Author's response to reviews

Title: Clinical and microbiological characteristics of purulent and non-purulent cellulitis in hospitalized Taiwanese adults in the era of community-associated methicillin-resistant Staphylococcus aureus

Authors:

Yao-Shen Chen (u9371003@gmail.com)
Chun-Yuan Lee (Leechy8801131@gmail.com)
Hung-Chin Tsai (hctsai1011@yahoo.com.tw)
Calvin M Kunin (ckunin@columbus.rr.com)
Susan Shin-Jung Lee (9811anita@gmail.com)

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Author's response to reviews: see over
Dear Dr. Logan,

Re: Manuscript reference No. 201843135165305

Please find attached a revised version of our manuscript “Clinical and microbiological characteristics of purulent and non-purulent cellulitis in hospitalized Taiwanese adults in the era of community-associated methicillin-resistant *Staphylococcus aureus*”, which we would like to resubmit for publication as a research article in *BMC Infectious Diseases*.

Your comments and those of the reviewers were highly insightful and enabled us to greatly improve the quality of our manuscript. In the following pages are our point-by-point responses to each of the comments of the reviewers, as well as to your own comments.

Revisions in the text are highlighted in yellow. In accordance with the suggestions of Reviewers 1 and 2, we have added Tables 6 and 7. We hope that the revisions in the manuscript and our accompanying responses will be sufficient to make our manuscript suitable for publication in *BMC Infectious Diseases*.

We look forward to hearing from you at your earliest convenience.

Yours sincerely,

Yao-Shen Chen
Division of Infectious Diseases, Department of Medicine, Kaohsiung Veterans General Hospital, 386 Ta-Chung 1st Rd., Kaohsiung 813, Taiwan.
Tel: +886-7-342121 x 1540
Fax: +886-7-3468292
E-mail: u9371003@gmail.com
Responses to the comments of Reviewer #1

1. Line 58. It is not clear here what is meant by the term “wound”. Can the authors rephrase this to indicate whether they mean a pre-existing ulcer or other lesion?  
   Also, see below on this issue.  
   Response:  
   A definition for our use of the word “wound” has been added to the methods section as follows: “Wound is defined as a pre-existing skin lesion at the time of skin infection onset, such as a chronic ulcer, or a trauma-related skin lesion, such as lacerations, abrasions, or punctures. Surgical site infection is not included in the present study”. Page 7, lines 144–146.

2. Lines 63-64. “staphylococci” -- Are the authors here including other species of Staphylococcus (i.e., CONS) or does the denominator for this percentage (50%) reflect all S. aureus only?  
   Response:  
   We are only referring to Staphylococcus aureus in this instance. The manuscript has been revised, as follows: “The etiological agent was identified in 83.3% of the purulent cases, with Staphylococcus aureus the predominant pathogen (60%): 50% of these were methicillin-resistant S. aureus (MRSA).” Page 3, lines 61–63.

3. Lines 87-88. It may be important to note here that these data are derived from 3 cited studies in the U.S. If there are similar data available from Taiwan, can the authors cite them? If not, this is another reason that the present study is very important.  
   Response:  
   A new reference 7 from Taiwan has been cited. Page 20, lines 467–469.

4. Lines 128-130. I am concerned about a bias that may be introduced into the study with limited number of ICD-9 codes included. Patients with more severe, deeper skin and soft tissue infections, such as necrotizing fasciitis, likely had worse outcomes than those with an uncomplicated cellulitis or skin abscess. The patients with such severe infections may not have been given a separate ICD-9 diagnosis code among those listed as inclusion criteria although their severe infection may have originally developed from a purulent or non-purulent cellulitis or an abscess of the skin. The omission of patients with ICD-9 codes indicating more severe skin and soft tissue infections thus may bias the reported outcome data on recurrence, death, length of stay and duration of antibiotic therapy. This should be noted as a limitation of the study or perhaps the authors could examine the medical records of patients with ICD-9 coded diagnoses for more severe soft tissue infections at this center during 2013 to determine 1) what type of infection of the skin they derived from and 2) what the reported
outcomes were for the infections in these patients.
Response:
We thank the reviewer for this observation. We have added a section to the methods under “study design” to clarify this issue, as follows: “In our initial investigation, chart review of cases with International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) codes of 729.4 (fasciitis), 728.86 (necrotizing fasciitis), and 608.83 (Fournier's gangrene) were also carried out. Although some cases were initially diagnosed as cellulitis because of spreading erythema and swelling, these were finally diagnosed as deeper skin and soft tissue infections, and were not included in our study.” Page 6, lines 121–127.

