Author’s response to reviews

Title: Emerging serotype III Sequence type 17 group B streptococcus invasive infection in infants: the clinical characteristics and impacts on outcomes

Authors:

Yi Kao (cathaykao@gmail.com)
Ming-Horng Tsai (mingmin.tw@yahoo.com.tw)
Mei-Yin Lai (lmi818@msn.com)
Shih-Ming Chu (kz6479@cgmh.org.tw)
Hsuan-Rong Huang (qbonbon@gmail.com)
Ming-Chou Chiang (cmc123@cgmh.org.tw)
Ren-Huei Fu (rkenny@cgmh.org.tw)
Jang-Jih Lu (janglu45@gmail.com)
Jen-Fu Hsu (jeff0724@gmail.com)

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RE: INFD-D-19-00204

Emerging serotype III Sequence type 17 group B streptococcus invasive infection in infants: the clinical characteristics and impacts on outcomes

Ming-Horng Tsai; Yi Kao, MD; Mei-Yin Lai, MD; Shih-Ming Chu, MD; Hsuan-Rong Huang, MD; Ming-Chou Chiang, MD; Ren-Huei Fu; Jang-Jih Lu, MD, PhD; Jen-Fu Hsu, MD

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Dear Editor,

Thank you for your appreciated comments on our manuscript. We had the manuscript revised, all according to the reviewers’ and editor’s suggestions. We underline every change and highlight in red color on the revised manuscript. The replies for the reviewers’ criticisms are as followings. We hope this revised version can be acceptable.
Best regards,

Ming-Horng Tsai

Chief, Division of Neonatology and Pediatric Hematology/Oncology, Department of Pediatrics, Yunlin Chang Gung Memorial Hospital, Taiwan, R.O.C.

Comments from Reviewers:

This is a manuscript describing the serotype distribution, antimicrobial resistance, clinical features and molecular characteristics of invasive GBS isolates recovered from 182 GBS isolates that caused invasive disease in infants younger than one year of age in Taiwan, between 2003 and 2017. This paper is interesting because of lack of information about invasive GBS topic in Asian countries. Therefore, I think this is a much needed study and will provide valuable information regarding invasive GBS in infants in Taiwan.

I have listed points below for author's consideration.

BACKGROUND:

*Line 67-69: "Group B Streptococcus (GBS) or Streptococcus agalactiae is a Gram-positive coccus found in 15% to 30% of healthy women as part of normal gastrointestinal and genital tract flora". Only two papers were cited here, please include more references to support the range.

Reply:

Thanks for your instructive advice. I will increase more citations for this range. Please see the revised manuscript, the new reference no.3, and no. 4, thank you.

*Similar suggestion for Line 71-76, authors cited reference 5-9 to state the invasive GBS could cause life-threatening infections in infants and long-term adverse outcomes. As I know, there are lots of high-quality papers indicating these two points, including meta-analysis and systematic review, can authors add some more important references in this field.

*It is better to clarify that if intrapartum prophylaxis for pregnant women was implemented in this study center.

Reply:

Thanks for your instructive advice. I will add more high-quality papers indicating these two points. Please see the revised manuscript, the reference no. 7-12. Intrapartum prophylaxis for
pregnant women has been implemented in this study center since 2012, I will clarify this issue in the introduction section, page 4, line 84-86.

2. MATERIALS and METHODS

* Line 93: "Between January 2005 and December 2017....." . I assume the study period should start from 2003 instead 2005, Please keep consistency in the manuscript.

Reply:

I am sorry for this mistake. I will correct this mistake, revise it as 2003 and keep consistency in the manuscript, thank you. (Line 94)

* Line 93-95: "all young infants aged less than one year with invasive GBS diseases were enrolled and their data were retrieved retrospectively from the database of Chang Gung Memorial Hospital (CGMH)", it is unclear about the database of CGMH, if cases of GBS were identified based on laboratory, or clinicians or from both?

Reply:

Thanks for your instructive advice. The cases of GBS were identified from the database, which were filled by the clinicians. We can retrieve the GBS isolates from the bacterial library of CGMH’s laboratory. I will make this issue clear in the MATERIALS and METHODS section, line 96-99 as following: .......their data were retrieved retrospectively from the database of Chang Gung Memorial Hospital (CGMH). This database was filled by the clinicians. We reviewed the electronic chart records for patients’ demographics, clinical characteristics, treatment and outcomes. All GBS isolates were obtained from the bacterial library of CGMH’s central laboratory.

