Author's response to reviews

Title: Healthcare-associated infections in Pediatric Cancer Patients: Results of a Prospective Surveillance Study from University Hospitals in Germany and Switzerland

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Author's response to reviews: see over
Dear colleagues,

today we submit the revised version of our original article

**Healthcare-associated infections in Pediatric Cancer Patients: Results of a Prospective Surveillance Study from University Hospitals in Germany and Switzerland**


duly considering the comments of the reviewers.

Please find attached the point by point list, as requested.

Best regards on behalf of all authors

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Point by Point List

First of all, thanks to the reviewers for their excellent contribution aiming at an improvement of our first submission.

Reviewer 1

MAJOR COMPULSORY REVISIONS

1. It is not clear why you included 6 medical centers of one country and only one from another country; please clarify it.

   *This situation was a consequence of our cooperative working group on febrile neutropenia in pediatric cancer patients (German Society of Pediatric Infectious Diseases and German Society of Pediatric Hematology and Oncology), which comprises one colleague from Switzerland (RA. Ammann, Bern) beneath many other pediatric oncologists from Germany.*

2. On page 3, in the abstract, the number of patients enrolled is not clear; I suggest clarifying it.

   *Only patients with an NI (n=181 patients) or with nFUO (n= 230 patients) were enrolled as 'Cases' into the study. Together 411 patients (added to the abstract).*

3. On page 3, in the abstract, Incidence density is not clear; I suggest expressing it as number of HAI per 1000 patient-days, and as HAI per 100 admissions as well.

   *The term 'nosocomial infection' was changed to healthcare associated infection (HAI). In the abstract, the definition number of events per 1000 inpatient days is added. We did not document or report admissions in the basic data form of this study; thus we are not able to express infection rates per 100 admissions.*

   *Sentence added to the Method section:*
   *'The number of admissions to the unit was not documented in this study.*'

4. On page 7. In agreement with the authors, I consider it is better to show incidence density of HAI per 1000 patient days and BSI per 1000 central line days, than HAI per 100 admissions; but in order to compare your data with some other publications, I suggest including rates of HAI per 100 admissions as well.

   *Please refer to our comment on Point 3.*

5. On page 11. I congratulate the investigators for reducing 16% of the HAI per year. In order to avoid confounders and to analyze the real impact of infection control for reducing HAI rates, I suggest providing demographic characteristics of patients and severity illness score of them comparing years. If it is not possible to provide such demographic characteristics, I suggest clarifying this as a limitation of the study, or deleting this comment.

   *New sentence added to the discussion: 'While we did not control for confounding variables as demographic characteristics of the patients or illness severity, further studies are needed to confirm, that participation in such a surveillance study results in a decrease in HAI rates.*'

6. On results. On the one hand, you have a low rate of MRSA; on the other hand, you already included on the table #4 your VRE rate. I suggest adding a table showing your MRSA rate as percentage, and also the bacterial resistance of all
the following bacteria to be able to benchmark them with CDC NISS report and other reports: Methicillin-resistant CNS, Ciprofloxacin/ofloxacin-resistant Pseudomonas aeruginosa, Levofoxacin-resistant P aeruginosa, Imipenem-resistant P aeruginosa, Ceftazidime-resistant P aeruginosa, Piperacillin-resistant P aeruginosa, Cef3-resistant Enterobacter spp, Carbapenem-resistant Enterobacter spp, Cef3-resistant Klebsiella pneumonia, Cef3-resistant Escherichia coli, Quinolone-resistant E coli, Cefotaxime/ceftriaxone-resistant pneumococci

As shown in Tab 4, 2 out of 145 blood culture isolates were VRE. No MRSA was detected in blood cultures or related to any other HAI in this study.

Added to the Method section: 'Multidrug-resistant isolates’ referred to bacterial pathogens in vitro resistant to at least three of the corresponding first-line antimicrobials.

Only 2 out of 145 blood culture isolates (1 Pseudomonas spp. 1 Klebsiella spp.) displayed this MR phenotype in vitro. In addition, there was 1 MR Pseudomonas spp. documented in 10 UTIs (not related to a urinary tract catheter).

Therefore, we do not agree with the reviewer, that additional data are necessary to add important information concerning the low rate of antimicrobial resistance in this study. The NNIs data refer to pooled ICU results [1]. We do not agree, that it might be helpful to compare the NNIS data with the results from our pediatric oncology study.

MINOR ESSENTIAL REVISIONS
7. Due well known reasons, the current used name of "Nosocomial Infections" is "Health care associated infections"(HAI); I suggest using the current name.

Please refer to Point 3; HAI is now consistently used instead of NI.

8. On page 3, in the abstract, you used the term "blood culture positive BSIs" instead of “laboratory confirmed bloodstream infections”; I suggest using the name following CDC NNIS definitions on methods section you said you are using.