5. Lines 155-156. How was it decided which patients were tested for initial ASOT? How was it decided which patients were tested for convalescent ASOT? Were all patients tested in this way if they had no positive wound or blood culture? If not, this is likely a major limitation of the study that should be noted in the discussion
Response:
In our clinical practice, we measure both acute and convalescent ASO, with an interval of 2 to 4 weeks. However, it is not always feasible to do this, and not every clinician remembers to take the second set of ASOT readings. Additionally, over the study period some clinicians did not measure ASOT because the patient presented with the typical manifestation of Streptococcus cellulitis. The limitations of the ASOT screening have been added to the discussion in response to this suggestion. Page 15, lines 331–355.

6. Lines 181-182. The criterion of previous MRSA infection is no longer used in CDC surveillance criteria to exclude a person from the category of “CA-MRSA.” The authors should note that there is this difference in their criteria from the current CDC criteria. They might also consider a secondary analysis determining the percentage of patients in each study group who had CA- and HA-MRSA infections excluding this “previous MRSA infection” criterion.
Response:
We thank the reviewer for this observation. We have added a section to the methods under “Definitions” to clarify this issue, as follows: “Modified case definition, which excludes the previous isolation of MRSA as a criterion for HA-MR, was also analyzed in the present study [19].” Page 8, lines 159–161.
We also have added a section to the result under “Microbiological findings”, as follows: “CA-MRSA defined by both epidemiological criteria reported the same number of cases, and were isolated in 21.3% of cases in the purulent group and 3.8% of cases in the non-purulent group (p = 0.681).” Page 11, lines 257–260.
7. Line 210, Table 1. “wound” -- it is not defined in the manuscript what is meant by this term. Please define the term in the Methods. Does this refer to a pre-existing skin lesion at the time of skin infection onset? Does it include surgical site infections? Does it include trauma? There is a brief and inadequate list of examples of “wounds” in the Discussion (lines 279-280), but this is not adequate.
Response:
The definition of our use of “wound” has been added to the methods (please see the above response to question 1). Page 7, lines 144–146.

8. Lines 231 and 234. “rate” would be better denoted “prevalence” in both lines.
Response:
This has been corrected as suggested. Page 11, lines 233, 236.

9. Lines 283-288. This paragraph includes interesting data from the literature. Can you engage it by comparing and contrasting your results with those cited here?
Response:
In response to this comment we have added the following comparison of the cited data to that of our current study, as follows: “The present study demonstrates similar results. Of the purulent cases in which the etiological agent was identified, 60% were caused by S. aureus, 35.4% of which were CA-MRSA.” Page 14, lines 318–320.

