Author's response to reviews

Title: Uncommon manifestations of Listeria monocytogenes infection

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Version: 3 Date: 16 October 2014

Author's response to reviews: see over
Dear Editor/section editor,

We would like to thank the reviewers for taking time for going through our manuscript and providing feedback. We have addressed the comments raised by the reviewers in a point-by-point response.

We would be happy to be contacted should any further clarification be required on any aspects of the manuscript.

Reviewer's report
Title: Uncommon presentations of Listeria monocytogenes infection
Version: 2
Date: 3 May 2014
Reviewer: Franz Allerberger

Reviewer's 1 report:
Minor Essential Revisions

1) The submitted case report "Uncommon presentations of Listeria monocytogenes infection" is a diligently prepared manuscript. The authors might consider to change the title to "Uncommon manifestations of Listeria monocytogenes infection".

Authors' response- this change has been made in the title.

2) In INTRODUCTION, it reads: "Listeriosis is a serious food borne disease caused by the bacterium Listeria monocytogenes, affecting mostly pregnant women, neonates and immune-compromised hosts with relatively high mortality rates in these groups." The authors should rephrase this sentence (by including also "the elderly") to "affecting mostly pregnant women, neonates, the elderly and immune-compromised hosts", as two of their three patients presented without "any history of underlying immunosuppression".

Kasper et al. studied the underlying diseases of reported listeriosis cases in Austria, 1997 – 2007, and found that of the 150 reported listeriosis cases, 32 cases (21.3 %) greater than 65 years of age had no underlying disease or risk factor besides their age (Kasper S, Huhulescu S, Auer B, et al. Epidemiology of listeriosis in Austria. Wien Klin Wochenschr. 2009;121(3-4):113-9. doi: 10.1007/s00508-008-1130-2).

Authors response- this has been changed as requested.

3) Therefore, also the sentence in INTRODUCTION line 30 ("However it may only manifest as self-limiting gastrointestinal illness in immunocompetent hosts") could be reworded, to e.g.: 
"However it may also manifest as a self-limiting gastrointestinal illness in immunocompetent hosts".

Authors' response- this has been changed as suggested.

4) Please provide a reference for "A multitude of focal infections with Listeria monocytogenes have been reported in the literature affecting various organs" (line33); e.g. Allerberger F, Wagner M. Listeriosis: a resurgent foodborne infection. Clin Microbiol Infect. 2010 Jan;16(1):16-23. doi: 10.1111/j.1469-0691.2009.03109.x.

Authors' response-a reference has been inserted here.

5) Line 48 presently reads: "The minimum inhibitory concentration (MIC) of this organism to penicillin tested by EtestR (AB Biodisk; Solna, Sweden) was ....". It is the antibiotic, not the pathogen, that has an MIC! Please rephrase to e.g.: The minimum inhibitory concentration of penicillin tested by EtestR (AB Biodisk; Solna, Sweden) was ....".

Authors' response- this has been changed as suggested.

6) Line 50: "The patient completed a 2 week course of intravenous ampicillin [provide details of dosing e.g. 2 grams every 4 hours] followed by benzyl penicillin (14.4 gram/daily) as intravenous infusor [infusion?] and then completed a 6 month course of [oral] amoxicillin (1 gram/TDS)."

Authors' response- this has been changed as requested.

7) Line 68: ".... [ MIC of Proteus mirabilis to ampicillin <2 mg/L by Vitek2,(bioMerieux, France) and of Listeria monocytogenes to penicillin was 0.5 mg/L by Etest]" should read "[.... MIC of ampicillin against Proteus mirabilis was <2 mg/L by Vitek2,(bioMerieux, France) and MIC of penicillin against Listeria monocytogenes was 0.5 mg/L by Etest]". Provide a city for the Vitek 2 producer (and empty space missing; it could read: "Vitek2, (bioMerieux, Marcy-l'Etoile,France)").

Authors' response- this has been modified as suggested

8) Line 75 presently reads: "a plan was made for continuing oral amoxicillin (500 mg/TDS) with an aim of lifelong antibiotic suppression". Either delete this sentence or discuss the medical basis for this plan (which is an extremely unusual approach in the case of listeriosis-therapy).

Authors' response- Reason for this was partial retention of the graft which has now been mentioned in the text.

9) Line 85: "He underwent a surgical incision and drainage of the perianal abscess which revealed positive microbiological culture of Listeria monocytogenes and mixed bowel organisms". Please rephrase this sentence, avoiding the term "mixed bowel organisms"; it could read "mixed bowel flora".

Authors' response- this has been changed as suggested.

10) Next sentence: "The MIC of the organism to penicillin tested by Etest was 0.38 mg/L." The value 0.38 is not a valid E-test value; according to the manufacturer's instructions you have to upround to the next valid MIC-value, i.e. 0.5 mg/L.

