PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Primary bacteremia is associated with a higher mortality risk compared with pulmonary and intra-abdominal infections in patients with sepsis: a prospective observational cohort study
AUTHORS	Mansur, Ashham; Klee, Yvonne; Popov, Aron; Erlenwein, Joachim; Ghadimi, Michael; Beissbarth, Tim; Bauer, Martin; Hinz, José

VERSION 1 - REVIEW

REVIEWER	Mette Søgaard Department of Clinical Epidemiology Aarhus University Hospital Denmark
REVIEW RETURNED	30-Sep-2014

GENERAL COMMENTS	The authors have conducted a cohort study of the association between foci of infection and 90-day mortality among 327 ICU patients with sepsis. Although the study presents some interesting data, it also has a number of limitations. I have the following comments and suggestions: Title I find the title slightly confusing. “Patients with BSI have higher mortality”. Compared to what? Abstract: In the abstract, the authors state that they aim to study the association between common infection foci (pulmonary, intra-abdominal and primary BSI) and mortality. However, only results for BSI are presented in the abstract results and as a reader you want to know what the impact of the other foci were. Please also state the actual 90-day mortality according to foci instead of merely providing a p-value which offers little clinical information. Regarding the study design: The authors state that it is a “prospective, observational, blinded cohort study. I find it very unusual to use blinding in observational studies – this usually applies to RCTs. Please describe in detail how this blinding was conducted. The authors report a hazard ratio of 2.20 for the association between primary BSI and mortality. What was the reference group in this analysis? Introduction: The intruduction is quite long and I think it would benefit from more brevity. For instance the authours do not have to provide detailed

	definitions in the intruduction. These can be presented in the materials and methods. I suggest that the authors are more specific, eg instead of merely stating that e.g. BSI leads to poor patient outcomes I suggest that the state more explicedtly how high mortality is in patients with BSI and sepsis, or how much higher mortality is in patients with BSI versus abnobinal foci. The same applies for the discussion relating to previous findings; please provide some estimates from the previous studies. The authors mention that Respiratory, intra-abdominal, urinary and primary BSI are the most frequent foci. Why did you not evaluate the impact of urinary foci? Material and Methods: Please briefly state the exclusion criteria instead of only referring to another paper. I think these are critical for the interpretation of the findings. Please describe how you define primary BSI Please provide more detail on the datasources, e.g. medical records, microbiology reports. Were infection foci microbiologically verified? Were any of the patients discharged before 90 days? And if so where you able to follow these patients or were they censored? Did you have any information on comorbidity (e.g. COPD, diabetes, cancer, heart disease) prior to sepsis which might have affected the outcome? It appears from the description of the analyses that the authors in fact do have information on BMI and some chronic diseases. This should be described in a little more detail – for instance in a section on “covariates”. First section of the results describe in more detail which comorbidities that were evaluated but this – and in particular where the information comes from – also needs to be described in the methods. Results section: Throughout the paper, the authors focus mainly on presence or absence of statistical significance instead on the size of their estimates. P-values tend to mix estimate size with sample size. Please see Rothman KJ. Epidemiology – an introduction, Oxford 2002, regarding this. Instead of relying so heavily on the p-values I recommend that the authors describe the differences among the different groups in more detail. I do not understand the 2 first lines of the section “Mortality analysis”. Did the authors examine changes in mortality over follow-up or what does this sentence mean? This is not described as a study aim or in the methods. Why do the authors provide estimates on 28-day mortality? Is this also a study outcome? Then please state this in the results. I do not understand Table 2 either. Please describe this in more detail. What exactly is meant by disease progression? And does this Table actually describe disease progression or is it disease severity?