10. Lines 302-304. These are results and would be best included in the results section of the manuscript. It would be very relevant to assess whether the use of an appropriate medication (i.e., covering the pathogen that was cultured if one was cultured) or a non-appropriate medication for each of the infections was used and if there was a correlation between using an active antimicrobial agent and the risk of recurrence, for example.
Response:
In response to this suggestion, new paragraphs have been added to both the results and discussion sections, and Table 7 has been added to present this data. The following has been added to the results: “The empirical prescription of antimicrobial agents is detailed in Table 7. In this study, the five most commonly prescribed antimicrobial agents were penicillin (29.5%), oxacillin (28.6%), cefazolin (19.4%), β-lactam/β-lactamase inhibitors (3.7%), and penicillin plus clindamycin (3.4%). The prescription of antimicrobial agents differed significantly between the purulent and non-purulent groups. Penicillin was the most frequently prescribed agent in the non-purulent group (35.2%), whereas oxacillin was the most frequently prescribed agent in the purulent group (39.6%). The appropriate antimicrobial agent was more frequently prescribed in the non-purulent group...
than in the purulent group (83.2% vs. 53.8% of cases, \( p < 0.001 \)). Among the 32 cases of MRSA identified, 12.5% (4/32) of cases received the appropriate antibiotic therapy, and the prevalence of appropriate antimicrobial agent use was not significantly different between the two groups (16.7% vs. 0%, \( p = 0.55 \)).” Pages 12–13, lines 274–286.

The following has been added to the discussion: “In the present study, cellulitis cases were treated by a range of practitioners, including primary care, emergency, and other specialist physicians. Multiple antibiotics were empirically prescribed for cellulitis, and these differed significantly between the non-purulent and purulent groups (Table 7). The rate of prescription of inappropriate antimicrobial agents was higher in the purulent group than in the non-purulent group (46.2% vs. 16.8%, \( p < 0.001 \)). Overuse of antibiotics is associated with increased antibiotic resistance and cost of treatment [30, 31]. However, inappropriately withholding necessary antibiotics may have adverse effects on outcomes. The impact of inappropriate antimicrobial agent use on length of hospital stay, duration of antimicrobial therapy and medical cost needs further analysis.” Page 16, lines 356–366.

11. How was a recurrence of infection defined in this manuscript? Was the recurrent lesion at necessarily at a different anatomic site? Was it required that there be evidence of a cure prior to the diagnosis of a “recurrence”?
Response:
The following has been added to the methods: “Recurrence of cellulitis was defined as an attack of cellulitis in the same anatomical site within 6 months of cure of the previous episode of cellulitis.” Page 8, lines 164–165.

12. Lines 323-324. “most commonly” This seems like an overstatement. Is this statement a reflection of data in just the one cited manuscript? There are no data that I have seen to demonstrate what the most commonly used combination therapy is in the U.S.
Response:
It is a reflection of data in the cited manuscript. That study showed that in 41% of cases (9/22) in an emergency department, SMX/TMP plus cephalaxin was chosen as the course of therapy. To avoid confusion, the sentence has been revised as follows: “Some primary physicians may use a strategy known as double coverage, which refers to the use of at least two antibiotics with Gram-positive coverage (such as trimethoprime-sulfamethoxazole plus cephalaxin) to target MRSA, methicillin-sensitive S. aureus, and β-hemolytic streptococci.” Page 17, lines 382–384.

13. Lines 338-342. Was logistic regression performed all on patients in the study,
including those who had no pathogen identified? If so, the result here may be biased. Among the many patients with an unknown pathogen in the non-purulent group, is it not possible that they had an infection caused by S. aureus (including MRSA)? Because of this problem, which is always present in studies of non-purulent cellulitis, the choice of empiric therapy is difficult. The implication that I derive from the logistic regression analysis is that S. aureus (and MRSA) is relatively rare as a cause of non-purulent cellulitis, but I am not sure that the dataset demonstrates this (see also note on Table 4).

Response:
In response to this comment, the logistic regression analysis was repeated using the 211 cases with a final pathogen diagnosis. Table 6 has been added to show these data, and the following paragraph has been added to the results: “Following adjustment for age, sex, sepsis, lower limb involvement, history of tinea pedis, diabetes, and wound, purulence was a positive predictor of MRSA infection (odds ratio (OR), 5.188; 95% confidence interval (CI), 1.995–13.493; p = 0.001).” Page 12, lines 267–272.

14. Table 2. For recurrence within 6 months, does this denominator include those who died within 3 months?
Response: Yes, this includes those who died within 6 months.

