

Peer Review File

Article information: <http://dx.doi.org/10.21037/apm-20-2120>

**Reviewer A**

The purpose of this study is quite important. As mentioned in this study, the prognostic factors of DNM have been gradually clarified and a treatment strategy has been formulated. However, efficient prognostic analysis including causative bacteria has not yet been reported. The authors concluded that SAG infection was a risk factor for aggression and spread to the inferior mediastinum and thoracic cavity in DNM patients. However, the study design and results are problematic, and the design should be more clarified. In addition, there are some concerns and important errors.

There are some fundamental questions in the main affecting study design and results.

**Comment 1:** Above all things, SAG, previously called the *Streptococcus milleri* group, is a resident bacteria in the oral and upper respiratory tracts. SAG tends to cause deep infection in the soft tissue organs and they are one of the most common causatives of infection in oral and upper respiratory tracks. Gas bubbles on a CT scan in other organs are also known as an independent risk factor for poor prognosis and SAG can cause gas bubbles. Therefore, they should analyze the causatives in oral or deep infection and compare them with ones in the thorax. In addition, they should analyze and compare causative ones between patients with and without DNM,

**Reply 1:** We appreciate your insightful suggestions. As you commented, there are some reports that the anatomical location of the infection and clinical features of the patients with DNM correlate with aggravation and prognosis of the DNM.

In our study, its significance could not be proved. As advised, we have added the text and reference accordingly, and revised Table 3.

**Changes in the text:** Some articles also reported the relationship between the infection site and DNM (20), and that the presence of comorbidities and complications, with higher mortality or modality rates observed in patients with comorbidities including diabetes mellitus (21) as well as those with sepsis and septic shock (22). The relationship between the infection site, comorbidities, and initial antibiotics, and aggravation and prognosis of DNM could not be proved in our study, further analyses may clarify the risk factor. (see Page 10, line 164-166)

**Comment 2:** As they mentioned in their study, because the sample size is too small

and SAG infection is common, their results has little value. I think that the more important factors are patient's factor, such as immunity, comorbidity...

**Reply 2:** We agree with your valuable comment. As you suggested, we additionally analysed between the immunity and comorbidities such as age, sex, body mass index, comorbidity, and infection site, and the outcomes such as reoperation, complications, and postoperative hospital stay. However, we could not clarify the significant factors to predict the prognosis of DNM. We have revised Table 3 as advised.

As reported in the manuscript, the efficient prognostic analysis including causative bacteria has not yet been reported. Thus, we mentioned about the causative bacteria.

**Changes in the text:** Same as Reply 1, and we revised and Table 3.

**Comment 3:** They should clarify antibiotic effects in patients with DNM.

**Reply 3:** We appreciate your pertinent comment. In our study, 2 patients received sulbactam and ampicillin, and other 4 patients received carbapenem from day of hospitalization. We could not clarify the effects, and as advised, we revised Table 2 and Table 3 to compare the effects of initial antibiotics.

**Changes in the text:** Same as Reply 1, and we revised Table 2 and Table 3.

**Comment 4:** Although above questions, this topic is very important and should be studied. You should perform above suggested analyses to improve their study value.

**Reply 4:** We appreciate your pertinent comment. We performed analyses as suggested to improve our study value.

#### **Reviewer B**

**Comment 1:** Line 77: Please better define diffuse DNM? You use the term in the beginning but only define on line 184.

**Reply 1:** Thank you for reviewing our manuscript. We appreciate your insightful suggestion. As advised, we have added the following text of the introduction to define diffuse DNM.

**Changes in the text:** which is defined as diffuse DNM (see Page 4, line 63)

**Comment 2:** Line 77 should read: The reported predictors of mortality of DNM include...

**Reply 2:** We agree with your comment and revised the text as advised.

**Changes in the text:** The reported predictors of mortality of DNM include (see Page 5, line 74)

**Comment 3:** Remove sentence starting with "Further analysis"

**Reply 3:** We agree with your comment and removed the following text as advised.

**Changes in the text:** ~~Further analysis, including that of the causative bacteria, may clarify the pathophysiology and improve the prognosis of DNM. We investigated patients with diffuse DNM who underwent surgery in our hospital and analyzed further prognostic factors including bacteriological features.~~

**Comment 4:** Line 80-81 should read: We present six cases of DNM at our institution and further analyze the bacterial features along with the reported predictors of DNM morbidity and mortality stated previously.

**Reply 4:** Thank you for your valuable comment. We have revised the text as suggested.

**Changes in the text:** We present six cases of DNM at our institution and further analyze the bacterial features along with the reported predictors of DNM morbidity and mortality stated previously. (see Page 5, line 75-77)

**Comment 5:** Very good statement of definitions under Methods.

**Reply 5:** We appreciate your pertinent comment.

**Comment 6:** Treatment strategy: In US - Infectious Disease would be involved. Can you mention why ID was not included in the multidisciplinary discussions? Maybe you could mention.. here we did this but it is recommended to have ID included for appropriate antibiotic selection and duration.. No need for a sentence for critical care was performed. Simply that they were involved in multidisciplinary discussions is adequate.