* Line 98-101: Classification of invasive GBS disease in infants also needs citation.

Reply:

Thanks for your instructive advice. The classification of invasive GBS disease is a world-wide accepted concept, and I will add the citation as the reference no. 6,11,12 (line 104 and 105)

* Line 108-117: Why did authors only state the definition for Meningitis, how about the definitions for other clinical manifestations such bacteremia, pneumonia, septic shock, etc. in the Table 2.

Reply:

Thanks for your instructive advice. I will state the definition of bacteremia, pneumonia, and septic shock, etc. based on the definition of CDC in the revised manuscript, line 119-120 and new ref. no. 20
* Please add information about if all the samples were collected before antibiotics given to infants.

Reply:

Thanks for your instructive advice. I will add this information in the line 100-102 as following: In our institute, all positive GBS cultures were collected before antibiotics were given to infants.

3. RESULTS

* Line 160-161: "In this 15-year study period, we found a significant increase in serotype III in young infants with invasive GBS diseases (Figure 1)". The figure 1 described the percentage of serotype, please provide the GBS case number as well. Furthermore, it will be better if authors can add the 95% CI for percentage in the figure 1 and figure 2.

Reply:

Thanks for your instructive advice. I will provide the GBS case number in the figure 1, thank you. However, it is very difficult to add the 95% CI for percentage in the figure 1 and figure 2, which will make the figures very crowded and too complicated. It is also uncommon to see these data in the figures of other papers. Therefore I bag not to add 95% CI. If the reviewer insisted to add the 95% CI for percentage in the figure 1 and figure 2, please let me know and I will try my best, thank you.

* Line 170-172: "and 29 (15.9%) had neurological complications. Among those who survived and with neurological complications, 14 (45.4%) had long-term neurological sequelae at discharge". What is the definition for neurological complications and long-term neurological sequelae? My understanding is long-term neurological sequelae needs to be observed for longer time after discharge, at least months later from discharge.

Reply:

Thanks for your instructive advice. I will cite the definition for neurological complications and long-term neurological sequelae in the revised manuscript. We also evaluated the presences of neurological complications and long-term neurological sequelae of these patients, based on the definition of previous studies [12, 21]. (Line 122-124).

In this study, all the survival children were clinically followed in our outpatient clinics, and we can observe their long-term neurological sequelae several months from discharge.

* Line 185: "All STs have been identified in the database". Please clarify what database.

Reply:
Thanks for your instructive advice. This database is GBS MLST database (http://pubmist.org/sagalactiae). I will clarify this issue in line 193, thank you.

*Line 191-193: Please add the case number and 95% CI for the percentages.

Reply:

Thanks for your instructive advice. I will add the case number and 95% CI for the percentages accordingly, in Line 196-198, as …..87.3% (n= 103, 95% confidence interval [CI] 86.6-88.0%) of all serotype III isolates. The other 15 serotype III isolates belonged to ST19 (11.0%, n= 13), ST335 (0.8%, n= 1), and ST438 (0.8%, n= 1)….., thank you.

4. DISCUSSION

* Line 215-218: "Although type III GBS strains accounted for more than half of neonatal meningitis in the cohort, it appeared to be unrelated to the worst prognosis. On the contrary, type Ib and……". I think that it is a bit risky to come to this conclusion, same issues for Line 235-244. I suggest authors read more literatures and give a more appropriate statement.

Reply:

Thanks for your instructive advice. The statement “Although type III GBS strains accounted for more than half of neonatal meningitis in our cohort, ……” is just a description of our cohort, not to make a conclusion. Therefore, I have discussion and read other literatures in the subsequent paragraph, and I use the term “It appears to be unrelated……”. It is also for line 243-252. Besides, we did not make it as a important conclusion or result in the abstract or the final conclusion section. I appreciate the reviewer the re-think about the appropriateness of these statements, thank you.

* Line 215-218: replace out cohort with "our cohort".

Reply:

Thanks for your instructive advice. I will replace out cohort with our cohort, thank you.

* Line 249-250: "The overall mortality in our cohort was 6.6%, which was lower than the average mortality in other countries….." Any reasons to explain these differences?

Reply:

Thanks for your question. I think it is due to the enhanced improvement of neonatal care in our institute. However, I do not have evidence, so I will not comment on this issue, thank you.
* Line 250: "average mortality of 9.6%....". This data has already been updated in 2017, the mortality was 8.4%, please cite the latest paper published in Clinical Infectious Disease, the first author is Lola Madrid.