15. Table 2. Please indicate “days” as the unit for the “length of stay” and “Duration of antimicrobial therapy”.
Response: This has been corrected.

16. Table 3. It is not clear to me what is meant by “diagnostic tool”.
Response: It means blood culture, wound culture, ASOT, and puncture biopsy.

17. Table 3. “rate” is not appropriate in any of the 4 times it is used in this table –this would be better “prevalence” or simply to provide the n and percent.
Response: This has been corrected.

18 Table 3. What is meant by “one set” compared with “paired”? Is “one set” the same as one single-time testing point?
Response: Yes, one set means a single testing point.

Response:
20. Table 4. Footnote. For “CA-MRSA”, you might want to add that you are defining this by epidemiologic criteria, and not by genotypic criteria.
Response: This has been added.

21. Table 4. Consider a footnote to define the meaning of “GNB”.
Response: This has been defined.

22. Table 4. The authors are not consistent in using “(%)” for each row of data. It may be easier to simply indicate this notation at the top of the relevant columns.
Response: (%( has been added to each row of data.

23. Table 4. It may be more relevant to use as a denominator in this table (after the first row of data) the n of isolates in each group that did have a final bacteriologic diagnosis made (rather than the total n in each group). As it is, comparing (and assigning a p-value to) the percentage of purulent and non-purulent lesions, for example, with MRSA or GNB, is difficult to interpret. This is because those lesions with no final bacterial diagnosis were presumably caused by some unknown bacterial pathogen, and we usually presume that the majority were caused by staphylococci or streptococci. As this table now stands, I believe, the comparisons do not reflect the data actually in hand; the analyses shown are skewed by the large number of “unknown” lesions in the non-purulent group. The unknown lesions add noise to the analysis. Can the authors either show the results of an analysis using a denominator omitting the unknowns or discuss the issue in the text of the manuscript to justify the current presentation of the data?
Response: We thank the reviewer for this suggestion. Table 4 has been revised to reflect this new denominator.

24. Table 5. I believe that there is a typo in this Table. In the row for “Levofloxacin” in the column under “Non CA-MRSA”, should it state “5 (50)”?
Response: Yes, this has been corrected.

25. Table 5. Please define what is meant by the abbreviation “TMP-SMX”.
Response: This has been defined.

26. Table 5. Footnote. Does the susceptibility result for clindamycin reflect results
of the D-test for inducible resistance? If so, can the authors note this in the footnote?
Response:
The following has been added to the footnote: “The D-test was performed to detect inducible clindamycin resistance for isolates found to be resistant to erythromycin, but susceptible to clindamycin.” Page 33, lines 591–593

Discretionary revisions
1. Lines 309-311. Why did the authors choose to cite the Sanford Guide? While it is a clinically useful guide, it is not a peer-reviewed document. The authors may thus want to consider omitting this citing this guidebook in their paper
Response:
The Sanford guide has been omitted.
Responses to the comments of Reviewer #2

Major Compulsory Revisions

1. One of the most important findings in this study was the higher positive rate of beta-hemolytic streptococci in non-purulent cellulitis (92, 24.9%) than in purulent cellulitis (4, 4.2%, P < 0.001). However, a majority (82.6%) of the diagnosis of beta-hemolytic streptococci infection was made solely by the measurement of the antistreptolysin O (ASLO) titer. A single ASLO titer >200 was used to define streptococcal cellulitis in this study. A single ASLO >200 did not necessary indicate active streptococcal infection but can be due to an infection occurring some time before. The authors should provide solid evidence supporting the use of ASLO in this scenario. Otherwise, those with a single ASLO titer > 200 should not be considered having streptococcal cellulitis