Authors' response- Many thanks for pointing this out and this has been changed as suggested.
10) Line 98: "None of these 3 cases appear to be epidemiologically linked to each other. All three of them were unrelated strains (non-outbreak). [2, 3]" Please rephrase in order to clarify the message of these two sentences, which presently seem to carry the same message.

Authors’ response- this has been rephrased to be consistent

11) Line 101 presently reads: "Listeria monocytogenes is a gram-positive bacillus that is ubiquitous in the environment; it is present on unwashed vegetables and also found from foods that have been contaminated after processing. It has a mortality rate of 10-44% ... " . It is not Listeria, that has a mortality, it is listeriosis.

Please also avoid the using term Bacillus for other bacteria than spore-forming organisms.

Authors’ response- this has been modified as suggested

12) Lines 106 and 107: "61% of patients were over 65 years and had underlying immunosuppression compared to 24 % patients who were under 65.[5]". What bout being exactly 65 years old?

Authors’ response- this has been addressed as requested.

13) Line 120: Rephrase "84% patients had associated orthopaedic devices..." avoiding the term "84% patients; e.g.: "In these patients, 84% had ....".

Line 136 (but also all over the manuscript: Be specific when talking about listeriosis versus invasive listeriosis: The statement "Laboratory confirmation of listeriosis requires isolation or detection of L. monocytogenes from a site that is normally sterile." Is only correct in the case of invasive listeriosis, not in gastroenteritis due to Listeria.

Authors’ response- We have incorporated the various definitions of Listeriosis from CDNA (Communicable diseases network Australia), CDC, Atlanta, US and ECDC, Stockholm, Sweden. Since the public health investigations were done based on the CDNA definition we have changed the wordings to say- ‘Australian national notifiable case definition’.

14) Line 138: “tumbling motility” by light microscopy (at room temperature and at 37 °C); to my experience listeria do not produce flagella at 37°C and are always nonmotile when grown at this temperature.

Authors’ response- We appreciate in pointing out this fact and it has been corrected.

15) Line 147: Check on the validity of the claim "It is mandatory to report cases of listeriosis in all jurisdictions in Australia.", is this valid also for cases on non-invasive listeriosis?

Authors’ response- reference for ‘Comlaw’ from Australian Government’s Department of Health has been incorporated and this states the list of nationally notifiable diseases in all health jurisdictions. ‘Listeriosis’ is on the list.

16) In line 165, the case definition definitely does not include gastroenteritis. Please consider to write ", including meconium" instead of "including foetal gastrointestinal contents".

Authors’ response- this has been changed as suggested.

17) Line 170: Rephrase "The recommended management of invasive listeriosis is with a combination of penicillin or ampicillin with the synergism of an aminoglycoside in severe cases" to "The recommended therapeutic management of invasive listeriosis is intravenous application of penicillin or ampicillin with or without an aminoglycoside. The added value of
gentamicin is disputed and based solely on alleged in-vitro synergism” (Hof H. An update on the medical management of listeriosis. Expert Opin Pharmacother. 2004 Aug;5(8):1727-35.). Authors’ response- this reference has been added and the text modified as suggested.

18) Line 186: Please reword the sentence "About 5% of healthy adults can have asymptomatic carriage of Listeria. [15]" to "Up to 5% ...... and adding other references might be prudent. Sauders et al. cultured 827 stool specimens from individuals from four large metropolitan areas of New York state for L. monocytogenes and found only 1 (0.12%) positive specimen (Sauders BD, Pettit D, Currie B, et al. Low prevalence of Listeria monocytogenes in human stool. J Food Prot. 2005 Jan;68(1):178-81). Grif et al. cultured Listeria monocytogenes from 10 of 868 (1.15%) stool specimens (Grif K, Patscheider G, Dierich MP, Allerberger F. Incidence of fecal carriage of Listeria monocytogenes in three healthy volunteers: a one-year prospective stool survey. Eur J Clin Microbiol Infect Dis. 2003 Jan; 22(1):16-20]. Authors’ response- this has been changed as suggested and reference added.

Discretionary Revisions

19) Line 40: Rephrase "She had a background of metastatic colorectal carcinoma ...." (e.g. by simply deleting "a background of". The f in "5-Fluorouracil" should not be a capital letter. 20) Line 94: the hyphen after "terms" should be deleted.

21) Line 152: empty space missing after "isolates." And before "Binary".

22) Empty space missing after the term "Listeriosis" in Table 1 of supplementary material in "Listeriosis(NSW Health)".

23) Empty spaces missing in lines 119 after hip and in line 120 after knee.

24) Line 180: delete the term "also"

25) Line 182: Rephrase the sentence "Although only Case 1 had a history of gastroenteritis, these cases highlight the fact that gastrointestinal symptoms may not be present in all patients", as presently it is not clear why the authors use "Although"; e.g.: "The finding that only Case 1 had a history of gastroenteritis, highlights the fact that gastrointestinal symptoms may not be present in all patients."