Changed in the abstract to: laboratory confirmed BSI, as requested.

DISCRETIONARY REVISIONS
9. On page 1, lines 2 & 4, where the title reads “Nosocomial infections in pediatric cancer patients: results of a prospective surveillance study from 7 University hospitals in Germany and Switzerland” since it is a title, the every content word must be written in capital letters. So, it should say "Nosocomial Infections in Pediatric Cancer Patients: Results of a Prospective Surveillance Study from 7 University Hospitals in Germany and Switzerland."

Changed as requested

10. On page 1, line 7, where the running title reads “Nosocomial infections in pediatric cancer” since it is a title, the every content word must be written in capital letters. So, it should say "Nosocomial Infections in Pediatric Cancer."

Changed to; Healthcare associated Infection in Pediatric Oncology

11. On page 2, line 4, where it says “…and prepared the manuscript…,” for punctuation reasons, a comma should follow the noun "manuscript”, for
there continues an enumeration. So, it should say ...and prepared the manuscript, ...

12. On page 2, line 7, where it says ...were local investigators in Cologne,..., a comma should follow the proper noun Cologne, for there continues the enumeration. So, it should say ...were local investigators in Cologne, ...

13. On page 2, line 8, where it says ...local investigator in Erlangen,..., a comma should follow the proper noun Erlangen, for there continues the enumeration. So, it should say ...local investigator in Erlangen, ...

14. On page 2, line 11, where it says ...investigator in Duesseldorf, for grammatical reasons, after the last enumeration the coordinating conjunction "and" should follow the comma (,) after the proper noun Duesseldorf. So, it should say ...investigator in Duesseldorf, and...

All changed as requested.

15. On page 2, line 21, where it says 'Fone' a more proper spelling should be used. So, it should say 'Telephone' or 'Phone'.

Changed as requested

16. On page 3, line 26, where it says "Key words pediatric cancer patients," for punctuation reasons, the noun "words should be followed by a colon (:) to introduce the coming list. So, it should say Key words: pediatric cancer patients,

Changed as requested

17. On page 4, line 6, where it says ...anticancer treatment [1-3]. ..., for punctuation reasons, the reference [1-3] should be placed after the punctuation mark, which in this case is a full stop (.). So, it should say anticancer treatment. [1-3] This comment applies to all the references contained in the manuscript.

18. On page 4, line 8, where it says ... (CVAD) [4], a comma should be placed after the punctuation mark, which in this case is a full stop (.). So, it should say (CVAD). [4]

19. On page 4, line 9, where it says ...studies [5-8]. ..., a comma should be placed after the punctuation mark, which in this case is a full stop (.). So, it should say ...studies. [5-8]

20. On page 4, line 12, where it says ...patients [10]. ..., a comma should be placed after the punctuation mark, which in this case is a full stop (.). So, it should say ...patients. [10]

21. On page 4, line 18, where it says ...unit [8], a comma should be placed after the punctuation mark, which in this case is a full stop (.). So, it should say ...unit. [8]

22. On page 4, line 19, where it says ...neutropenia [11], a comma should be placed after the punctuation mark, which in this case is a full stop (.). So, it should say ...neutropenia. [11]

23. On page 4, line 23, where it says ...patients [5], a comma should be placed after the punctuation mark, which in this case is a full stop (.). So, it should say ...patients. [5]

24. On page 4, line 24, where it says ...infections [12], a comma should be placed after the punctuation mark, which in this case is a full stop (.). So, it should say ...infections. [12]

25. On page 4, line 25, where it says ...therapy [13], a comma should be placed after the punctuation mark, which in this case is a full stop (.). So, it should say ...therapy. [13]
reasons, the reference â##[13]â## should be placed after the punctuation mark, which in this case is a comma (,). So, it should say â##...therapy, [13]â##.

27. On page 4, line 26, where it says â##...itraconazole [14].â## for punctuation reasons, the reference â##[5]â## should be placed after the punctuation mark, which in this case is a full stop (.). So, it should say â##...itraconazole. [14]â##.

30. On page 6, lines 8 & 9, where it says ‘...age [16].’ for punctuation reasons, the reference â##[16]â## should be placed after the punctuation mark, which in this case is a full stop (.). So, it should say â##...age. [16]â##.

31. On page 6, lines 13, where it says â##...CVAD [4].â## for punctuation reasons, the reference â##[4]â## should be placed after the punctuation mark, which in this case is a full stop (.). So, it should say â##...CVAD. [4]â##.