Response:
A paragraph has been added to the discussion to address this issue: “An increased ASOT between the acute and convalescent phases provides a more accurate reflection of a preceding streptococcal infection than a single titer [26]. However, it is not always feasible to obtain paired sera. Therefore, the occurrence of a single isolated titer that is higher than the upper limit of normal value is also evidence of a previous streptococcal infection. In patients with group A streptococcal infections, ASOT begins to rise after approximately 1 week, reaching maximal levels at 3–6 weeks post-infection [27, 28], and begins to decline in uncomplicated infections at 6–8 weeks post-infection, although in some patients the titer may remain elevated for indefinite periods [29]. We reviewed the charts of the 70 non-purulent cases with a single positive ASOT in the current study, which showed that only six of these cases experienced another episode of cellulitis in the year preceding the current episode. These findings provide further support for β-hemolytic streptococci being the causal organism in the majority of the 70 cases with a single positive ASOT.” Page 15, lines 331–343.

2. Following the comment #1, ASLO was measured in only 18.8% of patients with purulent cellulitis. The rate was significantly higher for patients with non-purulent cellulitis (52.0%). This selection bias may lead to an underestimate of the incidence of streptococcal infection in purulent cellulitis.

Response:
In response to this comment, the following paragraph has been added to the discussion: “The lower rate of ASOT performed in the purulent group compared with the non-purulent group may have led to an underestimation of the incidence
of Streptococcus infection (purulent vs. non-purulent, 18.8% vs. 52.0%, p < 0.001). This selection bias is unavoidable in a retrospective study, but may be limited. First, the lower rate of ASOT testing in the purulent group may reflect the fact that these patients did not present with typical Streptococcus cellulitis, which is characterized by rapidly spreading areas of inflammation in the lower extremities, sometimes accompanied by lymphangitis and regional lymphadenitis in cases with predisposing conditions, such as tinea pedis, stasis dermatitis, compromised lymphatic drainage, and venous insufficiency. Second, the prevalence of positive ASOT, whether as single or paired results, was significantly lower in the purulent group than in the non-purulent group (purulent vs. non-purulent, 11.1% vs. 42.75%, p = 0.031).” Page 15, lines 344–355.

3. I am surprised that the antimicrobial regimen was not analyzed in this study. This can be an important parameter affecting the treatment outcome and should be included in the analysis.

Response:
In response to this comment, paragraphs have been added to both the results and discussion sections, and a new table (Table 7) has been added to present this data. The paragraph added to the results is as follows: “The empirical prescription of antimicrobial agents is detailed in Table 7. In this study, the five most commonly prescribed antimicrobial agents were penicillin (29.5%), oxacillin (28.6%), cefazolin (19.4%), β-lactam/β-lactamase inhibitors (3.7%), and penicillin plus clindamycin (3.4%). The prescription of antimicrobial agents differed significantly between the purulent and non-purulent groups. Penicillin was the most frequently prescribed agent in the non-purulent group (35.2%), whereas oxacillin was the most frequently prescribed agent in the purulent group (39.6%). The appropriate antimicrobial agent was more frequently prescribed in the non-purulent group (83.2% vs. 53.8% of cases, p < 0.001). Among the 32 cases of MRSA identified, 12.5% (4/32) of cases received the appropriate antibiotic therapy, and the prevalence of appropriate antimicrobial agent use was not significantly different between the two groups (16.7% vs. 0%, p = 0.55).” Pages 12–13, lines 274–286.

The following has been added to the discussion: “In the present study, cellulitis cases were treated by a range of practitioners, including primary care, emergency, and other specialist physicians. Multiple antibiotics were empirically prescribed for cellulitis, and these differed significantly between the non-purulent and purulent groups (Table 7). The rate of prescription of inappropriate antimicrobial agents was higher in the purulent group than in the non-purulent group (46.2% vs. 16.8%, p <
Overuse of antibiotics is associated with increased antibiotic resistance and cost of treatment [30, 31]. However, inappropriately withholding necessary antibiotics may have adverse effects on outcomes. The impact of inappropriate antimicrobial agent use on length of hospital stay, duration of antimicrobial therapy and medical cost needs further analysis.” Page 16, lines 356–366.