	Please describe our findings in the section “multivariate analysis” instead or merely writing how and why you conducted this analysis (this would be more appropriate to in the methods section). Discussion Again please avoid focussing only on statistical significance. In a cohort of twice the size, some of the estimates would easily have turned out highly statistically significant. Did you have any information on antibiotic treatment? The methodologically limitations of the study are discussed rather superficially. This should be done, preferably in a systematic way: risk of selection bias, measurement bias, confounders that may not be sufficiently adjusted for, and statictical imprecision. Uncontrolled confouning (eg by appropriateness of antibiotic treatment) and impression would be especially relevant.

REVIEWER	Prof. Dr. Weigand Head of department Klinik für Anaesthesiologie Universitätsklinikum Heidelberg Germany
REVIEW RETURNED	01-Oct-2014

GENERAL COMMENTS	In the introduction, the presentation of the sepsis guidelines is missing. Here the authors should indicate some sentences about diagnostic, therapy goals and guidelines at all (compare Rivers et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med. 2001 Nov 8;345(19):1368-77. and Dellinger et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med. 2013 Feb;41(2):580-637.). The authors see the number of patients as a limitation factor. For a mono-center study the number of patients seems to be acceptable. But please explain why only Caucasian people are included. Do they have special genetic variants or is it just because of the research center location? Also the groups should be sub-analyzed by their principal threating department (surgical, internal, traumatic, etc.) Blood stream infections have been demonstrated as risk factor for death. But there is no information given about the methods for the microbiological research, which has been performed. Have blood cultures been taken only to begin or also during the observational period? Are the findings of bacteremia only cultural findings or also PCR-analyses? In a study about sepsis and infection sides, laboratory infection markers and vital parameters must be shown. In the present paper all information about leukocytes, CRP, Procalcitonin, Interleukin 2, Interleukin 6 and TNF-alpha are missing. Also facts about fluid management, mean arterial pressure, central venous oxygenation, kidney function and use of vasopressors should be mentioned in a separated table. The authors present data about ventilation. These findings have to be more detailed. Please provide information how the patients had been ventilated (frequency, tidal volume, structured Weaning, oral tube vs. tracheostomy, etc.).

	In table 4, microbiological findings are mentioned. Here, the information about bacteria differentiation, antimicrobial resistance screening results and fungal differentiation with resistograms should be provided. The early use of antibiotics is a relevant fact in the sepsis therapy. So please present information about starting point, length and escalation/de-escalation of the antibiotic therapy as sign for antibiotic stewardship. Minor comments In the abstract the study is indicated as a blinded study. An observational study can't be blinded, because there is no intervention. In the key word list the term "Apache" seems to be relevant as search item. The word 'Literature' is missing to indicate the beginning of the cited papers. (page 19)) Introduction and not ntroduction on page 5 suffered instead of uffered (page 10)

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name Mette Søgaard
Institution and Country Department of Clinical Epidemiology
Aarhus University Hospital
Denmark
Please state any competing interests or state ‘None declared’: None declared

The authors have conducted a cohort study of the association between foci of infection and 90-day mortality among 327 ICU patients with sepsis. Although the study presents some interesting data, it also has a number of limitations.

I have the following comments and suggestions:

Title
1. I find the title slightly confusing. “Patients with BSI have higher mortality”. Compared to what?
Response: Thank you very much for this comment. We have changed the title to, “Primary bacteremia is associated with a higher mortality risk compared with pulmonary and intra-abdominal infections in patients with sepsis: a prospective observational cohort study.”
Abstract:
2. In the abstract, the authors state that they aim to study the association between common infection foci (pulmonary, intra-abdominal and primary BSI) and mortality. However, only results for BSI are presented in the abstract results and as a reader you want to know what the impact of the other foci were. Please also state the actual 90-day mortality according to foci instead of merely providing a p-value which offers little clinical information.
Response: Thank you very much for this suggestion. We have added to the abstract the percentages of the deceased patients that were deceased in each study group.
3. Regarding the study design: The authors state that it is a “prospective, observational, blinded cohort study. I find it very unusual to use blinding in observational studies – this usually applies to RCTs. Please describe in detail how this blinding was conducted.
Response: We have removed the term “blinded” from the study design to avoid confusion. By “blinded”, we had meant to convey that the doctors treating the patients did not know about the study protocol; therefore, our study did not have any effect on the treatment received by the patients.

