Author's response to reviews

Title: Clinical Characteristics and Antimicrobial Susceptibilities of viridans Streptococcal Bacteremia during Febrile Neutropenia in Patients with Hematologic Malignancies: A Comparison between Adults and Children

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Version: 2 Date: 20 April 2013

Author's response to reviews: see over
We thank for your faithful review on this report.  
We pondered over the reviewers’ comment on our report, and tried to correct the commented contents appropriately according to the reviewers’ opinion.  
We responded to the reviewers as mentioned below, and attached a revised manuscript as another file.  
Please review our response and revised manuscript carefully.  
Lastly, we ask to add an additional affiliation of authors, Vaccine Bio Research Institute, College of Medicine, The Catholic University of Korea. Please permit it.

Reviewer 1

Reviewer’s report

Title: Clinical Characteristics and Antimicrobial Susceptibilities of viridans Streptococal Bacteremia during Febrile Neutropenia in Patients with Hematologic Malignancies: A Comparison between Adults and Children

Version: 1  Date: 6 February 2013

Reviewer: Lionel Tan

Reviewer’s report:
The authors performed a retrospective study of 202 episodes of viridans streptococcal bacteraemia in febrile neutropaenic patients with haematological malignancies over a three year period in a University teaching hospital in Seoul, Korea. The stated aim was to compare 1) clinical characteristics including severe complication occurrence and 2) antibiotic susceptibilities of viridans streptococci 3) between febrile neutropenic adults and children with hematologic malignancies, and 4) to propose appropriate antibacterial treatment strategies in adults and children.

Whilst this is a relatively large cohort of patients from which some interesting data has been extracted, the main questions posed have not been well thought out.

There is limited recent epidemiological data from South Korea regarding (1) prevalence and (2) antibiotic resistance profiles of viridans streptococcus in this population. Additionally, (3) risk factors associated with severe disease due to viridans streptococcus and (4) risk factors associated with antimicrobial resistance are not completely defined within the current literature. Unlike the Western world, the most frequently isolated isolates according to the Korean guidelines of neutropaenic fever are Gram negative rather than Gram positive organisms. Hence, the data from this cohort could be used to answer some important questions that would inform clinicians in South Korea and elsewhere. In many ways, the authors have not utilized the data fully. The authors have compared adults with viridans streptococcal bacteraemia with children, and also undertaken a limited comparison of individuals with severe disease compared to uncomplicated disease and cefepime resistant to cefipime susceptible disease. The comparisons they have undertaken are not systematic and some interesting variables have not been analysed.

→ We sincerely thank you for your faithful review of our report. Until now, there have been few reports on viridans streptococcal bacteraemia in Korea regardless of patient immune status. So, we conducted this study in our BMT center, the largest BMT center in Korea, to investigate the characteristics of viridans streptococcal
bacteremia in Korean neutropenic patients. Gram negative bacteria were more common than Gram positive bacteria as the cause of bacteremia in febrile neutropenia in Korea. However, the proportion of Gram positive bacteria has been increasing. Recent reports from Korea indicate that Gram positive bacteria are more common than Gram negative bacteria as the cause of bacteremia in febrile neutropenia and the proportion of viridans streptococci has been increasing among Gram positive bacteria, and this was cited from reference No. 4 and No. 7. The two reports were results of studies conducted in our institute, and one concerned children while the other dealt with adults. We thought that this change in the epidemiology of causative microorganisms of bacteremia would be observed in other institutes in Korea and in other developing countries, and that our study would give helpful information to that effect. References No. 4 was written in the Korean language and reference No. 7 had not been published at the moment of review, so the reviewer may have a problem in looking for and reading the references, so we add here the abstracts of the two references. Now, reference No. 7 is published and you can see it on the website (www.icjournal.org).

Reference No. 4
Title: Clinical Investigation of Bacteremia in Children with Hemato-Oncologic Diseases.

Background: The purpose of this study was to determine the spectrum of locally prevalent pathogens and their susceptibility patterns responsible for bacteremia in pediatric hemato-oncologic patients for empiric antimicrobial therapy.