4. In line 190-191 on page 8, the statement ‘Multivariable analysis of predicting factors for MRSA...’ was of much confusion. What exactly did the authors want to predict? The factors of purulent cellulitis, or the factor of MRSA infection? Further, how was the multivariate analysis performed? The detailed methods including the factors and the case numbers included in the final model of regression should be stated.

Response:
We aimed to analyze factors associated with MRSA. The candidate variables were mentioned in the methods. A new paragraph has been added to the results: “Following adjustment for age, sex, sepsis, lower limb involvement, history of tinea pedis, diabetes, and wound, purulence was a positive predictor of MRSA infection (odds ratio (OR), 5.188; 95% confidence interval (CI), 1.995–13.493; \( p = 0.001 \)).” Page 12, lines 267–272.

Additionally, Table 6, titled “Multivariable analysis of MRSA in the 211 adult patients with final pathogen diagnosis” has been added.

5. MRSA was identified as a significant factor associated with purulent cellulitis. Was it the only significant factor in the analysis? The other significant factors should also be listed.

Response:
The manuscript has been revised to clarify this as follows: “Following adjustment for age, sex, sepsis, lower limb involvement, history of tinea pedis, diabetes, and wound, purulence was a positive predictor of MRSA infection (odds ratio (OR), 5.188; 95% confidence interval (CI), 1.995–13.493; \( p = 0.001 \)).” Page 12, lines 267–272.

Minor Essential Revisions

1. Were all the cases in-patients? If yes, the finding in this study should be limited to those with severe infections requiring hospitalization, but not be generalized to all patients with cellulitis. This should be clearly stated in the manuscript.

Response:
We agree with this assessment and have added the following to the discussion: “Finally, the patients in this study were limited to hospitalized cases, meaning that infections were more severe. Therefore, the results of this study cannot be
generalized to all patients with cellulitis in Taiwan”.

The title of the manuscript was also revised as follows: “Clinical and microbiological characteristics of purulent and non-purulent cellulitis in hospitalized Taiwanese adults in the era of community-associated methicillin-resistant *Staphylococcus aureus*”.

2. **Background, line 79-80, page 4, ‘The microbiological findings are ...failure to distinguish non-purulent from purulent cellulitis’. This meaning of the sentence was not clear. Revision is needed**

Response:

This sentence has been revised as follows: “and because of the identification of widely different causative organisms depending on the diagnostic tools used.” Page 5, lines 86–87.

3. **For non-purulent cellulitis, 18.2% had wound cultures. What specimen was obtained for the wound culture if it was ‘non-purulent’?**

Response:

In our study, non-purulent cellulitis was defined as cellulitis without purulent drainage or exudate or associated abscess. However, sometimes clinicians may still attempt to collect microbiological evidence via superficial swab even if the wound does not present obvious exudate or discharge.

4. **Results, line 212, page 9, the statement was not true. The comorbidity score was also different for purulent and non-purulent cellulitis (Table 1).**

Response:

The sentence “or other underlying diseases” has been deleted.
Responses to the comments of Reviewer #3

Minor Essential Revisions

5. Are the discussion and conclusions well balanced and adequately supported by the data?
   Comments: Generally acceptable.
   Line 280, references should be provided.
   Line 293-295, not misdiagnosed, but not fit your inclusion criteria (arbitrary definition)
   Line 302, “In our investigation”, you mean “in this study” or your other investigations.
   Response:
   1. Reference numbers 2, 11 and 25 have been added.
   2. These cases were initially misdiagnosed as cellulitis, but were ultimately diagnosed as other diseases. Therefore, these cases were excluded even though their initial ICD9 classification fit our inclusion criteria.
   3. These sentences have been moved to a new paragraph in the results: “The empirical prescription of antimicrobial agents is detailed in Table 7. In this study, the five most commonly prescribed antimicrobial agents were penicillin (29.5%), oxacillin (28.6%), cefazolin (19.4%), β-lactam/β-lactamase inhibitors (3.7%), and penicillin plus clindamycin (3.4%). The prescription of antimicrobial agents differed significantly between the purulent and non-purulent groups. Penicillin was the most frequently prescribed agent in the non-purulent group (35.2%), whereas oxacillin was the most frequently prescribed agent in the purulent group (39.6%). The appropriate antimicrobial agent was more frequently prescribed in the non-purulent group than in the purulent group (83.2% vs. 53.8% of cases, p < 0.001). Among the 32 cases of MRSA identified, 12.5% (4/32) of cases received the appropriate antibiotic therapy, and the prevalence of appropriate antimicrobial agent use was not significantly different between the two groups (16.7% vs. 0%, p = 0.55).” Page 12, lines 274–286.

