

Format for ANSWERING REVIEWERS

August 12, 2014



Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 13022-review.doc). We have highlighted the reviewers comments in bold and written our response in italics for the reviewers' convenience.

Title: Endotipsitis: A case report with a literature review on an emerging prosthetic related infection

Author: Annalan M D Navaratnam, Matthew Grant, David B Banach

Name of Journal: *World Journal of Hepatology*

ESPS Manuscript NO: 13022

The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer as highlighted below:

Reviewer 1:

In this paper Navaratnam et al. present a case of "endotipsitis" and performed a review of the existing literature on this field. They identified 22 papers reporting 54 patients with endotipsitis. The great majority had monomicrobial infections (gram positive agents were the majority). Infections with *Staphylococcus aureus* and *Candida* were associated higher mortality. No homogeneous management was applied for the treatment of this condition and guidelines of antibiotics use are usually derivate from the treatment of endocarditis. Although the subject is very interesting and because of the rarity of this condition strong data is lacking, there are some aspects that authors should be clarified. Here are my comments:

Introduction: probably the existing criteria for diagnosis of endotipsitis should be stated in the introduction. That will make the case presentation clearer. Only with the provided data alternative diagnosis, as stent thrombosis and sepsis, could be possible.

This has now been included in the introduction (Page 5 L15-21)

Case report: the diagnosis and the indication of TIPS insertion is not very clear. The patient had previous right hepatectomy, so probably the insertion of the stent was atypical. Authors should state the indication for TIPS insertion (refractory ascites? If the EV were not bleeding).

The indication for stent insertion has now been included in the case report (Page 5 L14-15)

Also some data about technical particularity of TIPS insertion would be interesting to know.

This has been included in the introduction (Page 5 L5-7)

The lab values should be provided in a standard way (for example, it is difficult to understand the

value of platelets count).

The lab values have been standardised, including platelets count (Page 6 L24-31)

According to US examination and CT scan the TIPS is dysfunctional. The catheterization of the stent was made after the control of the infection? After the antibiotic treatment the filling defect inside the TIPS has disappeared? This specific issue should be discussed because the diagnosis relies on it. Moreover, by TIPS catheterisation quantitative bacteriology can be an alternative diagnostic method in cases with diagnostic uncertainty. The comparison of bacterial colonies counts from portal blood and peripheral venous blood may provide important evidence of the stent device as a source of the infection.

No catheterization of the stent was made as the thrombus was identified on US examination and CT scan. The use of catheterisation in the diagnosis of endotipsitis is discussed on Page 11 L12 – 20 specifically its potential role in improving diagnostic accuracy.

Review of the literature: -A figure with selection algorithm could be helpful.

This has been included as one of the figures to supplement this manuscript.

Also it would be better to state how many papers are isolated case reports and how many are case series. –

This has now been included in the results section, as there were 15 case reports and 7 case series (Page 9 L6)

It would be interesting to provide also the number of cases with early onset of endotipsitis (3 months after insertion for example) and where the infection process could be related to the insertion. Maybe a comparison between the two groups (early onset vs late onset) regarding the infection agent and outcome would give interesting results.

This has been discussed on Page 11 – 12, in reference to Bouza et al 2004 who discuss categorising these cases into 'early (within 120 days of TIPS insertion) and 'late' (>120).

Minor comments: -

A legend of table one is missing: especially to explain the outcome (R, Tx, D). -

The legend is now included with the table

The presented case is not the first case described in the United States, so probably the phrase “We report a case in the United States supplemented by a review of the literature” from the abstract should be reformulated.

This has been rephrased; please see Page 5 L22. We have included that this case is has the longest reported latency from insertion to infection in the literature. This has been included in the title, abstract and summary.

Reviewer 2:

The manuscript presents an interesting case of "endotipsitis" and reviews the literature. Suggestions:

Case report: it is unclear why "suppressive" (?clarify term) oral ciprofloxacin 500 mg daily was prescribed; how long was treatment maintained (reading the text, it appears that it lasted 9 months?).

Thank you kindly for bringing this to our attention. Given the inability to remove the suspected infected material in the TIPS, the patient was prescribed long-term, potentially lifelong, therapy to prevent infection relapse. This was clarified in the text; please see Page 7 L14 – 17

Review of the literature:

a) TABLE: the authors provide only a table of antibiotic treatment; an additional table detailing all other data on the case reports/series could be helpful;

Table 1 included the duration of treatment, duration of bacteraemia, micro-organism isolated, choice of antibiotic and outcome of cases. We have now included the etiology of cirrhosis and the time between insertion of TIPS and onset of infection.

In the table on antibiotic treatment, please specify duration of bacteremia/treatment (days? weeks?);

This has now been included in the table.

b) RESULTS, page 9, line 18: please express percentage of mortality also in absolute numbers;

Both the percentages and total (N) have been included in this sentence (Page 10 L18)

c) DISCUSSION: please comment on the differences in the duration of treatments;

Our results (Page 10 L10-12) demonstrate a variation in treatment strategies in the literature. We have discussed (Page 12 L9-11) this issue and that recommendations on treatment in general cannot be based on the results of the literature review.

Contrary to the statement in the abstract, no comments/conclusions are drawn from other guidelines relevant for the treatment of endotipsitis.

The duration of antibiotic therapy for endotipsitis has been quite variable. We propose extrapolation from the guidelines of treating prosthetic valve endocarditis and how it is applicable in to the treatment of endotipsitis, which is discussed on Page 12 (L11 - 19). This was not emphasised in the conclusion however, and has now been included in this section of the manuscript.

Please address, for instance, the problem of selection of antibiotic, duration of treatment.

This is discussed, in particular about Staph aureus infections, in Page 12 L20-27 and in the last paragraph of the discussion.

d) REFERENCES: please revise references (e.g. ref. 19 is missing).

Many thanks for pointing this out. It has been revised and the error has been corrected

Reviewer 3: Comments To Author

Very interesting case report and review on a rare disease. I have some minor suggestions.

Page 5 line 24 – platelet count – units are missing It would be of interest to the reader to know AST, ALT and GGT levels on admission.

This has been corrected on Page 5 L24-35

Page 8 line 13 – please correct grammar “The mean age was 54.3 years of age”

This has been corrected Page 8 L13

Page 8 line 14 - with a predominance of males (38 vs 9). Please insert % and make the comparison clear

This has been corrected Page 8 L14

3 References and typesetting were corrected

Thank you again for considering our manuscript for publication in the *World Journal of Hepatology*.

Sincerely yours,

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