4. The authors report a hazard ratio of 2.20 for the association between primary BSI and mortality. What was the reference group in this analysis?
Response: The reference group is patients without BSI.
Introduction:
5. The intruduction is quite long and I think it would benefit from more brevity. For instance the authours do not have to provide detailed definitions in the intruduction. These can be presented in the materials and methods.
Response: We have moved detailed definitions from the introduction to the materials and methods section; please see the Definitions subsection of the Material and Methods section.
6. I suggest that the authors are more specific, eg instead of merely stating that e.g. BSI leads to poor patient outcomes I suggest that the state more explicedtly how high mortality is in patients with BSI and sepsis, or how much higher mortality is in patients with BSI versus abnobinal foci. The same applies for the discussion relating to previous findings; please provide some estimates from the previous studies.
Response: Thank you very much for this suggestion. We have revised the manuscript in accordance with this request.
7. The authors mention that Respiratory, intra-abdominal, urinary and primary BSI are the most frequent foci. Why did you not evaluate the impact of urinary foci?
Response: We did not evaluate urinary foci because our previous investigations have suggested that urinary foci were not frequent in the surgical ICUs at our University Medical Center. Furthermore, urinary foci were largely associated with good outcomes.
Material and Methods:
8. Please briefly state the exclusion criteria instead of only referring to another paper. I think these are critical for the interpretation of the findings.
Response: We have added the exclusion criteria; please see the Exclusion criteria subsection of the Material and Methods section.
9. Please describe how you define primary BSI
Response: Primary BSI comprises BSI of unknown origin in patients without an identifiable focus of infection and intravascular catheter-related BSI (related to the presence of a catheter, implantable cardioverter-defibrillator or pacemaker), according to the International Sepsis Forum Consensus Conference on Definitions of Infection in the Intensive Care Unit (Crit Care Med 2005 Vol. 33, No. 7).

10. Please provide more detail on the datasources, e.g. medical records, microbiology reports.
Response: All relevant clinical data were extracted from the electronic patient record system (IntelliSpace Critical Care and Anesthesia (ICCA), Philips Healthcare, USA). All medical records, including microbiology reports, can be found in this system. We sought to determine whether patients suffered from preexisting conditions, for example, comorbidities, by examining physicians' notes, administering an anamnestic questionnaire to the patients or their legal representatives and consulting each patient's family doctor.

11. Were infection foci microbiologically verified?
Response: Sometimes, infection foci could not be microbiologically verified, especially if the patients were pretreated with antibiotics on normal wards before they were admitted to the ICU.
12. Were any of the patients discharged before 90 days? And if so where you able to follow these patients or were they censored?
Response: Many patients were discharged before 90 days. We were able to follow all of these patients. If the patient or legal representative could not be reached by telephone or mail, we confidentially contacted the local registry office and inquired whether the patient was still alive (still registered).
13. Did you have any information on comorbidity (e.g. COPD, diabetes, cancer, heart disease) prior to sepsis which might have affected the outcome? It appears from the description of the analyses that