6. Are limitations of the work clearly stated?
   Comments: Partly.
   By your definition, rare pus specimens could be obtained from most cellulitis cases, so the etiologic investigation would be inadequate. Otherwise, there is no serologic study for Staphylococcus aureus and this etiologic agent might be underestimated for cellulitis. In addition, no molecular characterization was done for CA-MRSA, also a limitation.
Response:
In response to this comment the following have been added to the discussion:
“Because of the retrospective nature of the present study, we were unable to access the bacterial isolates for molecular epidemiological studies.” Page 17, lines 401–404.
“The major limitation of this study is information bias, which is inherent in all retrospective studies. It also unavoidably contributes to selection bias because not all patients received paired ASOT testing, and none of the patients underwent a serological test for S. aureus. Both of these factors may lead to an underestimate of the role of β-hemolytic streptococci and S. aureus as etiological agents of cellulitis.” Page 18, lines 410–414.

8. Do the title and abstract accurately convey what has been found?
Comments: Generally acceptable. Suggest add “hospitalized adult patients” and provide full spelling for CA-MRSA. The conclusions in the abstract are not appropriate and need revision.
Response:
In response to this suggestion we have amended the title as follows: “Clinical and microbiological characteristics of purulent and non-purulent cellulitis in hospitalized Taiwanese adults in the era of community-associated methicillin-resistant Staphylococcus aureus.”

We have also revised the conclusions in the abstract as follows: “The epidemiology, clinical features, and microbiology of purulent and non-purulent cellulitis were significantly different in hospitalized Taiwanese adults. Purulence was a positive predictor of MRSA as the causal agent of cellulitis. These findings provide added support for the adoption of the IDSA guidelines for empirical antimicrobial therapy of cellulitis in Taiwan.” Page 4, lines 71–75.

9. Is the writing acceptable?
Comments: Yes, generally.
The term “community-acquired” or “community-associated” should be clearly stated in “background” part.
Response:
“Community-acquired” was replaced with “Community-associated”.
Table 2. The percentage should be “0” but not “0.8” for death within 30 days in the purulent group. The unit (days?) should be provided for “length of stay and duration of antimicrobial therapy”. Also for these 2 items, numbers in ( ) are standard deviation or what?
Response:
These have all been corrected.  
Full spellings for the abbreviations in the Tables should be provided as footnotes, such as ASOT, GNB, CA-MRSA etc.
Response:  
These definitions have been added to the footnote.
Response to comments of editor:

Authors’ Contribution:

Please include individual author’s contribution. We suggest the following kind of format (please use initials to refer to each author’s contribution):

**AB** carried out the molecular genetic studies, participated in the sequence alignment and drafted the manuscript. **JY** carried out the immunoassays. **MT** participated in the sequence alignment. **ES** participated in the design of the study and performed the statistical analysis. **FG** conceived of the study, and participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

Response:

The following has been added to the section Authors’ contributions: “**C-YL** conceived and designed the study and drafted the manuscript. **H-CT**, **CMK**, and **SS-JL** conceived and designed the study, and analyzed and interpreted the data. **Y-SC** critically revised the manuscript. All authors read and approved the final manuscript.”