Format for ANSWERING REVIEWERS

March 30, 2015

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 16680-review.doc).

Title: Origin of de novo daptomycin non susceptible enterococci

Author: Theodoros Kelesidis

Name of Journal: World Journal of Clinical Infectious Diseases

ESPS Manuscript NO: 16680

Thank you very much for your email dated 3/26/14 stating that my manuscript may be considered for publication in your Journal provided that I revise it further according to your suggestions. Please find enclosed the edited manuscript in Word format (file name: 16680-edited TK. doc).
I resubmit the manuscript entitled "Origin of de novo daptomycin non susceptible enterococci" by Kelesidis, which has been revised according to your suggestions. I would like to thank you for your comments, which prompted me to revise the manuscript extensively. Please see my specific responses to your comments in the following page. Please do not hesitate to email or call me if I can be of further assistance.

Response to comments from the Editorial office
The manuscript has been improved according to the suggestions of the editorial office:
Format has been updated
References and typesetting were corrected

Response to reviewer comments

I have very minor comments about the manuscript entitled "Origin of de novo Daptomycin Non-susceptible Enterococci" that I hope can be fulfilled in order to make this review and hypothesis stronger. In general the review is interesting and easy to read with up to date information. I think it is relevant and deserves to be published so it can help physicians and public health workers in managing preventive and therapeutic measures against these antibiotic resistant microorganisms.
I would like to thank the reviewer for his/her comments.

1) The author should describe the antibiotic per se including the origin and if available the mechanism of action. This might help understanding the relation with the environment related non-susceptible isolates characterized and their co-evolution.

This is summarized under the section "The mechanisms of emergence of daptomycin nonsusceptibility in enterococci are complex." In addition the relationship of the possible mechnisms with the environment (for example soil actinomycetes and DNSE) is reviewed under the section:

"Transfer of genes that determine antimicrobial resistance between soil bacteria and DNSE may contribute to emergence of de novo DNSE. Daptomycin resistance genes ….whether transfer of resistance between soil bacteria and enterococci may contribute to emergence of DNSE. "

2) The routes of infection and types of pathologies and how prevalent are these pathogens should be introduced first as well specific data about mortality and morbidity if available.

The goal of this manuscript is to introduce a novel hypothesis about the origin of DNSE and summarize data that directly or indirectly support this hypothesis. I have previously reviewed in detail the epidemiology and the clinical presentation of DNSE infections and the appropriate references have been cited throughout the manuscript (Kelesidis et al Clin Infect Dis 2011; 52:228-234.

3) Are the genes linked with the resistance present in mobile genetic material such as bacteriophages or transposons?

This is discussed throughout the manuscript; for example in section "Acquired daptomycin resistance in enterococci may be mediated by bacteria of animal origin" Daptomycin resistance genes may be transferred between… in many bacteria found in poultry"

4) Mention that enterococci are facultative anaerobes and how that could impact the development of daptomycin non-susceptible microbes.

This is discussed in the section "Limited data from observational studies suggest that transfer of genes that determine antimicrobial resistance between anaerobes and DNSE may contribute to emergence of de novo DNSE."

Reviewer 2

The manuscript can be very useful to the scientific community and deserves publication as proper use of antibiotics and changes in microbial resistance are to be dealt with in a stringent manner for patient care and improved public health.

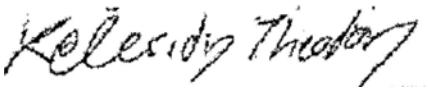
I would like to thank the reviewer for his/her comments.

I believe that this paper may help in clarifying available literature on this issue and that this article will be of major interest to the global readership of *World Journal of Clinical Infectious Diseases*. This manuscript has not been previously published and is not being considered for publication elsewhere. There are no potential conflicts of interest for the participating authors. Please do not hesitate to contact me should you have any further questions regarding this manuscript.

Thank you again for publishing our manuscript in the *World Journal of Clinical Infectious Diseases*.

Sincerely,

Theodoros Kelesidis, M.D, PhD



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