Materials and Methods: A one-year retrospective study of pediatric hemato-oncologic patients with bacteremia in Seoul St. Mary’s Hospital, the Catholic University of Korea, from April 2009 to March 2010 was conducted using previous medical records. The findings were compared with our previous data obtained from 2004 to 2006.

Results: Sixty-five episodes of bacteremia were recorded in 41 patients. Of them, 55 (84.6%) occurred in neutropenic and 10 (15.4%) in non-neutropenic patients. Gram-positive organisms were more commonly isolated than Gram-negative organisms (56.9% vs. 41.5%) in the following order: viridans streptococci (23.1%), Klebsiella pneumoniae (21.6%), coagulase-negative staphylococci (12.3%), Staphylococcus aureus (7.7%), Enterococcus faecium (7.7%). Susceptibility rates of viridans streptococci to penicillin, cefotaxime and vancomycin were 33.3%, 60% and 100%, and those of Enterobacteriaceae to amikacin, ceftazidime, piperacillin/tazobactam and meropenem were 94.7%, 73.7%, 78.9%, and 100%, respectively. Compared to our previous data, infection still contributed towards a major fraction of mortality and morbidity in the management of patients with cancer. No differences in mortality rate were observed between isolated organisms from bacteremia.

Conclusions: Gram-positive organisms were more prevalent than Gram-negative organisms in our population. The monitoring of causative agents and antimicrobial resistance should be considered in therapeutic strategies of pediatric hemato-oncologic infection.

Reference No. 7
Title: Epidemiology and Clinical Features of Bloodstream Infections in Hematology Wards: One Year Experience at the Catholic Blood and Marrow Transplantation Center
**Cited from:** *Infect Chemother* 2013, **45**(1):51-61.

**Background:** The aim of this study was to investigate the clinical features and epidemiology of bloodstream infections (BSIs) in 2 distinctive hematological wards of the Catholic Blood and Marrow Transplantation (BMT) center.

**Methods:** We retrospectively reviewed medical data of patients who developed BSIs from June 2009 to May 2010 in 2 hematologic wards at the Catholic BMT Center. Ward A is a 44-bed unit mainly conducting conventional high dose chemotherapy and ward B is a 23-bed unit exclusively conducting BMT.

**Results:** Overall, 222 BSI episodes were developed from 159 patients. Acute myeloid leukemia in ward A and multiple myeloma in ward B were more frequent than in ward B and A, respectively. Sex, age, neutropenia, shock, Pitt bacteremia score, type of central catheter, level of C-reactive protein, duration of admission days, type of BSI, overall mortality and distribution of organisms were not different between the 2 wards. There were 202 monomicrobial and 20 polymicrobial BSI episodes including 2 fungemia episodes. The incidence rate of overall BSIs per 1,000 patient-days was higher in ward A than that of ward B (incidence rate ratio 2.88, 95% confidence interval 1.97-4.22, \( P < 0.001 \)). Among 243 organisms isolated, the number of gram positives, gram negatives and fungi were 122, 119 and 2, respectively. *Escherichia coli* was the most common organism in both ward A and B (27.6% and 42.4%) followed by viridians streptococci (18.6% and 15.2%) and *Klebsiella pneumoniae* (13.3% and 9.0%). Extended spectrum beta-lactamase (ESBL) producers accounted for 31.9% (23/72) of *E. coli* and 71.0% (22/31) of *K. pneumoniae*. Out of 19 *Enterococcus faecium*, 7 isolates (36.8%) were resistant to vancomycin. The crude mortality rates at 7- and 30-day after each BSI episode were 4.5% (10/222) and 13.1% (29/222) and were significantly higher in the patients with shock compared with those without shock (20.5% vs. 1.1%, \( P < 0.001 \) and 38.5% vs 7.7%, \( P < 0.001 \), respectively).

**Conclusions:** The incidence rate of BSIs was higher in patients receiving chemotherapy than those receiving BMT but the distribution of organisms was not different between the 2 wards. *E. coli* was the most common causative BSI organism in hematologic wards followed by viridians streptococci and *K. pneumoniae*.

The methods are appropriate for the questions posed by the authors. However, the whole study would have benefitted from a comparison with age/sex / disease matched controls. i.e. case-control analysis. → We agree that this study has limitations because this is a retrospective study rather than a case-control study or prospective study. So, we consulted with statisticians to avoid selection bias and conducted this study with a review of whole cases of VSB in patients with hematologic malignancy, and we added the word ‘consecutive’ to the abstract and methods (line 47, 95).