**Reply 6:** We appreciate your comment. Department of Microbiology and Infectious Diseases were also involved in multi-disciplinary discussions in our hospital. We have, therefore, added the following text.

**Changes in the text:** an infectious disease expert (see Page 6, line 102)

**Comment 7:** Lines 113-116 delete. Include in previous paragraph: follow up CTs were performed when necessary and recurrent drainage performed in three cases.

**Reply 7:** We agree with your pertinent comment and revised the text as advised.

**Changes in the text:** follow up CTs were performed when necessary and recurrent drainage performed in three cases. (see Page 7, line 111)

**Comment 8:** Results/patient characteristics: Did all of your patients have "diffuse

DNM?" If so - state this. For ex: ... who underwent thoracic surgery for Type IIB DNM (diffuse DNM) during the period.

**Reply 8:** Thank you for your valuable comment. We have revised the text as suggested.

**Changes in the text:** (diffuse DNM) (see Page 8, line 115)

**Comment 9:** Results/Bacterial paragraph: All you need to say here is 4/6 had SAG detected in the setting of mixed aerobic and anaerobic infection. In the other 2.... what was detected (one was not detected) ?

**Reply 9:** We agree with your comment and revised the text as suggested. We also revised Table 3, added the column of "abscess bacteriology", deleted the column of "SAG", and changed the column "mixed infection" to "mixed infection including SAG".

**Changes in the text:** The causative bacteria were detected in five patients (83%) and polymicrobial infection with aerobic and anaerobic bacteria including Streptococcus anginosus group (SAG) in four patients (67%). ~~Other aerobic bacteria were detected in three patients and anaerobic bacteria were detected in four patients. Candida was detected in two patients.~~ (see Page 8, line 122-124)

**Comment 10:** Remove lines 134-138 - you already stated this information at the start of results section. The part about sepsis and DIC -- and you repeat yourself about DIC/sepsis later in analysis.

**Reply 10:** We agree with your comment and removed the following text as advised.

**Changes in the text:** ~~The infection extended to both the anterior and the posterior part of the mediastinum inferior to the carina (Endo classification: type IIB) in all patients according to CT scans. Before surgery, unilateral thoracic fluid collection was detected in one patient and bilateral collection in five patients. Four patients had DIC and five patients had sepsis, three of whom were in septic shock at surgery.~~

**Comment 11:** Remove sentence starting line 146: "The bilateral approach"

**Reply 11:** We agree with your comment and removed the following text as advised.

**Changes in the text:** ~~The bilateral approach was selected in five patients because of bilateral thoracic fluid collection.~~

**Comment 12:** Remove "at once" in line 148 or change wording to combine sentences from line 147-149.

**Reply 12:** We agree with your comment and removed "at once" as advised.

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**Changes in the text:** ~~at once~~

**Comment 13:** I do not understand -- the patient who had unilateral surgery -- is this the same one in Figure 1? Please shorten this as it becomes confusing.

**Reply 13:** We agree with you and shorten the text.

**Changes in the text:** ~~One patient was in a poor general condition with severe septic shock and DIC and was, thus, unable to undergo bilateral surgery at once. The second surgery was performed 1 week after the initial surgery.~~ The patient underwent only a unilateral approach for unilateral thoracic fluid collection; however, re-operation was performed 2 days after the first surgery because of the appearance of fluid collection in the opposite thoracic cavity (Figure 1). (see Page 8, line 132-134)

**Comment 14:** Please remove all words after Figure 1 (lines 152-155) and instead ok to say: "2 patients required additional debridement at Day 8 (Figure 2) and Day 10. From me to you: Recurrent debridement is common and not unexpected -- there is nothing that went wrong, it just occurs.

**Reply 14:** Thank you for your valuable comment. We agree with your comment and have revised the text as suggested.

**Changes in the text:** 2 patients required additional debridement at Day 8 (Figure 2) and Day 10. (see Page 9, line 135)

**Comment 15:** Line 156: Please add the median post hospital stay in SAG group compared to all comers.

**Reply 15:** We agree with you and added the following text as advised.

**Changes in the text:** the median duration of hospitalization after surgery in patients with mixed infection including SAG was 82 days. (see Page 9, line 136-138)

**Comment 16:** In Detailed analysis of prognosis: Table 3 sentence is fine. Next sentence, change to: "In all patients where SAG was detected, there was a mixed aerobic and anaerobic infection, as well as presence of gas bubbles on imaging and sepsis on presentation. DIC was present in three out of four with SAG detected. Therefore, presence of SAG was associated with sepsis, DIC, and longer post operative hospitalization." Do you have any p values for this?