Authors’ response- all these have been addressed as requested

26) In REFERENCE there are empty spaces missing and the way the authors write "et al." lacks uniformity: References

234 [1] OzFoodNet working group: Monitoring the incidence and causes of Diseases

235 potentially transmitted by food in Australia: annual report of the OzFoodNetwork


239 [3] (EMPTY SPACE


Authors’ response- these changes have been made in the references.

27) Figure 1 EMPTY SPACE MISING before "Image3"
Figure 2 EMPTY SPACE MISING after the "2" and full stop missing at the end after "(see arrow)"
Figure 3 EMPTY SPACE MISING after the "3" and full stop missing at the end

Authors’ response- this has been changed as requested

Level of interest: An article of importance in its field
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests: 'I declare that I have no competing interests'

Reviewer's 2 report
Title: Uncommon presentations of Listeria monocytogenes infection
Version: 2 Date: 8 October 2014
Reviewer: Renata Karpiskova
Reviewer’s report:

Major revisions needed:
1. Because the case definition of listeriosis (only invasive cases) differs in various countries, it is needed to state the official case definition that was used in this study (rows 165-169) and discuss the difference with case definition used by ECDC or in USA. Case 2 didn’t meet the case definition?
Authors’ response- We thank the reviewer in pointing this out. We have mentioned the various definitions early on the discussion in this revised version. We have used the CDNA (Communicable Diseases Network, Australia) definition for ‘listeriosis since public health investigations are based on this CDNA definition in our jurisdictions. We have included the CDC and ECDC definitions for ‘listeriosis’ and CDC definition for ‘invasive listeriosis’ as suggested. Differences have been outlined in the text. Case 2 didn’t meet the case definitions as per NSW Public health; hence there was no case investigation (or environmental investigation) into the illness apart from a telephonic interview.

2. Methodology of L. monocytogenes confirmation, typing and testing of sensitivity to antimicrobial agents is not clear.
Authors’ response- We have included more details to address these points. MALDI-TOF MS has been previously validated in our laboratory and this has been included with a reference. Susceptibility testing was done as per CLSI methodology which has been described in further detail and a reference provided for AST as well.
In terms of typing of Listeria monocytogenes, this is determined by NSW Department of Health (Central public health unit based in Sydney) and is not performed by clinical microbiology laboratories in Australia. Public health microbiology laboratory (reference laboratory) based in Sydney performs binary typing (BT) and MLVA. NSW DoH in conjunction with the public microbiology laboratory determines the promptness and necessity of typing especially in non-outbreak settings. Local laboratories (including ours’) are provided information in cases of outbreaks for increased surveillance purposes and for active case finding. Whilst we agree that details of typing are very important in cases of ‘outbreak management’ we seem to have no operational jurisdiction in determining which isolates
require typing and what methodology to use (ie PFGE vs MLVA vs Binary typing vs molecular serotyping). Also the CDNA website states—“The methods of typing chosen for use in specific jurisdictional laboratories differ according to public health operational priorities but can be regarded as complementary”. Public health microbiology laboratory provided information about BT/MLVA types for the three cases, which in discussion with NSW DoH were not thought to be part of any ongoing outbreaks. Hence we did not have any further information about serotypes/PFGE. We also agree that certain serotypes (1/2a, 1/2b, 1/2c and 4b) have been associated with majority of human infections.

3) L. monocytogenes is usually non-motile at the temperature of 37 °C (row 137)
Authors’ response- We appreciate in pointing this out and we have corrected it in the text.

4) Molecular serotyping, PFGE and/or MLVA typing are basic for any epidemiological investigation. Serotype and PFGE pattern should be added to table 1. It has been demonstrated that some serotypes may be less virulent and thus they do not overcome the cerebral barrier so often. This could explain why the described cases caused only focal occurrence. Binary typing is not widely (internationally) used typing method and thus the results cannot be compared within other studies.
Authors’ response- Please see above comments about Listeria typing. Unfortunately the details of molecular serotyping and PFGE on the three isolates were not available to us other than the details of BT/MLVA which have been included.

5) Results of the resistotyping are missing (spectrum of agents tested, their Concentrations and interpretation criteria - which clinical breakpoints were used?).
Authors’ response- We have included the details of Etest performed as per CLSI document (M45-A2) and clinical breakpoints have been included.

6) references concerning the methodology of bacteriological investigations are missing (rows 137-164).
Authors’ response- Details have been included in the revised manuscript.

Level of interest: An article whose findings are important to those with closely related research interests
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests: I declare that I have no competing interests.

We would again thank the reviewers for their invaluable comments.

Kind regards,

Dr Ruchir Chavada