The results section could be improved by analysis of further characteristics of the patients and putting them in the context of patients with neutropenic fever seen in the unit as a whole. → We added a simple comment on the characteristics of the whole cases with VSB to the results section. (line 199-205)

The tables are well constructed and provide a useful summary of the findings.

The discussion needs a bit more clarity, but in general there is a logical flow to the discussion and a review of the data from the study. The authors fail to reference the publications looking at bacteraemia in Korea (that are
to be found in the Korean Clinical Guidelines) and hence miss the opportunity to place the study in the context of the local environment.

As we said, the proportion of Gram positive bacteria and viridans streptococci have been increasing in Korea among causative microorganisms of bacteremia in febrile neutropenic patients. The cited articles detailing the Korean guidelines were results of studies conducted before 2005, and our references (No. 4 and No. 7) were the results of studies conducted in 2009 and 2010. Hence, we thought that these references better reflected the current status of Korea.

The language and style of writing could be improved to ensure that the message is understood by the readership.

The main limitation is stated as “Although a limitation of this study is its retrospective analysis, we tried to eliminate selection bias by including all hematologic malignancy patients with VSB who were treated in the same hospital environment.” Other limitations of the study are not stated clearly, for example there is missing data from 35 patients.

Statements on other limitations were added in the discussion (line 378-390).

1. Antibiotic susceptibility tests were conducted using an E-test, and there may be discrepancies between the results of an E-test and a microdilution test.
2. While we used piperacillin/tazobactam in many cases, antibiotic susceptibility to piperacillin/tazobactam was not determined due to the policy of the clinical laboratory of our institute. We assumed that cefepime and piperacillin/tazobactam had similar effects against viridans streptococci. However, the in vivo effects of the two antibiotics against viridans streptococci may be different.
3. Past histories of patients on previous broad spectrum antibiotic use could not be evaluated in 35 patients, and the results may be incorrect.

Major Compulsory Revision:

The authors should concentrate on analyzing the cohort from the point of view of systematically answering the following questions: (1) prevalence of viridans streptococcal bacteraemia in the haematological malignancy population (2) antibiotic resistance profiles of viridans streptococcus in this population. (3) risk factors associated with severe disease due to viridans streptococcus (4) risk factors associated with antimicrobial resistance

Results part was reconstructed into five paragraphs: four paragraphs according to the reviewer's opinion and one additional paragraph comparing the clinical and laboratory features between adults and children.

Methods section:

1. Definitions – overall the definitions could be made clearer. What is definition of hypotension? What is ARDS an acronym for? What mechanical ventilator care (CPAP / BIPAP / SIMV etc)?

Hypotension was defined as mean arterial pressure less than 60 mmHg in adults, and systolic blood pressure less than the 5th percentile in children according to textbook of internal medicine and pediatrics, respectively,
and cited references were stated. (line 150-153, reference No.13 and 14) The full name of ARDS was introduced in the background paragraph (line 77). We included all types of mechanical ventilator methods, and all patients initially received SIMV. (line 149)

2. “VSB was defined as growth of viridans streptococci from at least one peripheral or central blood sample of a patient with symptoms or signs such as fever, chills, or shock”. This is a definition of bacteraemia with the systemic inflammatory response syndrome, rather than bacteraemia alone. Please can the definition be clarified?
   → We re-defined VSB as growth of viridans streptococci regardless of other systemic symptoms or signs. (line 144-145)

3. Sentence beginning “If there was no clinical improvement…” needs to be reworded to state that no new infectious isolates were detected, no deterioration in underlying malignancy and no other clinical diagnoses were made
   → We corrected the sentence according to your advice. (line 155-158)

Results section:

4. The figures do not add anything to the manuscript and should be removed and replaced by the tables. Figure 1A shows a survival curve which is likely to represent the underlying haematological disease rather than VSB. Figure 1B shows a survival curve with no difference. The ROC curve does not add anything from what is stated in the text.
   → We agree with your opinion and removed the figures. Mortality attributable to VSB and overall mortality were stated in Table 1.

