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**Name of Journal:** *World Journal of Clinical Pediatrics*

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**Manuscript Type:** Original Article

We thank the referees and the editor for their valuable advices and for their good opinion regarding our manuscript.

The change through the text we made for answering to the referees are written in red color

#### **referee 1**

It is a very interesting paper, and I think that now a lot of units worldwide are doing the same. I am not agree with this sentence "There are insufficient evidence-based recommendations for managing well-appearing neonates at-risk for early-onset sepsis". I think that there are. "At-risk newborn is defined as an infant whose mother is group B Streptococcus colonized" I think that this is not correct.

We used the following definition (see Definition" in "Methods"): At-risk newborn is defined as an infant whose mother is group B Streptococcus colonized or has RFs for EOS.

If the mother has received correct prophylaxis or is a cesarean section without rupture premature of membranes, there is no significant risk.

This is a controversial issue, cases of EOS after adequate IAP may still occur, especially after chorioamnionitis (see 3 cited references Berardi A, et al, Impact of Perinatal Practices for Early-Onset Group-B Streptococcal Disease Prevention. *Pediatr Infect Dis J*. 2013;32:e265-71; Wortham JM, et al, Chorioamnionitis and Culture-Confirmed, Early-Onset Neonatal Infections.*Pediatrics*. 2016;137 (1); and Berardi A, et al, Safety of physical examination alone for managing well-appearing neonates  $\geq$  35 weeks' gestation at risk for early-onset sepsis. *J Matern Fetal Neonatal Med* 2015;28:1123-7)

You defined culture proven sepsis in 72h, but early onset sepsis from 0 to 6 days.

The definition of EOS usually is 0-6 days for GBS only; when all EOS cases are considered, the definition of EOS may be 0-48 or 0-72 hours (see Ganatra HA, et al. International perspective on early-onset neonatal sepsis. *Clin Perinatol*. 2010;37:501-23, and Wortham JM, et al, Chorioamnionitis and Culture-Confirmed, Early-Onset Neonatal Infections.*Pediatrics*. 2016;137; (1), and Vergnano S et al, Neonatal infections in England: the NeonIN surveillance network. *Arch Dis Child Fetal Neonatal Ed*. 2011 Jan;96(1):F9-F14)

Are you speaking about time of culture? Do you know this paper? Central-peripheral temperature gradient: An early diagnostic sign of late-onset neonatal sepsis in very low birth weight infants. Leante-Castellanos et al. Clinical signs, like temperature, can be useful to suspect sepsis in premature babies.

We know this paper, but it refers to late-onset sepsis in very-low birth weight neonates, that is not the case of our study

**referee 2**

Dear Authors, Your article raises an important issue in neonatology. Observations carried out on a large territory, but it is the right application for research on a much larger population of patients. Your opinion would be needed on the topic on non-GBS maternal colonization potentially resulting in neonatal EOS (eg. E. coli) and the question if SPE would be sufficient in such cases. Would you consider the heart rate observation and tolerance of feeding as the evaluating parameter in SPE? Do you take into account the result of the pulse oximetry test when assessing clinical condition of the baby. Overall, a good paper emphasizing the value of direct medical observation and physical examination.

We thank the referee for his good opinion regarding our manuscript, however to date there are no guidelines for preventing EOS due to E. coli. The method we use for an early suspect of EOS is based on simple vital signs, that may be easily assessed by midwives, nurses or clinicians. As we reported, every neonate with a reasonable suspicion of EOS is immediately referred to a neonatologist for a full and accurate evaluation.

As we experienced in our clinical practice, every evaluation requires up to 1 or 2 minutes and is very sensitive for the early detection of cases of EOS

We added this information in the section "methods" This method seems useful in sepsis caused by all pathogens, not only GBS. Therefore it is clear that other tools, such as pulse oximetry or others, are too laborious for a quick search of the first signs of sepsis. Feeding intolerance is always reported by nursing staff, independently from the suspect of EOS.

In order to highlight this aspect, we also changed the title in "Serial physical examinations a simple and reliable tool for evaluating and managing neonates at risk for early-onset sepsis"

**referee 3**

I am not a clinician but a quantitative analyst, and am assisting with this manuscript as much as I know. It is well-written with a need for grammatical improvement.