the authors in fact do have information on BMI and some chronic diseases. This should be described in a little more detail – for instance in a section on “covariates”. First section of the results describe in more detail which comorbidities that were evaluated but this – and in particular where the information comes from – also needs to be described in the methods.
Response: All information regarding comorbidities and chronic diseases is listed in Table 1, Patient baseline characteristics with regard to the infection site. We sought to determine whether patients suffered from preexisting conditions, for example, comorbidities or chronic conditions, by examining physicians’ notes, administering an anamnestic questionnaire to the patients or their legal representatives and consulting each patient’s family doctor.
Results section:
14. Throughout the paper, the authors focus mainly on presence or absence of statistical significance instead on the size of their estimates. P-values tend to mix estimate size with sample size. Please see Rothman KJ. Epidemiology – an introduction, Oxford 2002, regarding this. Instead of relying so heavily on the p-values I recommend that the authors describe the differences among the different groups in more detail.
Response: Thank you for this recommendation. We have changed the description of the differences in accordance with your suggestions.
15. I do not understand the 2 first lines of the section “Mortality analysis”. Did the authors examine changes in mortality over follow-up or what does this sentence mean? This is not described as a study aim or in the methods.
Response: We have changed the first sentence of this section to the following text: “Kaplan-Meier survival analysis showed that the 90-day mortality risk was significantly higher among patients with primary bacteremia than among those with pulmonary and intra-abdominal foci (58%, 35% and 32%, respectively; Figure 1).” The mean outcome parameter was mortality risk within 90 days (within the whole observational period), as calculated by Kaplan-Meier survival analysis.
16. Why do the authors provide estimates on 28-day mortality? Is this also a study outcome? Then please state this in the results.
Response: We provide estimates on 28-day mortality because it is a secondary outcome parameter that is typically evaluated in this type of study. We have stated this in the results section.
17. I do not understand Table 2 either. Please describe this in more detail. What exactly is meant by disease progression? And does this Table actually describe disease progression or is it disease severity?
Response: Table 2 describes disease severity (morbidity scores, use of organ support, mortality, and other factors). We have changed the title of this table.
18. Please describe our findings in the section “multivariate analysis” instead or merely writing how and why you conducted this analysis (this would be more appropriate to in the methods section).
Response: The effect of primary bloodstream infection on the outcome (90-day survival) is independent of age, BMI, gender and comorbidities/baseline characteristics, which were significantly different at baseline (IDDM, Cancer and “No history of surgery”) among the groups.

Discussion
19. Again please avoid focussing only on statistical significance. In a cohort of twice the size, some of the estimates would easily have turned out highly statistically significant.
Did you have any information on antibiotic treatment?
Response: We have added a supplemental table that shows which antibiotics were used.
20. The methodologically limitations of the study are discussed rather superficially. This should be done, preferably in a systematic way: risk of selection bias, measurement bias, confounders that may not be sufficiently adjusted for, and statictical imprecision. Uncontrolled confouning (eg by appropriateness of antibiotic treatment) and impression would be especially relevant.
Response: Thank you very much for this helpful comment. We have incorporated this suggestion into the discussion section.

Reviewer: 2
Reviewer Name Prof. Dr. Weigand, Head of departement
Institution and Country Klinik für Anaesthesiologie
Universitätsklinikum Heidelberg
Germany
Please state any competing interests or state 'None declared': None declared

Major comments

1. In the introduction, the presentation of the sepsis guidelines is missing. Here the authors should indicate some sentences about diagnostic, therapy goals and guidelines at all (compare Rivers et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med. 2001 Nov 8;345(19):1368-77. and Dellinger et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med. 2013 Feb;41(2):580-637.).
Response: Thank you very much for this comment; we have incorporated this suggestion into the introduction section.

2. The authors see the number of patients as a limitation factor. For a mono-center study the number of patients seems to be acceptable. But please explain why only Caucasian people are included. Do they have special genetic variants or is it just because of the research center location? Also the groups should be sub-analyzed by their principal threating department (surgical, internal, traumatic, etc.).
Response: We have removed the discussion of this potential limitation. Because interracial genetic differences may affect the clinical course of infectious diseases, we have exclusively recruited Caucasians, who form the majority of patients admitted to our surgical ICUs, into this clinical investigation. All patients enrolled in this study were treated in the surgical ICUs of the University Medical Center-Goettingen; thus, we have added information regarding operative status to the baseline characteristics listed in Table 1.
Since the covariate "No history of surgery" (Table 1) was significantly different between the groups, we have included this into the multivariate model. According to the multivariate Cox regression analysis, primary bacteremia impacts significantly on mortality independently from "No history of surgery" (Table 3).