5. It is unclear how many patients were diagnosed with VSB as only number of episodes are stated. Did any of the patients have more than one episode of VSB?
   → Two hundred and two episodes (141 in adults and 61 in children) of VSB were diagnosed in 188 patients (134 adults and 54 children), and a total of 11 patients experienced multiple episodes of VSB. Among them, 8 patients experienced 2 episodes and 3 patients experienced 3 episodes. This content was added to the results section. (line 181-186, 190-195)

6. 42 cases of VSB had severe complications – are these separate patients or new episodes in the same patients?
   → Among 202 episodes with VSB, 42 cases with severe complications occurred, and there was no patient who experienced multiple episodes of severe complications of VSB. This comment was also added to the results section. (line 186-189, 193-195)

7. What was the rate of VSB in comparison to other bacteria isolated during the two years of the study? How many patients were treated overall at the centre and how many experienced febrile neutropaenia?
   → During the study period, there were 2,677 admissions in 1,248 adults and 4,219 admissions in 511 children for conventional chemotherapy, HCT, or febrile neutropenia following chemotherapy. Seven hundred forty-five episodes and 305 episodes of bacteremia were diagnosed in adults and children, respectively. The incidence of bacteremia and VSB were 9.17 episodes and 1.74 episodes per 1,000 person-days in adults, and those were 6.64 episodes and 1.35 episodes per 1,000 person-days in children. This content was added to the results section as a separate paragraph. (line 179-186)

8. More children were male – does this actually reflect the number of boys being treated for haematological malignancies anyway? What is the male:female ratio of the population under treatment in this unit?
During the study period, the male to female ratio of the whole children with hematologic malignancy in our hospital was 2,608 to 1,611 as admission episodes and 306 to 205 as patient numbers. The proportion of boys were 61.8% of admissions, 59.9% of patients and 67.2% of VSB cases, and these proportions were not significantly different ($p = 0.814$).

9. What were the absolute numbers of children versus adults receiving prophylaxis with trim/sulfa versus ciprofloxacin. Was the rationale for NOT using ciprofloxacin in children due to the risk of skeletal abnormalities?

Among 141 adults, 134 patients received ciprofloxacin and no patient received TMP/SMX, and 4 patients received no prophylaxis and 3 patients had been receiving ceftazidime as empirical antibiotic therapy on diagnosis of VSB. Among 61 children, 53 patients received TMP/SMX, 7 patients received ciprofloxacin, and 1 patient received no prophylaxis. This content was explained in results (line 214-221) and table 1. In Korea, fluoroquinolones are not commonly given to children aged less than 18 years due to the risk of skeletal abnormalities, and the Korean FDA also recommends not using fluoroquinolones in children. The seven children who received ciprofloxacin prophylaxis were older than 18 years.

10. Is there any information about co-morbidities present in this cohort i.e. renal and cardiac dysfunction which may have an impact on overall outcome.

There were no patients under renal replacement therapy, and echocardiography was done in all patients before conventional chemotherapy or HCT and patients received therapy if there was no abnormality in echocardiography. All of the deaths non-attributable to VSB were due to uncontrolled hematologic malignancy in this study. This comment was also added to the results. (line 189-190)

11. What was the mean number of days between beginning of chemotherapy to diagnosis of VSB? A median of 12 days versus 13 days with overlapping ranges seems a quirk of the statistics used. Also the nadir neutrophil count will vary depending on the chemotherapy used and different regimens are likely to be used between children and adults.

We compared the variable using Mann-Whitney test and Student’s t-test again, and all the results of two tests showed a significant difference. We described all the numerical variables as a median and inter quartile range rather than full range because most had a wide range, and then we could recognize the difference more easily. (line 211-214) We also thought that the difference in days from the preceding therapy to VSB was caused by different chemotherapeutic regimens. However, we were unable to prove this hypothesis. We did not discuss this topic in greater detail in this paper because we believed that this temporal difference was unrelated to the main foci of this report.

12. “…within a week…” was the CRP always measured at the same time point in each patient? The half life of CRP is only 18 hours. Patients with severe disease are likely to have had CRP measured more often and hence a difference of a day in when the CRP was measured between to two groups may account for the difference in peak CRP. The authors need to state when the CRP was measured.

