Author’s response to reviews

Title: Sporadic isolated congenital asplenia with fulminating pneumococcal meningitis: a case report and updated literature review

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Author’s response to reviews:

Response to Reviewer 1 (Dr. Emma Best): Thank you for your comments. I completely agree with you. The manuscript has been revised in accordance with your comments. In the case presentation section, I have added the reason why the patient had been unimmunized with a pneumococcal vaccine and have added the subsequent management approaches used in this case. In the discussion section, I have modified the discussion regarding the prevention of invasive infections in asplenic patients with current recommendations and have updated the related references. I have also replied to your comments point by point below.

1) Abstract: Page 2, line 29: “The patient was hospitalized” Unimmunized
Answer: I have changed “The patient” to “The pneumococcal vaccine-unimmunized patient.”

2) Background: Page 4, line 26: change “fairly more infrequently” to simply “more infrequently”
Answer: I have changed the phrase “fairly more infrequently” to “less frequently.”

3) Background: Page 4, line 57: “S. pneumoniae” italicise S. pneumoniae
Answer: Thank you for your comment. I have italicized “S. pneumoniae.”

4) Case presentation: Page 5, line 25: “The patient had not … vaccination.” Why - was this due to parental choice or lack of these vaccines from the schedule? This statement needs clarification.
Answer: Thank you for your comment. The patient had received all routine vaccines at the appropriate timing. However, pneumococcal and Hib vaccines were not included in the routine immunization program at the time of treatment in Japan. I have added this explanation to the text.

5) Case presentation: Page 5, line 32: “She had a restless level of consciousness” This is an unusual term to describe LOC - perhaps impaired level of consciousness or was irritable would be a more typical way to describe infant presentation with meninigits.
Answer: Thank you for your comment. I agree with you. I have changed “She had a restless level of consciousness” to “She was irritable.”

6) Case presentation: Page 6, line 54: “… heterotaxia were detected. These facts led to a diagnosis of ICA.”
Answer: Thank you for your comment. According to your suggestion, I have connected the two sentences using “leading to the diagnosis of ICA.”

7) Case presentation: Page 7, line 3: There is a concerning lack of comment about subsequent vaccination, offer or discussion of antibiotic prophylaxis and travel and sepsis advice given for this family with an asplenic young child.
Answer: Thank you for your opinion. I completely agree with you. I have added the subsequent course of this patient; vaccination, antibiotic prophylaxis, and parent education.

8) Discussion: Page 11, line 32: “In fact, the case … the PCV or Hib vaccine.” Which seems unusual to have missed out on routine childhood immunisations in a developed country.
Answer: Thank you for your comment. Pneumococcal and Hib vaccines had not yet been included in the routine immunization program in Japan when the patient experienced overwhelming sepsis. I have added this explanation to the text. 

9) Discussion: Page 11, line 41: “…
management of asplenic individuals [33].” The references regarding guidelines from other countries are very out of date. Perhaps look at the updated versions Davies JM, et al. Review of guidelines for the prevention … the Haemat-Oncology Task Force. Br J Haematol 2011;155:308-317. Answer: Thank you for your comment. I agree with your opinion. I have changed the reference according to your suggestion. 10) Discussion: Page 11, line 57: “… still possessing a spleen [35].” Again this is an out of date reference and the evidence for use of conjugate protein bacterial vaccines in splenectomised patients supports that better immunity is given as conjugate vaccines induces not just humoral response. Forstner C, et al. Effectiveness and immunogenicity … asplenic patients. Vaccine 2012; 30: 5449-52. Breukels MA, et al. Pneumococcal conjugate vaccines … pneumococcal polysaccharides. Infect Immun 2001; 69: 7583-7. Answer: Thank you for your comments. I agree with you. I referenced the current guideline, recommendation, and studies and have changed the paragraph concerning the focus of current practices to prevent sepsis. 11) Discussion: Page 12, line 3: “The decisions on … are also difficult.” The evidence for use of vaccinations in splenectomised or asplenic individuals is still very strongly in favour of ensuring they have maximal protection against the encapsulated bacteria. The authors should ensure that the current recommendations particularly the need for completion of pneumococcal, Hib, meningococcal and yearly influenza vaccine are outlined and referenced e.g Rubin LG, et al. 2013 IDSA clinical practice guideline … immunocompromised host. Clin Infect Dis 2014;58:309-318. Answer: Thank you for your comment. I agree with you. I have referenced the immunization guideline you mentioned and have added the current recommendations regarding vaccinations for asplenic patients; pneumococcal, Hib, meningococcal, and influenza vaccines. 12) Discussion: Page 12, line 10: “… in asplenic patients [36];” Again this is not a recent reference but it is true there is a lack of evidence supporting antibiotic prophylaxis. The data is essentially derived from use of penicillin prophylaxis in children with sickle cell disease and prevention of pneumococcal disease. Hirst C, Owusu-Ofori S. Prophylactic antibiotics … sickle cell disease. Cochrane Database Syst Rev 2014; 11: CD003427. Answer: Thank you for your comment. I agree with you. I have changed the reference according to your suggestion. 13) Discussion: Page 12, line 13: “… life-long use of antibiotics [33].” These are neither recent nor universal recommendations. The referencing is out of date and this section needs more attention and improvement to be considered relevant to current practice. Different situations will lead to differing practice and guidance around lifelong antibiotic prophylaxis in splenectomise patient for example in in this case most would expect a child to continue on penicillin until age 5 years at least. Prophylaxis is also considered in patients with asplenia/hyposplenism who are immunosuppressed (from haematologic malignancy) or have had a prior episode of severe sepsis. Some consider it for 1-3 years following surgical splenectomy however it is acknowledged that the risk of OPSI is actually lifelong. Answer: Thank you for your comments. I completely agree with you. I have changed this paragraph completely and mentioned current practices for asplenic patients to prevent overwhelming sepsis, including antibiotic prophylaxis. 14) Discussion: Page 12, line 26: “… a possible infection [37];” “…so called "emergency" or "stand-by" antibiotics for episodes of fever. There is a lack of data to support this practice. Answer: Thank you for your opinion. The practice of “stand-by” antibiotics for episodes of fever is recommended by some experts but there is a lack of evidence supporting its efficacy. However, this practice should be followed if the patient is unable to receive prompt medical attention. Therefore, I have modified the description and the relevant reference. 15) Discussion:- Page 12, line 35: “… minimum can be achieved.” Most guidelines agree that vaccination, prophylactic antimicrobial therapy in selected patients particularly children up to the age of 5 years and provision of early empirical antimicrobial therapy for febrile/unwell episodes is reasonable for