3. Blood stream infections have been demonstrated as risk factor for death. But there is no information given about the methods for the microbiological research, which has been performed. Have blood cultures been taken only to begin or also during the observational period? Are the findings of bacteremia only cultural findings or also PCR-analyses?
Response: In our ICUs, it is standard practice to obtain appropriate cultures before antimicrobial therapy is initiated; two sets of blood cultures (both aerobic and anaerobic) are obtained for each sample, with at least one sample drawn percutaneously and one drawn through each vascular access device. Cultures of samples from other sites, such as urine, cerebrospinal fluid, surgical wounds, respiratory secretions, or other body fluids that may be the source of infection, are also obtained before antimicrobial therapy is initiated. In this study, blood cultures were taken at sepsis onset and over the observational period in the ICU in accordance with clinical judgment, as indicated. We have recorded the pathogens (bacteria, fungi, virus) identified in our CRF and categorized them initially as gram-positive bacteria, gram-negative bacteria, fungi, and viruses (Table 4). We have also now added a differentiation of these pathogens to the supplemental data (see Supplementary data 1, Table 2). The bacteremia findings were only cultural.

4. In a study about sepsis and infection sides, laboratory infection markers and vital parameters must be shown. In the present paper all information about leukocytes, CRP, Procalcitonin, Interleukin 2, Interleukin 6 and TNF-alpha are missing. Also facts about fluid management, mean arterial pressure, central venous oxygenation, kidney function and use of vasopressors should be mentioned in a separated table.

Response: We have added information about leukocytes, CRP, procalcitonin, lactate, temperature, mean arterial pressure, kidney function and the use of vasopressors to the supplemental data (see Supplementary data 1, Table 1). Table 2 (manuscript) also includes comprehensive information about organ dysfunction (e.g., SOFA-Cardiovascular data incorporates mean arterial pressure and vasopressor use, and SOFA-Renal incorporates creatinine and urine output). Patients with sepsis related hypotension became adequate fluid management. The presentation of our data on organ dysfunction conforms to international standards used in clinical sepsis research (JAMA, March 20, 2013—Vol 309, No. 11, JAMA, June 13, 2012—Vol 307, No. 22). The use of organ support (days; Table 3) is also a robust parameter for the analysis of organ failure. Interleukin-2, interleukin-6 and TNF-alpha are not measured routinely in our ICUs and are not standard parameters of sepsis, according to standard guidelines for the clinical management of sepsis. However, all of these cytokines are proinflammatory and, as such, do not provide information about the anti-inflammatory or immunosuppressed status of septic patients; immunosuppression and a lack of inflammatory response are increasingly recognized as a major problem in this patient group (The Lancet. Infectious diseases 13, 260-268, doi:10.1016/s1473-3099(13)70001-x(2013)).

5. The authors present data about ventilation. These findings have to be more detailed. Please provide information how the patients had been ventilated (frequency, tidal volume, structured Weaning, oral tube vs. tracheostomy, etc.).

Response: Patients in our surgical ICUs usually receive lung-protective ventilation (Tidal volume of 6–8 ml/kg predicted body weight). We also have structured weaning protocols in our ICUs. Patients who receive or require prolonged mechanical ventilation receive tracheotomies.

The way in which our results regarding ventilation (the requirement for mechanical ventilation at sepsis onset [Table 1] and the frequency of mechanical ventilation [Organ-support; Table 2]) are presented is in line with presentations in publications in top-tier journals (please see N Engl J Med. 2008 Jan 10;358(2):125-39; JAMA, June 20, 2012—Vol 307, No. 23; N Engl J Med 2014;370:2191-200.). The requirement for mechanical ventilation (days) is standard information used to assess respiratory failure. Information about the “(frequency, tidal volume, structured Weaning, oral tube vs. tracheostomy, etc.)” is beyond the scope of our study.

6. In table 4, microbiological findings are mentioned. Here, the information about bacteria differentiation, antimicrobial resistance screening results and fungal differentiation with resistograms should be provided.