CRP was measured according to the discretion of the attending physician based on the patient’s status. The first CRP level was measured on fever day 1 in 86.6% of patients, fever day 2 in 9.9%, and fever day 3 in 3.5%. If we had measured CRP levels every day, we could compare the increasing tendency between the patient groups and retrieve valuable information. In our patients, CRP levels were checked within the first week after the diagnosis of VSB a median of three times (IQR: 3-3). Although CRP levels may change or fluctuate day by day, we thought that the peak CRP level within a period of one week could represent the peak CRP level during
the VSB episode because peak CRP levels were checked within a week after the diagnosis of VSB in 95.5% of the patients and the peak CRP levels were checked at a median of 4 days (IQR: 3-5) after the diagnosis of VSB. The comment on the frequency of checking CRP and the time when peak CRP levels were checked was added to the results section: the comparison between adults and children and between patients with severe complications and those without complications. (line 227-232, 252-254)

13. The last paragraph and Table 3 of the results section comparing cefepime susceptible isolates with cefepime resistant isolates is potentially the most interesting. What are the MIC definitions for Intermediate and High level resistance used? How far back did the authors assess the use of broad spectrum antibiotics in these patients?

→ Culture methods were newly explained in the patients and data collection paragraph (line 130-137), and we checked antibiotic susceptibilities using an E-test on the Muller-Hinton agar plate including 5% sheep blood. The MIC results of cefepime were the following: susceptible ≤ 0.12, intermediate 0.25-2, resistant ≥ 4, and the results of cefotaxime were the following: susceptible ≤ 2, intermediate 2, resistant ≥ 4.

We wanted to review all previous histories of broad spectrum antibiotic treatment, so we only included patients who were diagnosed with hematologic malignancy in our hospital. All records of the previous histories of broad spectrum antibiotic treatment in 166 cases were reviewed from the diagnosis of hematologic malignancy onwards. The median of the interval from the diagnosis of malignancy to VSB were 3 months, and the intervals were a median of 3 months and 4 months in patients with VSB susceptible to cefepime and those with VSB non-susceptible to cefepime, respectively (p > 0.05).

Viridans streptococci were not identified to the species level in the laboratory of our hospital because antibiotic susceptibilities and clinical characteristics are not significantly different among viridans streptococcal species in previous reports. So we could not determine the distribution according to the specific species of viridans streptococci. We added the statement to this effect to the data collection paragraph of patients and data collection paragraph. (line 138-141)

**Discussion section:**

14. Paragraph 2 – state what the “lower frequency” rate of mucositis is in this study.

→ We wrote the exact rate of 20.3% additionally in the manuscript. (line 297-298)

15. “… mucosal surface in the body, it was a “natural” result.” What do the authors mean by this? An expected result?

→ We corrected the sentence to “it was a predictable result.” (line 302)


→ We divided viridans streptococci into those susceptible and non-susceptible to a specific antibiotic drug, and non-susceptible includes intermediately resistant and resistant cases. Because we cannot recommend the use of antibiotics in the case of intermediately resistant organisms, we categorized intermediate resistant and resistant cases to a non-susceptible case. This categorization was introduced in the patients and data collection part, and we maintained this categorization through the report consistently.

17. What is the rate of S. pneumonia resistance to penicillin / beta lactams in the local / national population?

→ There have been a few reports on the antibiotic resistance of *S. pneumoniae* in Korea. The most recent study
on community-acquired pneumococcal infections reported that penicillin resistances were 0.3% and 83.3% in non-meningeal isolates and meningeal isolates, respectively. Ceftriaxone resistances were 1.9% and 0% in non-meningeal isolates and meningeal isolates, respectively. These resistance rates were lower than those before the modification of CLSI breakpoints for resistance. (line 355-358)

18. “A viridans streptococci-targeted prospective study with well-controlled influencing factors is needed to investigate the prophylactic antibiotic effect on antibiotic resistance” What do the authors mean by this? How feasible is such a study?
→ The confusing sentence was removed.