**Reply 16:** Thank you for your valuable comment. We agree with your comment and changed the text as suggested. P values could not be calculated because the number of patients were too small.

**Changes in the text:** In all patients where SAG was detected, there was a mixed

aerobic and anaerobic infection, as well as presence of gas bubbles on imaging and sepsis on presentation. DIC was present in three out of four with SAG detected. Therefore, presence of SAG was associated with sepsis, DIC, and longer postoperative hospitalization. (see Page 9, line 141-145)

**Comment 17:** Line 156 Conclusions should read "Discussion"

**Reply 17:** We agree with you and have changed "conclusions" to "discussion".

**Changes in the text:** Discussion (see Page 10, line 146)

**Comment 18:** Line 168: I do not understand "based on the outcome of long hospitalization" Your outcomes were that all did well - so do you mean, "based on the medias post surgical hospitalization?" Please revise sentence 168-170.

**Reply 18:** We agree with you and have revised the text as suggested.

**Changes in the text:** Based on the medias postsurgical hospitalization, (see Page 10, line 149)

**Comment 19:** Suggest to remove entire paragraph 183-192. I like that you discuss Endo types, then you should just right into bacteria. No need to repeat the information in this paragraph.

**Reply 19:** We agree with your comment and removed the following text as advised.

**Changes in the text:** ~~Treatment delay, inadequate antibiotics, and insufficient drainage and debridement are also reported as prognostic factors (18, 22). Diffuse DNM spreads to the cervical region and the thoracic cavity to form multifocal abscesses requiring invasive and aggressive surgical approaches for treatment. The postoperative appearance of a new infection site often occurs and should be treated by re-operation and additional drainage (3). Aggressive initial surgery is a chance for sufficient treatment and should be considered by performing an adequate approach, as mentioned previously (6), with postoperative intensive monitoring and follow-up by blood tests and CT scans. In our cases, by intensive monitoring and CT scan follow-up, three cases underwent additional cervical or chest interventions for insufficient drainage areas that were quickly identified postoperatively. The patients then recovered from DIC and sepsis.~~

**Comment 20:** Paragraph starting with Line 206 -- Keep first sentence and last sentence starting with "Since DNM" and erase the middle.

**Reply 20:** We agree with you and have revised the text as suggested.

**Changes in the text:** Petitpas et al. also reported gas bubbles on a chest CT scan as



an independent risk factor for mediastinal spread from cervical necrotizing fasciitis (29). ~~The bacteria that ferment glucose in an anaerobic state produced gas bubbles. While Clostridium is a well-known gas-producing bacteria, non-clostridia bacteria have also been reported as the gas-producing bacteria in immune-compromised hosts (30). Mixed polymicrobial aerobic and anaerobic infections are often observed in non-clostridia gas-producing bacteria. In our case, gas bubbles were identified in all cases of mixed infections.~~

**Comment 21:** Line 212- DNM is not frequently detected in immunocompromised. Please revise.

**Reply 21:** We agree with you and have revised the text as suggested.

**Changes in the text:** ~~Since DNM is frequently detected in immunocompromised patients, g~~ Gas bubbles in the abscess on CT may suggest mixed polymicrobial aerobic and anaerobic bacterial infections. (see Page 11, line 181-182)

**Comment 22:** Line 222 - all of which WERE complicated. Add were.

**Reply 22:** We agree with you and have added "were" as suggested.

**Changes in the text:** were (see Page 11, line 190)

**Comment 23:** Line 224 - "It is also a predictor of poor prognosis"... All your patients did well. This sentence indicates poor outcomes. Perhaps drill down more on what you mean. Are you trying to say "increased complications?" or "need for second debridement" Or "longer hospital stay?" I would remove poor prognosis as you had 100% survival rate.

**Reply 23:** We agree with your comment and have revised the manuscript as suggested.

**Changes in the text:** The detection of SAG in the abscess of the DNM patients may be a risk factor for the spread of the infection to the inferior mediastinum and the thoracic cavity and longer hospital stay. (see Page 11-12, line 190-192)

**Comment 24:** Line 225-230 should be the conclusion. We will combine both paragraphs into one to make the conclusion. Please specifically combine line 229 with 241: "As the detection of SAG in the DNM abscess may be a risk factor for the spread of the infection to the inferior mediastinum and thoracic cavity, special attention to the potential for rapid deterioration should be paid when SAG is detected." No need for "conclusions" paragraph once this is combined - then this becomes your conclusion.

**Reply 24:** We agree with your comment and have revised the sentence as suggested, and delated the conclusions paragraph.

**Changes in the text:** As the detection of SAG in the DNM abscess may be a risk factor for the spread of the infection to the inferior mediastinum and thoracic cavity, special attention to the potential for rapid deterioration should be paid when SAG is detected. (see Page 12, line 193-195)