Author's response to reviews

Title: Retrospective study of Necrotizing Fasciitis and Characterization of Its Associated Oxacillin-Resistant Staphylococcus aureus

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Author's response to reviews: see over
Dear Editor

I acknowledge with sincere thanks to the reviewers for their critical and insightful review of our manuscript, MS: 1519810655507758, entitled “Retrospective study of Necrotizing Fasciitis and Characterization of Its Associated Methicillin-Resistant Staphylococcus aureus” My coauthors and I have followed the reviewers’ comments point-by point to revise the manuscript thoroughly and accepted almost all comments by Reviewers. We revised the manuscript fully in Abstract, Background, Results, and discussion We reconstructed the Table 1 and 2 and switched the order of Table 1 and 2 based on reviewer 1 comments. In addition, the revised manuscript was edited by our colleague who is native English speaker.

Attached please find the revised manuscript MS: 1519810655507758 and detailed response to the reviews’ comments. I hope our revision is satisfactory for publication in Journal of BNC Infectious Disease. If you need additional information or further clarification about this manuscript, please feel free to contact us.

Best regards,

Chishih Chu, PhD
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Reviewer's report

Title: Retrospective study of Necrotizing Fasciitis and Characterization of Its Associated Oxacillin-Resistant Staphylococcus aureus

Major Concerns
Article is not well written, in some points it's difficult to understand, must be re-evaluated for its English.

Response:

My coauthors and I have followed the reviewers’ comments point-by point to revise the manuscript thoroughly and accepted almost all comments by Reviewers. We revised the manuscript fully in Abstract, Background, Results, and discussion. We reconstructed the Table 1 and 2 and switched the order of Table 1 and 2 based on reviewer 1 comments. In addition, the revised manuscript was edited by our colleague who is native English speaker.

Title: It's better to change title may be as “Necrotizing fasciitis caused by community-associated and hospital associated methicillin-resistant Staphylococcus aureus in Taiwan”

Abstract
Authors must decide to use either oxacillin-resistant SA or MRSA and should use only one of them in a whole article body. (They used in some part of article ORSA but in other parts MRSA)

Response:
The title of your suggestion has been used. This manuscript containing two parts as indicated in the original title. Therefore, we used the original title by replaced the oxacillin by methicillin. In addition, we used the methicillin throughout the manuscript.

Abstract methods; instead of pulsotypes PFGE patterns should be used
Response:
Although the meaning of PFGE pattern is identical as pulsotype. However for better presentation in this manuscript, we preferred using pulsotype.
Abstract conclusion is not clear and not related with article purpose
Response: We rewrote the conclusion.

Background
*Authors should put a sentence related with how common MRSA infection in community in Taiwan. Instead of “Community-acquired ORSA (CA-ORSA) isolates are common pathogen for hemorrhagic necrotizing pneumonia and skin and soft tissue infections (SSTIs), and more virulent than hospital-acquired ORSA (HA-ORSA)”

**Following section should be re-written to be more clear “Virulence factors for toxemic syndrome, staphylococcal scalded-skin syndrome (SSSS), and NF include toxic shock syndrome toxin 1 (TSST-1, a super-antigen), exfoliatin A (ETA), exfoliatin B (ETB), and PVL [18-22]. However, these factors function differently in pathogenicity. TSST-1 can cause in part a desquamative skin rash, fever, inability to maintain homeostasis, and multiple organ failure, staphylococcal toxic shock syndrome (STSS) [23-24]; a pore-forming exotoxin, PVL, together with #-hemolysin (Hlg) can damage erythrocytes, polymorphonuclear (PMN) cells and macrophages [22]. The ETA and ETB are associated with localized bullous impetigo, generalized SSSS (Ritter’s disease), and a spectrum of blistering skin diseases [25-26]. Furthermore, CA-ORSA isolates with the PVL genes typically cause SSTIs and NF [4,27-28].” Its beter to give MRSA virulence factors and its association with pathogenicity in a simple manner not confusing manner above.