19. “… first line antibiotic therapy without initial glycopeptide use and subsequent changing of the antibiotic regimen according to clinical response and antibiotic susceptibility test results may be sufficient.” This is what the guidelines referred to previously already recommend and yet earlier in the background the authors state that the guidelines are inconclusive. Maybe this statement should be inserted into the background instead?
→ Because the guidelines do not recommend initial glycopeptide use for viridans streptococcal infections and our aim in this study is not to provide a guideline for glycopeptide use in viridans streptococcal infections but to evaluate the clinical and prognostic differences between adults and children, we removed the sentence about the use of glycopeptide in viridans streptococcal infections. And, we added the statement that this study confirmed that current IDSA and Korean guidelines could be applicable to febrile neutropenic children with VSB as well as adults with VSB to the conclusion. (line 362-368, 397-400)

20. “However, universal initial glycopeptide therapy…” This is a confusing sentence, where do all the percentages in the sentence come from i.e. 0.5% of febrile neutropenic children etc.
→ The occurrence rate of bacteremia in patients with febrile neutropenia was reported as 10-25% in previous reports (reference No.1-3), and roughly 20-30% of the bacteremia was caused by viridans streptococci according to previous reports and our experiences (reference No.1,4,5,7). If we multiply 25% and 30% in consideration of the highest occurrence rates, we can get 7.5% as the occurrence rate of VSB in febrile neutropenic patients. Severe VSB complications occur in 6.6% of patients with VSB in this study, and 7.5% multiplied by 6.6% is 0.5%, so an estimate of 0.5% incidence of severe VSB complications in febrile neutropenic children was made. We wanted to state that universal glycopeptide use targeting severe VSB complications is targeting only 0.5% of febrile neutropenic children. (line 370-377)

Minor essential revisions:

Background section
1) 1st para – Gram negative NOT Gram (-)
→ We corrected “Gram (-)” to “Gram negative.” (line 73)

2) “isolates” rather than “pathogens”. Not all the bacteria are necessarily “pathogens” in non-immunocompromised hosts.
→ We corrected “pathogens” to “isolates.” (line 73, 75)

3) Background 2nd para – the authors state the following “the Infectious Diseases Society of America (IDSA) and Korean guidelines recommend empirical glycopeptide therapy for febrile neutropenic patients with severe mucositis or septic shock with potential VSB” – yet the guidelines referenced do not make these recommendations, e.g. from reference [2] “Notably, monotherapy regimens, including cefepime, carbapenems
and piperacillin-tazobactam, provide excellent coverage of viridans streptococci and are considered to be adequate solo agents for the treatment of febrile neutropenia in patients with oral mucositis, precluding the need for the addition of vancomycin to the regimen.” This sentence needs to be reworded

→ We corrected the sentence to state that IDSA and Korean guidelines said that β-lactams are adequate for viridans streptococcal infections. (line 81-86) And, we added the statement that this study confirmed that current IDSA and Korean guidelines could be applicable to febrile neutropenic children with VSB as well as adults with VSB to the conclusions section. (line 397-400)

4) “However, it has not been conclusive whether the same practice guidelines can be applied to treat infections in adults and children, because of the different complication frequencies [12] and the different antibiotic susceptibilities of viridans streptococci in febrile neutropenic adults and children with VSB.” This sentence should be rephrased.

→ We corrected the sentence like the following: Although the Infectious Diseases Society of America (IDSA) and Korean guidelines state that β-lactam antibiotics are adequate for viridans streptococcal infections [2,12], it is not conclusive whether the same practice guidelines can be applied to treat infections in adults and children, because of the different complication frequencies [11] and the potentially different antibiotic susceptibilities to viridans streptococci in febrile neutropenic adults and children with VSB. (line 81-86)

5) “severe complication occurrence” should be “occurrence of severe complications”

→ We corrected it according to your advice. (line 88)

Methods section

6) Study design – first sentence needs to be rephrased to “Medical records of patients admitted to the Catholic Blood and Marrow Transplantation Center between April 2009 and July 2012 with hematologic malignancies…”

→ We corrected the sentence according to your advice. (line 95-99)

7) Patients and data collection – why was 20 years the cut off for children? Isn’t this usually 16 years?

→ The Korean Law designated the cut-off age for adults as 20 years, so the IRB of our hospital recommends the age of 20 years as the cut-off.