Response: We have added a table of bacteria, fungal, and virus differentiation to the supplemental data (see Supplementary data 1, Table 2). Antimicrobial regimens were reassessed daily for potential de-escalation according to microbiological findings and resistance screening, within the framework of antibiotic stewardship practiced by the Department of Clinical Microbiology of the University Medical Center-Goettingen. Pathogen susceptibility profiles were not the focus of our study. Moreover, the results of a large clinical investigation, a multicenter cohort study of 7,974 patients who had septic shock in 29 academic and community intensive care units, showed that the effect of anatomic source of infection on outcome was independent of the type of causative organism (Am J Respir Crit Care Med Vol 189, Iss 10, pp 1204–1213, May 15, 2014). Furthermore, research articles on clinical sepsis in top-tier journals do not always contain information about pathogen susceptibility (e.g., N Engl J Med 2014;370:2191-200).

7. The early use of antibiotics is a relevant fact in the sepsis therapy. So please present information about starting point, length and escalation/de-escalation of the antibiotic therapy as sign for antibiotic stewardship.

Response: Thank you very much for this comment. We have added a table listing all anti-infective agents that were used in the studied cohort (see Supplementary data 1, Table 3). In general, patients with severe sepsis or septic shock in our surgical ICUs receive prompt intravenous antimicrobials within the first hour of recognition, in accordance with current sepsis treatment guidelines. Patients receive initial empiric anti-infective therapy that includes one or more drugs that have activity against all likely pathogens (bacterial and/or fungal or viral) and that penetrate in adequate concentrations into the tissues presumed to be the source of sepsis. Antimicrobial regimens are reassessed daily for

potential de-escalation within the framework of antibiotic stewardship practiced by the Department of Clinical Microbiology of the University Medical Center-Goettingen. Procalcitonin levels are measured frequently to assist the clinician in the discontinuation of empiric antibiotics. Empiric combination therapy is not given for more than 3–5 days, and the duration of therapy typically does not exceed 7–10 days. In the present study, we do not have data indicating the precise time at which antimicrobial therapy was initiated; thus, we have added a discussion of this lack of data as a limitation and potential source of confounding in the discussion section.
Minor comments
In the abstract the study is indicated as a blinded study. An observational study can't be blinded, because there is no intervention.
Thank you for this comment. We have changed the manuscript accordingly.
In the key word list the term "Apache" seems to be relevant as search item.
We have made the recommended change.
The word 'Literature' is missing to indicate the beginning of the cited papers. (page 19)
We have made the recommended change.
Introduction and not ntroduction on page 5
We have made the recommended change.
suffered instead of uffered (page 10)
We have made the recommended change.

VERSION 2 – REVIEW

REVIEWER	Prof. Dr. M.A. Weigand Klinik für Anaesthesiologie Im Neuenheimer Germany
REVIEW RETURNED	04-Nov-2014

GENERAL COMMENTS	General comments In the present prospective, observational cohort study 327 adult Caucasian patients with sepsis due to a pulmonary focus, intra-abdominal focus or with a bacteremia were studied to determine the mortality as primary outcome and the sepsis-related organ failure scores (SOFA) as secondary outcome for organ failure. It was observed, that patients with primary bacteremia have a significantly higher risk for death within the first 28 days and also within the first 90 days compared to patients with sepsis due to an intra-abdominal or pulmonary focus. Furthermore these patients presented a significantly higher SOFA-Score and required more renal replacement therapy. These findings indicate the need for more studies about bacteremia. The authors present a revised version of their first manuscript including the headline, in which most of the claimed points have been edited. The initially missing sepsis guidelines are well implanted in the introduction. The infection marker and vital parameters are now described. Also the microbiological findings with infection site, resistances and the used antibiotic drugs are shown. Some major and minor comments are indicated below, but at all the manuscript now seems to be acceptable. Major comments Even in the presented revised version, the authors do not explain why only Caucasian people are included. Do they have special genetic variants or is it just because of the research center location? For the presented microbiological data, it would be good to show,