We reviewed our English. The agency that usually revises our English texts is experienced. We have provided the certificate

**referee 4**

It was a pleasure to review this manuscript. It is a multi-centric study that addresses an important and topical issue. I want to congratulate the authors for their work, but it must be revised. Notwithstanding its quality, some questions result from its reading:

**Global comments:** There is no reference regarding Ethics Committee. Has the study been approved?

This question has been addressed in the comments to the Editor

The authors sometimes are not very clear, concise and coherent in their language. There are so many abbreviations that the reading becomes difficult.

We deleted most abbreviations and added a short list at the top of manuscript

**Abstract: Background:** Regarding the period of the study: was it 3 or 4-months? As the authors describe in main text, it was probably 4-months.

We confirm (even in the text): 4 months

One of the limitations of the study is exactly fact: a small period of data collection (in main text I suggest to specify what months were included in data collection – example: January-April).

We added this information in “Methods”

**Results:** The authors only related one positive culture-proven... It would be important to be certain that the cultures met the criteria for collection (including mL of blood collected); the main cause for negative cultures in children with bacteraemia is insufficient blood, and this fact must be discussed in the main text. I understand that it would be difficult to access that data, but it must be discussed as a limitation.

As is clear from our previous studies, the GBS Prevention Working Group of the Emilia-Romagna region was created in 2003. Since then, much attention was paid to the diagnosis of neonatal sepsis. Blood cultures are collected by taking at least 1 ml of blood. In confirmation of the correctness of our methods, during the last 15 years we observed a continuous decline of EOS, while LOS have remained stable

The bacteria denomination is not correct; it must be *Haemophilus influenzae* or *H.influenzae* (and not *Haemophilus i.*).

Thank you, we changed this misspelling

The data presentation must be coherent; if you put percentage and total number, it must appear in all data. I suggest to introduce in this form: *n (%)*.

We added % rates in some results

Regarding the abbreviation RFs, the authors do not define it before

Thank you, we changed "RFs" in "risk factors"

## **Main Text**

### *Introduction:*

First paragraph: this is not the real concept of vertical transmission. I suggest to change this transmission to "*mother-to-child*" or "*transmitted by mother during deliver or shortly before*".

Thank you, we changed

The classification of early-onset sepsis is not consensual; some authors consider the age <72h, others prefer the age <7days. According to the methods, the authors included the neonates with age <72h; so, I suppose that this definition must appear in the introduction, introducing this two classifications.

Thank you, we added this definition, by citing Ganatra (ref. 3)

Second paragraph: the abbreviation WAARNs is not clear because the correspondence with the terms is not direct – it would be important to clarify that.

We deleted most abbreviations and added a short list at the top of manuscript

### *Methods:*

First paragraph:

4-months or 3-months (cf. abstract).

4 months

I guess level III is more correct (and not level 3).

Ok, thank you.

Second paragraph:

Why did you only define neonates during the period 0-6h as well appearing? – What were the criteria?

As stated, "Well-appearing refers to neonates with RFs for EOS without any clinical symptom of sepsis at age 0-6 hours". This is the time when some guidelines recommend laboratory test and empirical antibiotics for asymptomatic at risk neonates

The authors included the neonates within 72h of birth – the definition of early onset sepsis must be reviewed (cf introduction).

we added this definition in the introduction

Third paragraph: The initials of three reviewers are not important – it could be excluded.

Ok, thank you.

The numbers from zero to ten must be written out.

We are sorry, we do not understand which numbers....

Fourth paragraph: regarding CSF cultures, how many neonates did it? When was that not possible?

We added this information in results

What is IF/chorioamnionitis? – IF? I do not understand this last paragraph.

We added a list of abbreviations at the top of the manuscript

*Results:*

It would be important to uniform the data presentation and to clarify the numbers. For example in third paragraph, second sentence: “seven had signs” – seven of the 32? Seven of the total?

Ok, thank you.

Last paragraph: why did the neonate need oxygen support? A pneumonia?

We added this information

*Discussion:*

Third paragraph, fourth line: delete the point after chorioamnionitis.

Ok, thank you.

Please complete the limitations. Regarding last sentence of limitations, if you extend the period after the first week it will not be early-onset neonatal sepsis...

We changed the sentence, thank you.

*Table I:*

The numbers must be presented with a point in a decimal number.

We changed the sentence, thank you.