in a timely manner.

- changed to reviewer's comment. I appreciate

7. Introduction: Line 28: Change "Comprised" to "comprises of"

- corrected

8. Introduction: Lines 39-45 or last paragraph of introduction: Delete the sentence - In the field of bacterial infection Also overall this paragraph can be made succinct and to the point by decreasing redundancy

Suggested modification: Shifts in nosocomial pathogenic patterns, increasing antibiotic resistance, potent immunosuppression, improved diagnostic methods, grafts from marginal donors and broader epidemiologic exposure influence the risk and outcomes of bacterial infections.

Delete the sentence (line 43-44): Recently infections due to drug resistant....

Retain last sentence in that paragraph

- changed

9. Incidence and risk factors: Last 2 paragraphs can be shortened or referenced to the table as these are mentioned both in prose format and table

- corrected as reviewer's comment

10. Recommend adding a sentence or 2 about - Lack of classic signs and symptoms such as fever due to immunosuppressives and steroids lead to delay in diagnosis of infections and hence one should monitor carefully and maintain a high index of suspicion for infection.

- added

11. Types of infection: Line 4: continue to include penetration and manipulation of the hepatobiliary system

- changed.

12. Surgical site and intra-abdominal infections: Reconstruct sentence: Although the pretransplant patients' medical condition to: Although the medical condition of the patient pretransplant affects the occurrence of.....

- corrected

13. Bacteremia: Would suggest including data on indwelling central lines as a source of bacteremia both for GNB and GPB as this is a modifiable risk factor.

Suggest making this section more succinct.

Line 13: IV site: change it to intravenous site

Line 26-28: suggested change: The risk of mortality were related to the severity of underlying disease, source of bacteremia, and choice of antimicrobial agents

Line 32-34: suggested change: When timing of onset of bacteremia was considered, the one year mortality rate.....

- I appreciate your comments. I changed sentences, corrected words and added catheter related bacteremia data. To make section more succinct, I deleted sentences and corrected.

14. Donor derived infections:

Line 1: suggested change: Transplanted organs facilitate transmission of bacterial, viral, fungal and parasitic infections. (Reference Fishman 2007 NEJM article)

Line 2-4: Needs to be modified grammatically- Donor derived infections are divided into three major categories.....

- changed

15. Urinary tract infection: Suggest adding data regarding catheter use risk of UTIs

- added comment

16. Pathogens: Line 1: Delete word "somewhat"

- deleted

17. Prophylaxis and prevention: The entire section needs to be made more concise.

Lines 1-2: suggested change: Certain bacterial infections are preventable with appropriate prevention strategies which can be divided into 3 phases; pre-transplant, intra-operative and post-transplant.

Lines 23-26: Combine sentences to highlight importance of modifiable risk factors such as removal of unnecessary central venous catheters.

Line 28-29: Tailoring perioperative antibiotics to institutional antimicrobial susceptibility pattern. No clear data available regarding benefits of modifying perioperative antibiotics to donor cultures in liver transplantation.

Suggest making the discussion regarding bowel decontamination, lactobacillus and Rifaximin more succinct and shorter.

- Deleted some sentences to clarify the subject. Added recommended sentences. I appreciate your comments.

18. Summary:

Line5-7: Patients need to be monitored advertently to detect any subtle signs and symptoms of infection as the markers of infection such as fever may be lacking in LT recipients due to underlying liver disease and immunosuppression.

Line 8: Suggest changing “transplant medications” to immunosuppression

Lines 10-12: Individualized center specific strategies for prevention and treatment of bacterial infections in LT must be implemented based on patient’s risk factors, operative factors, nosocomial environments, local microbiologic epidemiology, center specific antimicrobial sensitivity and evidence based medicine.

- Changed to your recommendation. Thank you so much.

Reviewed by 00054680

November 13/11/13 Manuscript ID Manuscript Number 6744 Bacterial infection after liver transplantation Comments to the Author The authors present extensive epidemiological data regarding Bacterial infection after liver transplantation. Overall, too much information regarding the bacterial types and disease the data presented is so extensive; however, the manuscript is quite long and could be condensed.

- Many unneeded sentences were deleted to condense the manuscript.

Introduction: First paragraph: is repetition for the 1st paragraph of the abstract.

- I changed the first paragraph.

Suggest revision of this paragraph Incident AND risk factors Using Table 1 after modification to contain reference of the studies may be better than text as data can be easier to be understood

- Modified the text not to repeat in the table.

Types of Infection The authors used many Reviews as reference, I think it will be better to refer to the exact study and also use the exact % instead of using general words as common It will be better also to make it more condensed and refer only to the studies in the field of transplantation

- Revised and deleted some sentences and references as reviewer's comments. I appreciate your comments.

Pathogen Would combine the information that is currently under "Pathogens" with the "Types of Infection". The data is the same but just presented differently, as the article is too wordy.

- I agree with reviewer's comment. I tried to combine the information, however, after the revision, the manuscript changed to more complex and confused pattern. Please accept my apologies for the limitation of combining the information as your comments.

References Many References are used some are not indicative concerning cancer or other clinical situation than Liver transplant on the other hand some references which is relevant and not mentioned as Egawa H, Inomata Y, Uemoto S, Asonuma K, Kiuchi T, Fujita S, et al. Biliary anastomotic complications in 400 living related liver transplantations. *World J Surg* 2001;25:1300-1307. Shepherd RW, Turmelle Y, Nadler M, Lowell JA, Narkewicz MR, McDiarmid SV, et al.; SPLIT Research Group. Risk factors for rejection and infection in pediatric liver transplantation. *Am J Transplant* 2008; 8:396-403. Pattern of bacterial and fungal

infections in the first 3 months after pediatric living donor liver transplantation: an 11-year single-center experience. Nafady-Hego H, Elgendy H, Moghazy WE, Fukuda K, Uemoto S. *Liver Transpl.* 2011 Aug; 17(8):976-84 Iinuma Y, Senda K, Fujihara N, Saito T, Takakura S, Kudo T, et al. Surgical site infection in living-donor liver transplant recipients: a prospective study. *Transplantation* 2004;78:704-709. Long-term outcomes of 600 living donor liver transplants for pediatric patients at a single center. Ueda M, Oike F, Ogura Y, Uryuhara K, Fujimoto Y, Kasahara M, Ogawa K, Kozaki K, Haga H, Tanaka K. *Liver Transpl.* 2006 Sep;12(9):1326-36.

- I appreciate your comments. All the references were reviewed and corrected. Data that include pediatric transplant (Iinuma Y et al) were excluded.