	when the findings have been made (beginning of sepsis, in course of sepsis, etc.) and by which method they have been determined (cultural findings, PCR-Analyses). The authors only indicate, that all findings have been taken from their patient documentation system. For the shown data about mechanical ventilation, at least duration of the ventilation in the sub-groups and some facts about the ventilation protocol (lung protective ventilation, structured weaning) should be provided. Minor comments In case of two mentioned citations, they should be separated by comma. In Table 1 NIDDM and NIDDM should be written-out or explained in the base line. In Table 2 % has to be written as percent (%) Table 3 seems to be more visual, when presented in a graphic picture with table. In Table 1 of the supplementary data, the indications are written in German language.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 2
Reviewer Name Prof. Dr. M.A. Weigand
Institution and Country Klinik für Anaesthesiologie
Im Neuenheimer Feld 110
D-69120 Heidelberg
Germany
Please state any competing interests or state ‘None declared’: None declared

General comments
In the present prospective, observational cohort study 327 adult Caucasian patients with sepsis due to a pulmonary focus, intra-abdominal focus or with a bacteremia were studied to determine the mortality as primary outcome and the sepsis-related organ failure scores (SOFA) as secondary outcome for organ failure. It was observed, that patients with primary bacteremia have a significantly higher risk for death within the first 28 days and also within the first 90 days compared to patients with sepsis due to an intra-abdominal or pulmonary focus. Furthermore these patients presented a significantly higher SOFA-Score and required more renal replacement therapy. These findings indicate the need for more studies about bacteremia.

The authors present a revised version of their first manuscript including the headline, in which most of the claimed points have been edited. The initially missing sepsis guidelines are well implanted in the introduction. The infection marker and vital parameters are now described. Also the microbiological findings with infection site, resistances and the used antibiotic drugs are shown. Some major and minor comments are indicated below, but at all the manuscript now seems to be acceptable.
-Thank you very much for this comment.
Major comments
Even in the presented revised version, the authors do not explain why only Caucasian people are included. Do they have special genetic variants or is it just because of the research center location?
Response:
Thank you very much for this comment. We have added the relevant information to the revised manuscript (page 7, section MATERIALS AND METHODS: Patients).
For the presented microbiological data, it would be good to show, when the findings have been made (beginning of sepsis, in course of sepsis, etc.) and by which method they have been determined

(cultural findings, PCR-Analyses). The authors only indicate, that all findings have been taken from their patient documentation system.
Response:
We have added all relevant information about microbiological data to the manuscript (page 17, second last paragraph).
For the shown data about mechanical ventilation, at least duration of the ventilation in the sub-groups and some facts about the ventilation protocol (lung protective ventilation, structured weaning) should be provided.
Response:
We have incorporated all relevant information into the manuscript (page 16, lines 4-10).
Minor comments
In case of two mentioned citations, they should be separated by comma.
We used the BMJ Open reference style.
In Table 1 NIDDM and NIDDM should be written-out or explained in the base line.
We have made the recommended change.
In Table 2 % has to be written as percent (%)
We have made the recommended change.
Table 3 seems to be more visual, when presented in a graphic picture with table.
Thank you very much for this recommendation. We decided to present the data in a table because we believe that the results, given in percentages, are clearly demonstrated.
In Table 1 of the supplementary data, the indications are written in German language.
We have made the recommended change.

VERSION 3 - REVIEW

REVIEWER	Prof. Dr. M.A.Weigand Universitätsklinikum Heidelberg Klinik für Anästhesiologie Germany
REVIEW RETURNED	11-Nov-2014

GENERAL COMMENTS	The authors present a new revised version of their manuscript, in which all the claimed points for the minor revisions have been edited. The fact, that only Caucasian people are included is now better described. The microbiological findings are completely presented including the methods by which they have been determined. Also the missing data about mechanical ventilation is provided. The manuscript is now acceptable.