33. On page 6, lines 17, where it says â##...analysis [17].â## for punctuation reasons, the reference â##[17]â## should be placed after the punctuation mark, which in this case is a full stop (.). So, it should say â##...analysis. [17].â##

44. On page 12, line 10, where is says â##...strategies [18]....â## for punctuation reasons, the reference â##[18]â## should be placed after the punctuation mark, which in this case is a full stop (.). So, it should say â##Strategies. [18].â## This comment applies to all the references contained in the manuscript.

45. On page 13, line 4, where is says â##...Laws et al. [8].â## for punctuation reasons, the reference â##[8]â## should be placed after the punctuation mark, which in this case is a full stop (.). So, it should say â##Laws et al. [8]â##

This rule, requested by the reviewer, is not defined in the BMC Infect Dis instruction for authors. A short look at published manuscripts revealed, that the actual punctuation policy (punctuation mark or comma after the citation in square brackets) is correct.
24. On page 4, lines 23 & 24, where it says "module already has been used...", for grammatical reasons, the adverb "already" should follow the auxiliary for the perfective aspect "has". So, it should say "...module has already been used".

*Changed as requested.*

28. On page 5, lines 8 & 9, where it says "...The most important outcome parameter, the ID of events per 1,000 inpatient days was calculated...," for grammatical reasons, the noun phrase in apposition should be enclosed in commas (,). So a comma should be placed following the noun 'days', and thus, it should say 'The most important outcome parameter, the ID of events per 1,000 inpatient days, was calculated...'

*Changed as requested.*

29. On page 5, line 17, where it says 'Inclusion criteria', since it is a subtitle, the two content words Inclusion and criteria must be written in capital letters. So, it should say 'Inclusion Criteria'.

*Changed as requested.*

32. On page 6, lines 13 & 14, where it says '...term 'catheter-associated bloodstream infection referred..., for consistency purposes the phrase introduced by an opening inverted comma (â”) should be likewise enclosed by a closing inverted comma. So, it should say '...term catheter-associated bloodstream infection referred...'

*Changed as requested.*

34. On page 7, line 2, where it says "Ethic approval and informed consent," since it is a subtitle, every content word must be written in capital letters. So, it should say "Ethic Approval and Informed Consent,"

*Changed as requested.*

35. On page 7, lines 4 & 5, where it says "...Only data from patients in which the patient or his/her legal guardians had signed informed consent...", in order to avoid ambiguity in the use of the preposition "in", it could say "Only data from patients who had signed informed consent for participation, either by themselves or by representation of their legal guardians, ...

*Changed to: The patient or his/her legal guardians signed informed consent for participation before any data were included into the study.*

36. On page 7, lines 5 & 6, where it says "No patient or legal guardian..., for grammatical reasons, the conjunction "nor" should be used. So, it should say "No patient nor legal guardian..."

*Changed as requested.*

37. On page 7, line 7, where it says "Statistical analysis," since it is a subtitle, the two content words "Statistical" and "analysis" must be written in capital letters. So, it should say "Statistical Analysis"
Changed as requested.

38. On page 7, line 14, where it says “analysis,” the plural form of the noun “analysis” should be used. So it should say “Analyses.”

Changed as requested.

39. On page 7, line 16, where it says “Participating centers and basic data,” since it is a subtitle, every content word must be written in capital letters. So, it should say “Participating Centers and Basic Data.”

Changed as requested.

40. On page 7, line 23, where it says “...data on 54,824 inpatient days was collected,” for subject-verb agreement reasons, the singular form of the auxiliary “was” should be replaced by its plural form “were.” So, it should say “...data on 54,824 inpatient days were collected.”

'Data’ is always singular in this context.

41. On page 7, line 2, where it says “Device utilization,” since it is a subtitle, the two content words “device” and “utilization” must be written in capital letters. So, it should say “Device Utilization.”

42. On page 8, line 9, where it says “Overview of events,” since it is a subtitle, the content words must be written in capital letters. So, it should say “Overview of Events.” This recommendation applies to all subtitles appearing in the manuscript.

Changed as requested.

43. On page 8, line 22, where it says “...reported 27 NI in 30s months of...,” for grammatical reasons the numeral adjective 30 must not be pluralized, and what should be pluralized is the noun “NI” to show the cases of NI. So, it should say “...reported 27 NIs in 30 months of....”

Changed as requested.

46. On page 15, line 15, where it says “...consensus, how severely...,” for grammatical reasons the splitting comma (,) should be deleted and the preposition “on” should follow the noun “consensus.” So, it should say “...consensus on how severely...”

Changed as requested.

47. On page 16, line 10, where it says “Acknowledgement,” for language reasons, the plural noun “Acknowledgements” should be used to indicate correct meaning in such context. So, it should say “Acknowledgements.”

Changed as requested.