***“In this report, we did retrospective study of 247 NF cases during a 4-year period. Further, antimicrobialsusceptibility, SCCmec types, PFGE patterns, virulence factors, and MLST types of ORSA isolates associated with NF were characterized.” may be written as following

In this study, we retrospectively evaluated 247 NF cases during the 2004-2008 period and invastigated antimicrobial susceptibility, SCC mec types, PFGE patterns, virulence factors, and MLST types of ORSA isolates associated with NF.

Response:
We accepted the comment to revise the whole section of Background.

Methods
*Retrospective study heading should be changed as study population

***“For each patient, age and gender, infection site, and comorbid underlying chronic conditions such as diabetes mellitus, hypertension, chronic liver disease, coronary artery disease, chronic renal insufficiency, chronic obstructive pulmonary disease, and malignancy were analyzed.” may be written as “For each patient, age, gender, infection site, and comorbid underlying chronic conditions such as diabetes mellitus, hypertension, chronic liver disease, coronary artery disease, chronic renal insufficiency, chronic obstructive pulmonary disease, and malignancy were recorded”

***“Additionally, infectious pathogens, empiric antibiotics, number of operative debridement and reconstruction, need for amputation, duration of hospitalization, and in-hospital mortality rate were also evaluated.” may be replaced as “In addition, etiologic pathogens, empiric antibiotics used for initial treatment, number of surgical debridement and reconstruction underwent, need for amputation, duration of hospitalization, and in-hospital mortality rate of each NF cases were also evaluated”

Antimicrobial susceptibility testing
Should be written as “Antibiotic susceptibility testing was performed for SA isolates with respect to Clinical and Laboratory Standards Institute (CLSI) guideline by disc diffusion [29]. Isolates with zones of inhibition that fell into the category of intermediate susceptibility to a given antibiotic were considered susceptible isolates.

Characterization of NF-associated ORSA isolates
Not to start sentence with number “16 NF-associated……”

Response;
Thank you for your suggestions.
We changed the retrospective study to study population and revised the parts you indicated.

Results
This section must be re-written to make article more clear, I would recommend flow of this section as following: authors should give demographic data of 247 NF patients firstly (including age, sex, involved site, underlying conditions (DM, etc) then etiologic causes of them should summarized in table (table 1 is OK but A% and B% part make table confusing those must be removed). Secondly patient characteristics of MRSA-NF cases should reported (including age, sex, involved site, underlying conditions, operations, community accured or hospital occured) and they should report the risk factors for MRSA NF cases with respect to non-MRSA NF cases. After this authors should report the risk factors for hospital associated MRSA with respect to CA-MRSA. Also authors should give clinical and laboratory features of CA-MRSA. At the end PFGE and MLST types can be given as happened in body of article.

Response
We accepted your comments to rewrite this section.

Discussion

“In contrast to the high mortality of group A Streptococcus, Vibrio species or polymicrobial synergistic infections, ORSA was not an important pathogen to cause NF [4,7].” I am not agree with authors since MRSA is an emerging pathogen to cause NF and one of the aim of this study was to point importance of MRSA so this section must be re-written as MRSA was not common cause of NF.

** Authors can not use this sentence “all patients with ORSA infection required repeated surgical debridement and more patients required amputation, skin grafts, or reconstructive surgery, suggesting that ORSA may be actually important to cause destructive and deep-seated infection.” Since they did not make any comparison of MRSA vs MSSA NF cases so they should either compare those two and give results accordingly or should remove or re-write this section.

Response
We accepted your comments to rewrite this section.
Reviewer's report
Title: Retrospective study of Necrotizing Fasciitis and Characterization of Its Associated Oxacillin-Resistant Staphylococcus aureus

Reviewer's report:
The paper “Retrospective study of Necrotizing Fasciitis and Characterization of Its Associated Oxacillin-Resistant Staphylococcus aureus” by Changchien et al. characterized antibiotic susceptibility and the distribution of virulence factors of necrotizing fasciitis associated ORSA strains. They showed that ORSA strains are increasingly prevalent in NF clinical isolates. This study also suggested that several chronic diseases might predispose patients to NF. This report would be a very important reference for future clinical treatment of ORSA associated NF.

