

Format for ANSWERING REVIEWERS

November 25, 2014

Dear Editor,



Please find enclosed the edited manuscript in Word format (file name: 14531-review.doc).

Title: Role of quorum sensing in bacterial infections

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Name of Journal: *World Journal of Critical Care Medicine*

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

We thank all reviewers for their valuable suggestions that helped us to improve the manuscript, below our reply to their comments point by point.

Reviewer **00717554**

I would like to mention the following comments:

1- References 2 and 3 are different from others in the text.

We thank the reviewer for this observation and accordingly we had check and corrected all references in order to uniform them and give them the style required by the journal.

2- Many parts should be divided in more paragraphs ;i.e., sometimes the paragraphs are too long.

We agree with the reviewer and shortened several paragraphs of the manuscript.

3- The structure of text is not clear. For example, at first, the authors say that they are going to compare QS in vitro and invivo; however, many other subtitles will arise: drugs ... It might be better to divide to two parts: invitro and invivo; then in each parts: subtitles for : staphylococcus and Pseudomonas and treatment etc.

We thank the reviewer for the suggestion and in agreement the paper structure was modified, including *P. aeruginosa* and *S. aureus* role of QS in controlling virulence factors in vitro in the first part, and the in vivo effects (in animal models and infections) in the second part, in addition the drugs for QS inhibition of both bacteria were grouped in section 3. Sections 4 and 5 (QS in other important bacterial pathogens and QS beyond bacteria were left unchanged).

Reviewer **00058198**

Thank you

We thank the reviewer for reading our manuscript and recognizing its value.

Reviewer **00722050**

The article "Role of Quorum Sensing in Bacterial Infections" is very interesting. However, a few aspects

need to be addressed.

The core tip sentence is too long. It needs to be shortened.

Thank you so much for your suggestion, in agreement, the core tip was reduced from 83 to 34 words :

In this manuscript we discuss the basics aspects of Quorum sensing and its relationship with human infections, focusing in two major QS bacterial models, the opportunistic Gram negative bacteria *Pseudomonas aeruginosa* and *Staphylococcus aureus*.

Another similar problem is that many sentences are too long as seen on page 7.

We agree with the reviewer and shortened several paragraphs of the manuscript.

The concept of how 195 functional HSL-QS communication systems are able to produce elastase (LasB and LasA) is not clear and needs to be clarified.

We apologize for the confusion and modified that paragraph to make it clear:

“Of those isolates, 97.5% (195 isolates) had robust functional HSL-QS communication systems and hence were able to produce elastase (codified by the genes *lasB* and *lasA*, which expression is QS dependent through LasR) and high levels of both HSL autoinducers while only 5 isolates failed to satisfy those criteria”

What is the role in patients or mice harboring a deficiency of the alpha-1-antitrypsin gene? It may be clarified this aspect that may be important for the reasons of major pulmonary inflammation (pneumonia) events in patients with AATD (alpha-1-antitrypsin-deficiency).

We recognize the importance of the deficiency of the alpha-1-antitrypsin and hence incorporate information regarding to it and its effects in the lung in the rephrased paragraph shown below (this change is highlighted in blue).

The sentence: In addition, the elucidation of factors that shape the mosaic-like composition of isolates in patients or in animal models (severity and progression of the infection, nutritional status, bacterial load, etc.), need to be studied in order to design better anti-QS therapies than the current ones that are focused on laboratory strains with QS-proficient systems rather than clinical strains recently isolated from infections is too vague and needs clarified in detail.

Specifically, it should be indicated how we can address animal models targeting severity and progression of the infection, nutritional status, bacterial load, etc.

This is very important for the reader and a senior molecular biologist of their institution may indicate these aspects including a table and a figure.

We thank the reviewer for this valuable suggestion and accordingly the paragraph mentioned was modified and extended to:

In addition, the elucidation of factors that shape the mosaic-like composition of isolates in patients or in animal models need to be determined in order to design better anti-QS therapies since the current ones are focused on laboratory strains with QS-proficient systems rather than clinical strains recently isolated from infections [60, 61]. Although such factors are still unknown, some variables like: the severity and progression of the infection, the nutritional, health, and immunological status of the patients, the exposure of the susceptible individuals to only one, a few, or several strains and the bacterial loads during the infections could be involved. In this sense, animal models would be useful to evaluate the role of these and other valuables in the colonization diversity in the patients, for example experiments comparing the colonization of well feed animals and animals with a deficient nutrition, immune competent animals and immunosuppressed ones, or healthy animals compared to animals harboring important disorders such as the alpha-1-antitrypsin deficiency that promotes major pulmonary inflammation, degradation of lung tissue, and eventually manifestations of pulmonary

emphysema, etc. using several bacterial strains (QS proficient and QS deficient) alone or in combination could be very valuable to determine the factors involved in the *in vivo* bacterial ecology in infections.

However we do not consider that adding a figure or table about these questions is necessary since no experimental data about the factors contributing in the population diversity of *P. aeruginosa* infections is available and the factors mentioned are just our hypothesis.

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