Reviewer 2

Major compulsory reviews
In my opinion the major problem resides in the fact that in such patients the concept of hospital infection is questionable. In fact since it is defined as "occurring after 48 hrs from admission (and not incubating at that time) nad 30 days after discharge" it is difficult to not consider all the infections as nosocomial infections in patients that go in and out of the hospital for many reasons.

This opinion points correctly at an important difference between pediatric oncology patients and other high risk populations ('going in and out of the hospital'). But this is no reason to abandon any surveillance activities for HAI in pediatric oncology.

The study protocol requested to evaluate each episode of fever according to the definitions and to discuss, whether a nosocomial / healthcare associated infection had occurred. Specific time frames were only defined for specific infections, e.g. 3 days for rotavirus, 5 days for RSV, 48 hours for invasive aspergillosis, 24 hours for nFUO. Laboratory confirmed bloodstream infections in a patient with a CVAD in use were always considered as healthcare associated events.

Reporting HAI rates to the treatment team does not mean to blame someone for a preventable complication but it is an important prerequisite and motivation for internal discussions about the local policy considering preventive strategies. In addition, it enables the treatment team to identify outbreaks more timely.

however the issue of evaluating the rate of infections by the days of hospitalization may represent another point of view after those that have been used as the whole period of immunosuppression (Eur J Cancer. 2001 Dec;37(18):2413-9.; Eur J Cancer. 2005 Jul;41(10):1439-45, Pediatr Blood Cancer. 2007 Oct 15;49(5):672-7.; Bone Marrow Transplant. 2007 Nov 19; [Epub ahead of print] ) and neutropenia (Clin Infect Dis. 2007 Nov 15;45(10):1296-304.). Therefore I would change the whole study in "Health Care Associated Infections".

Our incidence density refers to the number events per 1000 inpatient treatment days or to 1000 inpatient utilization days (in case of CVAD associated infections).

As requested, we changed the terminology to 'healthcare associated infection' to account for the special context.

Other comments
1. the bibliography is quite old and need the evaluations of new studies (some of them suggested above)

We included 4 new references from the working group of the reviewer.

2. in the methods authors refer to anti-biotics that should indicated

Done: '(ceftazidime, ceftriaxone, aminoglycosides, piperacillin-tazobactam).'

3. the definition of CVC-related bsi should not be limited to the absence of other documentations. there are now many systems for defining this infection that should be used (in fact the rate of CVC-related BSI is very (too much) high)).

Our definition is the correct epidemiologic definition of such an event in surveillance systems for HAI. It does not confirm that the CVAD is the source of the bacteremia or sepsis. In 2005, Castagnola et al. [2] reported during a follow-up of 12,394 catheter-days, a total of 13 infectious episodes, with an overall incidence of 3.1% and 1.05 episodes/1,000 catheter-days. It has to be taken in mind that our incidence density only refers to inpatient utilization days (reported during the midnight statistic on the ward). Therefore, the resulting ID of CVAD related
BSI is much higher than the corresponding results in studies, in which the ID refers to all (in- and outpatient) catheter-days.

4. the report of the results should be changed: a) basic data including CVC utilization, b) infections (documented vs fuo), c) presence of neutropenia at the event; d) etiology and resistances

Done as requested.

Moreover, it is difficult for me to understand the definition of blood stream infection (BSI?) with negative blood cultures (table 3). I would prefer the definition of systemic inflammatory response syndrome (SIRS) that has been described also in neutropenic patients.

BSI with negative blood cultures are events of sepsis, septic shock or septic shock with multiorgan failure without detection of a causative pathogen and without another clinically confirmed focus of infection. As cited in the methods section, our definition referred to SIRS symptoms from the consensus paper of Goldstein et al. [3].

Moreover, the definition of surgical site infection (SSI) is different from that normally accepted (30 days after or up to 2 years in presence of prosthetic devices).

Sentence changed to: ‘... module may be utilized to detect early (< 30 days) or late (up to 2 years in presence of prosthetic devices) SSI.’

The data of changes in process of times are useless since the observation is not uniform.

The figure illustrating the change of ID over time refers to the single institution with the longest surveillance period. We added a sentence in the discussion:

While we did not control for confounding variables as demographic characteristics of the patients, duration of neutropenia or illness severity, further studies are needed to confirm that participation in such a surveillance study results in a significant decrease in HAI rates. This was not an interventional study and each participating center decided on its own responsibility about any practical consequence related to the reported HAI rates.

similarly are useless the figures.

No comment on that. We do not consider the figures as useless.

Finally the data are frequently reported in a confuse form that it is difficult to understand and follow.

No comment on that.

The discussion is a consequence of the data report and it seems a "propaganda" for the web system created by the authors more than a real discussion of the results.

All 'propaganda' has now been deleted in the revised discussion.

Thanks again to the reviewers.
Best regards,
Arne Simon  Jan 25, 2008