

Format for ANSWERING REVIEWERS



Dear Editor:

Please find enclosed the edited manuscript in Word format.

Title: “Antimicrobial resistance in clinically important biofilms”

Authors: Fatemeh Rafii and Mark E. Hart

Name of Journal: World Journal of Pharmacology.

ESPS Manuscript NO: 14199 (Edited)

Thank you for your Email and kind words. We also thank the reviewers for their time and comments. The following are the reviewers’ comments and responses to the reviewers:

Reviewer No. 1 comments

Authors The manuscript is detailed but it is unclear what is the novelty and addition to the literature since numerous other reviews have been reported on this topic. In addition the organization of the text throughout the manuscript is difficult to follow, lacks good flow since similar themes are mentioned randomly throughout the manuscript rather than in separate sections (e.g Pseudomonas biofilms, staph biofilms). The text can be shortened significantly and replaced by summary tables and figures as follows Summary tables summarizing the differences in biofilms a) between different organisms (e.g Staphylococcus versus pseudomonas vs other organisms) b) between in vitro formed vs in vivo formed biofilms should be presented. c) Differences between biofilm forming bacteria vs free living bacteria d) Summary of all the known virulence mechanisms of biofilm forming bacteria e.g specific names for PSA versus Staph rather than reporting them throughout the text Figures showing 1) Pathogenesis of biofilm formation 2) Mechanisms of resistance to antibiotics 3) Mechanisms of persisters The text can be better organized. For example CF is mentioned throughout the manuscript at different sections and the

text can be organized in certain sections per bacteria (e.g staphylococci) or per disease (pseudomonas and CF). In addition there is no mention of antibiotics and treatment for biofilms for example daptomycin , rifampin etc. Maybe a table can be added to emphasize this important topic. Spell out all abbreviations e.g TCA cycle

Response to the reviewer No. 1

We thank the reviewer for his/her time. We hope that the editor is in agreement with us on the following points:

Reviews on various subjects, including biofilms, are written periodically. In the current review, special efforts have been made to bring the readers up to date on the current knowledge of what is known on the subject of antimicrobial resistance in biofilms, and three reviews written on the subject have been recommended for further reading.

As the reviewer is well aware, biofilms consist of diverse communities of microorganisms and, as such, bacterial consortia in the biofilms could be responsible for a variety of infections. The diseases that are specifically associated with one particular organism, like cystic fibrosis, are mentioned in the text.

We hope that the editor also agrees with us that various characteristics of the bacterial biofilm, including those that the reviewer recommended, have been clearly described in the text in the well-organized sections, which precludes the necessity for tables.

Unlike infections caused by planktonic bacteria, the type of infections caused by biofilm are varied, and the selection of antimicrobial agents needs careful consideration by physicians. Suggestions for the use of antimicrobial agents in a review paper may be misleading.

The abbreviation TCA is spelled out in the revised manuscript, although others, like NAD and NADH, should not need to be spelled out (page 17).

Comments by the reviewer No. 2

This review is of superb quality and it will contribute importantly the area of microbial pathogenesis. The only topic that is missed and I strongly suggest to be included is amyloid bacterial proteins and their role in the biofilm formation and in antimicrobial resistance phenomena.

Response to the reviewer No. 2

We are grateful to the reviewer for his/her assessment of our manuscript and kind words. The section on “the role of amyloid bacterial proteins and their role in the biofilm formation and in antimicrobial resistance phenomena” has been included in the revised manuscript as follows:

Page 5: Curli fibers which are proteinaceous extracellular compounds produced by many *Enterobacteriaceae* and belong to class of fiber called amyloids have been shown to be involved in the bacterial attachment and biofilm formation ^[43].

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43: Michelle M. Barnhart MM, Chapman MR. Curli Biogenesis and Function Annual Review of Microbiology.2006;60131-60147 [PMID: 16704339 DOI: 10.1146/annurev.micro.60.080805.142106]

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In *Salmonella enterica* serovar Typhimurium, there is a link between the multidrug resistance efflux pump and biofilm formation ^[213]. In the mutants that lack a functional multidrug resistance efflux pump, such as AcrB and TolC, the transcription of proteinaceous materials of amyloid class (curli fiber) biosynthesis is repressed ^[213].

As you have recommended, the reference section has been revised to include “PMID and DOI numbers” and the short title and the Core Tip have been added to the manuscript as follows.

Thank you for inviting us to write this manuscript.

Sincerely yours,

Fatemeh Rafii

Fatemeh Rafii

Short title: Antimicrobial resistance in biofilms

Edited core tip < 100 words:

Biofilm formation on host tissues and medically implanted devices is a major health problem, and the infections caused by bacteria in biofilms are hard to treat with antimicrobial agents. They

are the cause of frequent and recurrent infections after the termination of antimicrobial treatments. The reasons for the recalcitrant nature of biofilms to antimicrobial treatment are varied and have been attributed to different factors, including impermeability of biofilms, slow rates of growth and metabolic activity, and the presence of small colonies and persisters. They have been the subject of many investigations that will be discussed in this minireview.