Reply:

Thanks for your instructive advice. I will revise data, and use 8.4% with new 95% CI, and cite the latest paper published in Clinical Infectious Disease 2017 with first author Lola Madrid (new ref no.11, Line 257, 258), thank you.

* Line 261-275: This paragraph described high resistant rate of erythromycin and clindamycin. As we know, the rise of Fluoroquinolones-resistant GBS have been reported in some studies. It will be preferred if the authors have FQ-resistant data to add.

Reply:

Thanks for your instructive advice. Unfortunately we did not have data of fluoroquinolone susceptibility or resistance. In our institute, it is not common to use fluoroquinolone to treat invasive GBS infection.

Reviewer no. 2 comments:

Thank you for this paper, which is on "emerging serotype III sequence type 17 group B streptococcus invasive infection in infants: the clinical characteristics and impact on outcomes". This is a very useful and well-written addition to an increasing body of literature. The authors have determined the serotype distribution, antimicrobial resistance and molecular characteristics of neonatal invasive GBS isolates from Taiwan, 2003-2017. Please see my comments below:

Introduction:

The authors should mention if routine GBS screening is carried out amongst pregnant women in Taiwan and if so, when was it introduced?

Reply:

Thanks for your instructive advice. I will add this information in line 84-86 as In Taiwan, routine GBS screening has been carried out among pregnant women since 2012 and the intrapartum prophylaxis of GBS for pregnant women was also implemented in our institute since 2012

Materials and methods:
Page 5, Line 98: Need to say what CGMH stands for?

Reply:

Thanks for your instructive advice. I have already said CGMH as Chang Gung Memorial Hospital in Line 95, thank you.

Page 6: Line 112: delete "be" in the sentence: Episodes reported by physicians with negative CSF cultures were also be included if CSF results showed…

Reply:

Thanks for your instructive advice. I will delete “be” in the sentence, thank you.

Results:

Page 8, Line 148: Suggest putting (iGBS) in brackets, after invasive GBS…

Reply:

Thanks for your instructive advice. I will put (iGBS) in brackets after invasive GBS in line 155, thank you.

Page 9, Line 169: Where the mothers who gave birth to EOD cases screened during their pregnancy? If so, where they identified as GBS positive.

Reply:

Thanks for your question. Routine screening of pregnant women for GBS is the Taiwan National policy since 2012. Before 2012, some of the mothers who gave birth to EOD cases had screened, and some may not have. We did not have the information whether they were GBS positive or not. I am sorry that this information is not available.

Discussion:

Page 11, Line 209: What does LOS stand for?

Why was there a huge upsurge in serotype III isolates from 2003 to 2013 (Figure 2). Was it because more cases were reported, or was there an increase in serotype III transmission associated with a particular hospital? Have there been attempts to identify the source for those iGBS cases that were LOD or LLOD?
Thanks for your question. LOS stands for late-onset sepsis. The huge upsurge in serotype III isolates from 2003 to 2013 may be the global trend, because this situation was also observed in other countries and other institute in Taiwan (please see ref no. 32-38,48). This predominance came from LOD mostly (please see ref no. 35,39,40). I have mentioned this issue in the discussion section, page 12, 2nd paragraph, line 228-242.

Page 13, Line 237: (DIC)-need to describe these acronyms if they are being mentioned for the first time.

Reply:

Thanks for your instructive advice. I will revise it as disseminated intravascular coagulopathy (line 245).

Page 13, Line 238: "However, only type Ib GBS strain often caused meningitis": not sure if this statement is valid, given that the number of these strains are very small in this study.

Reply:

Thanks for your instructive advice. I will revise this sentence as “Besides, these strains were associated with a higher rate of neurological complications, although only type Ib GBS strain often caused meningitis.” (Line 247-248). In this sentence, we just want to explain most of the neurological complications resulted from brain hypoperfusion rather than from meningitis. We are not going to conclude only type Ib GBS often caused meningitis.

Page 13, Line 249: The sentence should say: The overall mortality in our cohort was 6.6%.

Reply:

Thanks for your instructive advice. I will revise this sentence to be “The overall mortality in our cohort was 6.6%” (line 257), thank you.

Limitations:

The authors have mentioned serotyping by molecular methods but no mention of slide agglutination methods. Though molecular techniques are rapid and easy to perform, they don't inform us about the expression of the genes detected.

Reply:
Thanks for your instructive advice. I will list this issue as the limitation of this study in the discussion section, page 15, line 289-290: The slide agglutination was not performed in this study, so the expression of genes detected was unknown.