8) Patients and data collection – change to “VSB susceptible to cefepime and those resistant to cefipime”

→ We divided viridans streptococci into those susceptible and non-susceptible to a specific antibiotic drug, and non-susceptible includes intermediately resistant and resistant cases. Because we cannot recommend the use of an antibiotic in the case of intermediately resistant organisms, we categorized intermediately resistant and resistant cases to a non-susceptible case.

9) Patients and data collection – gender is not a clinical characteristic, it is part of patient demographics

→ We corrected the sentence that “Clinical characteristics consisted of ~” to “Data gathered on patients’ demographics and clinical characteristics consisted of ~.” (line 114)

Results:

10) Sentence starting “Conventional therapy preceded VSB…” needs to be rephrased i.e. “VSB occurred in 100% of children and 92.9% of adults after conventional chemotherapy…”

→ We corrected the sentence according to your advice. (line 209-210)

11) Change sentence “The type of preceding therapy…” to reflect point (5) above.
We apologize, but we did not understand your comment. Please clarify your remark, and we will correct accordingly.

12) Antibacterial prophylaxis was “administered to” / “given to” or “taken by” NOT “performed”
→ We corrected the sentence according to your advice, from “was performed” to “was administered to.” (line 215)

13) “Antibiotic susceptibility was assessed in 200/201 (99.5%) of bacterial isolates.” Antibiotic susceptibility tests are performed on bacterial isolates and not patients.
→ We corrected the sentence according to your advice. (line 236-237)

14) It would be better to state the susceptibility as proportion of resistant isolates for each antibiotic in text and table 2. e.g. penicillin resistance 122/201 (60.7%)
→ We corrected the sentences and table 2 according to your advice. (line 237-243)

15) Change to “The medians of “peak” CRP…”
→ We changed all of “maximum CRP” to “peak CRP” in the manuscript and tables.

Discussion:

16) Gram positive NOT Gram (+)
→ We corrected to Gram positive bacteria. (line 342)

17) Conclusion will need rewriting after major revision
→ The main point of our conclusion was to emphasize similar therapy for both adults and children with VSB, regardless of rates of complications or antibiotic susceptibilities. Our conclusion as it stands currently reflects these main findings. Hence, we only added the statement that current guidelines can be applied to febrile neutropenic children with VSB as well as adults. (line 397-400)
Reviewer 2

Reviewer’s report

Title: Clinical Characteristics and Antimicrobial Susceptibilities of viridans Streptococcal Bacteremia during Febrile Neutropenia in Patients with Hematologic Malignancies: A Comparison between Adults and Children

Version: 1 Date: 6 February 2013

Reviewer: Jeffrey E Rubnitz

Reviewer’s report:
The authors present a detailed description of viridans strep bacteremia in adults and children with hematologic malignancies.

Major revisions: None

Minor revisions:
1. The authors state that the difference in time to infection (12 days vs 13 days) was statistically significant. Please explain how such a small difference can be significant. What method was used? Is this difference clinically significant?

→ We thank you for your faithful review of our manuscript. This question was also asked from reviewer 1. We compared the variable using Mann-Whitney test and Student’s t-test again, and all the results of two tests showed a significant difference. We described all the numerical variables as a median and inter quartile range rather than the full range because most had a wide range. Then we could recognize the differences more easily. (line 211-214) We thought that the difference in days from the preceding therapy to VSB was caused by different chemotherapeutic regimens between adults and children. However, we were unable to prove this hypothesis. We did not discuss this topic in greater detail in the paper because we believed that this temporal difference was unrelated to the main foci of this report.

2. Please provide details on the use of ciprofloxacin and Septra prophylaxis. In particular, was Septra given daily for prevention of bacterial infection, or given 3 times per week for prevention of PCP?

→ TMP/SMX was given to children for prevention of PCP, and ciprofloxacin was given to adults and some children older than 18 years for prevention of bacterial infections. TMP/SMX was given once daily, 3 days a week with a dose of trimethoprim 150 mg/m²/day from the diagnosis of hematologic malignancy to the end of the whole course of chemotherapy, and ciprofloxacin was given as 500 mg twice daily from the beginning to the end of each separate chemotherapy schedule. The doses were added to the results part, in the section comparing adults and children. (line 214-218)

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare that I have no competing interests.