Response:
My coauthors and I have followed the reviewers’ comments point-by point to revise the manuscript thoroughly and accepted almost all comments by Reviewers. We revised the manuscript fully in Abstract, Background, Results, and discussion. We reconstructed the Table 1 and 2 and switched the order of Table 1 and 2 based on reviewer 1 comments. In addition, the revised manuscript was edited by our colleague who is native English speaker. Some of your comments were corrected in the manuscript, therefore, the revised text may not identical as your suggestion.

My biggest concern is that there are many typos and grammar mistakes. For example:

1. P13, line 7 “In this study, we found that Patients with HA-ORSA infection tended to having severe clinical characteristics in comorbidity, hospitalization days, amputation rate, and involvement of lower extremities A was more virulent than those with CA-ORSA infection."I guess what authors want to express here is that: “In this study, we found that patients with HA-ORSA infection tended to have severe clinical characteristics in comorbidity, hospitalization duration, amputation rate, and the involvement of lower extremities, suggesting that HA-ORSA was more virulent than CA-ORSA”.

Response:
We revised this section in p16 L1-7 as “investigation, the observed mortality rate did not significantly vary among the four groups, even though NF patients with HA-MRSA infection had a higher incidence of comorbidity on admission than those
infected by CA-MRSA, MSSA or non-
S. aureus group. However, the amputation rate and reconstruction rate for NF patients with MRSA infection were 18.4% and 30.6% respectively - significantly higher than those infected by non-
S. aureus. These analytical findings further highlight the role of MRSA as an important pathogen in causing a destructive and deep-seated infection.”

3. P5, line 5, “an MRSA” should be “a MRSA”
Response
We thought that “an” is much suitable here.

4. P5. line 13, please rewrite “TSST-1 can cause in part a desquamative skin rash, …..”
Response
We changed accordingly.

7. P11, line 8, “was significant difference” should be “was significantly different” or “had significant difference”. This also applies to P 12, line 9.
Response
Thank you for your suggestion. We used differed signicantly.

8. P12, line 4, please rewrite “Further the association…..”
Above are some apparent typos or grammar mistakes that I was able to pick up. Please read and check the language carefully. A native English speaker would be very helpful in improving the writing.
Response
Our manuscript was edited by a native English speaker.

2. P4, line 11, please rewrite sentence of “as the most prevalent…….”
5. P10, line 3, please rewrite “The prevalence of monomicrobial infection larger than……..” This sentence is very hard to understand. It would be more readable if “larger than” was changed to “over”.
6. P10, line 14, “those infected by (2.8 vs. 1.3)” should be “those infected by CA-ORSA (2.8 vs. 1.3)”
Response
In revision, we rewrote the manuscript thoroughly. Therefore, the change of your suggestions was not existed.
Some minor comments:
1. In the abstract, authors stated that:" other virulence factors TSST-1, ETA, and ETB of MRSA may be not the main virulence determinant for NF." I understand that those above mentioned virulence genes are not prevalent in that given set of ORSA isolates. However, this does not necessary mean that those virulence genes are not prevalent or important to other ORSA isolates identified in different time period and regions.
Response
We accepted your comments. Therefore we rewrote as “ Other virulence factors TSST-1, ETA, and ETB of MRSA may be not the main virulence determinant for NF.” in the Abstract section.

2. Too many abbreviations would be inconvenient to readers. I would encourage authors try to make a reader-friendly version.
Response:
Thank you for your suggestion. We limited the abbreviation in revised manuscript.

3. Be consistent with abbreviations. Although oxacillin and methicillin are the same class of antibiotics, ORSA and MRSA refer to the same type of antibiotic resistance, it is unnecessary to change between ORSA and MRSA frequently, which would confuse readers.
Response
We accepted your comments to use MRSA throughout the manuscript.