Article details	
Title	Risk factors for mortality among Canadian patients with Staphylococcus aureus bacteremia: a retrospective cohort study
Authors	Ram Venkatesh Anantha MD MSc, Januvi Jegatheswaran MD, Daniel Luke Pepe MD, Fran Priestap PhD, Johan Delport MD, S.M. Mansour Haeryfar PhD, John K. McCormick PhD, Tina Mele MD PhD
Abstract	Introduction: Staphylococcus aureus bacteremia (SAB) is a persistent and challenging disease, with few recent studies assessing its scope and burden in a Canadian population. We evaluated the magnitude of SAB in a large cohort of patients, and identified risk factors associated with increased mortality. Methods: We retrospectively reviewed adult (>18 years old) patients admitted with SAB between 2008 and 2012 at a regional tertiary-care centre in Southwestern Ontario. Hospital records were used to identify comorbidities, complications of SAB such as sepsis and need for mechanical ventilation (MV), and mortality. Multivariable logistic regression was performed to determine predictors of overall, in-hospital, and postdischarge mortality. Results: We identified 1114 patients in our study. The proportion of methicillin-resistant S. aureus (MRSA) strains rose significantly during the study period (p= 0.045), while in-hospital mortality declined significantly (29% in 2008 to 11% in 2012, p< 0.0001). Age, MRSA, sepsis, admission to the intensive care unit, hepatic failure, prolonged (> 21 days) MV, chronic obstructive pulmonary disease (COPD), and malignancy (primary and metastatic) were associated with overall mortality and— with the exception of COPD and primary malignancy— in-hospital mortality. In contrast, peripheral vascular and cerebrovascular disease, COPD, diabetes, and malignancy (solid and hematogenous) were associated with increased post-discharge mortality. Interpretation: This study features one of the largest retrospective cohort studies of SAB in Canada, and identifies key factors associated with inhospital and post-discharge mortality. Identification of these predictors may guide empiric therapy and provide prognostic clarity for patients with SAB during and after their hospital admission.
Version 1	
Reviewer 1	
Name	B. Foxman
Position	
Institution	University of Michigan, Epidemiology
Competing interests	
Date review returned	28-Mar-2014
General comments	the primary outcome. They have a large data set and the data are important. I would have liked more information on

	the time of follow-up in the cohort, and to have the analysis take into account time at risk. Abstract: The introduction could be more informative, why is it challenging? Some of the information from the introduction of the manuscript might be usefully put here. The interpretation could be strengthened, what are the key take home messages? Why has mortality decreased with increasing prevalence of MRSA? Introduction is very clear and informative. Methods: It is unclear if a recurrent SAB was included in the analysis more than once, or if only once what episode was selected. (p. 9 first paragraph). Please mention the length of follow-up per patient; was this defined? Results: P. 10 – first paragraph – did the authors mean that 39% of the SAB cases were caused by MRSA? I'm not clear what they mean by incidence, which would imply the number of new cases caused by MRSA. A similar comment with respect to sepsis. What was the definition of sepsis? In the methods it only refers to septic shock. p. 10 second paragraph – it might be easier to understand if the authors presented the average number of admissions for SAB per patient (presumably 1114/909?), then noted 205/909 had recurrences. I found the presentation here confusing, as I wasn't sure of either the denominator nor the risk period. Presumably the authors might be able to estimate the risk of adverse outcomes following initial admittance for SAB but that wasn't clear. Since these data are presented in Table 2, it should only be highlighted here. Interpretation: The first paragraph would be usefully revised to summarize major findings. Tables: The titles of the tables are not complete. They should include the study population and study period. Further, the column headers could be more descriptive rather than 'Value' I would recommend N (%) for table 2, for example. Tables 3 & 4 should state what variables were included in the multivariate analysis. Why is methicillin resistance not shown in Table 4?
Reviewer 2	
Name	Jane Buxton
Position	
Institution	UBC, School Population and Public Health
Competing interests	
Date review returned	19-Mar-2014
General comments	This paper is interesting and although not unique does have information which may be of interest to the journal readers. However we suggest a number of changes to improve clarity especially in the method section before it should be published. Title and Abstract:

	-Title should reflect study design and where occurred- currently could be interpreted as a national study. -Abstract should be tightened up. There are a lot of vague descriptions used eg "SAB is a persistent and challenging disease". In this example perhaps the author's meant to say that either that SAB has a high incidence, or perhaps that it imposes substantial morbidity and mortality. When reporting statistical results both the test statistic and the p value should be reported eg (chisquare= X; p=Y). Uses term intravenous drug users- this has been common practice in past but it is stigmatizing to identify someone by an action rather than as a person. People who inject drugs (PWID) is used fairly commonly now. IDU is fine as an action. Introduction: The readability of the paper would be improved by tightening the language. Several sentences have too many clauses, and there is an overuse of non-specific adjectives and adverbs. It is not clear what is meant by Not all concurrent co-morbidities "are alike in effect" . Furthermore a significant majority of post discharge mortalities occurred beyond 90 days. Does significant refer to statistical test if not please use a different term. The objective of the study should be stated more clearly. Perhaps the authors intended to say something like: "This retrospective cohort study describes the incidence of SAB and its corresponding morbidity and mortality in a tertiary care hospital in Ontario. It also describes risk factors associated with all-cause mortality, in hospital and post-discharge (30, and 90 day) in this population." Methods: The source of data is unclear. Was it pulled from electronic medical records (EMR) or an administrative data set e.g. provincial discharge abstract database? Were cases identified by the lab only? How was in hospital mortality ascertained eg via hospital database or via vital statistics? How was mortality after discharge ascertained? Presumably this came from vital stats, how was this linked to the EMR or hospital records? How complete were the data, when was the linkage performed i.e. was there issues of truncation if insufficient follow up time post discharge? Description of inclusion and inclusion criteria are inconsistent throughout the paper. Were patients eligible if they were >18 yo or ≥18 yo? When "overall mortality" is discussed do the authors mean "all-cause mortality"? Why was a Cochrane-Armitage chi-square test used instead of a pearson chi-square test? Please explain reasons for choosing. Results: -See previous comment about reporting statistical tests. In table 2 post –discharge mortality unclear as this 0-30 days, 30-90 all <90 days or 90+ days.etc. Please be specific in the table States some were excluded as were discharged against

	medical advice but not clear how many this was and how fit into Figure 1. Discussion: -In discussions of mortality it is unclear how long after discharge mortality was analyzed. –Potential sources of bias in this study or this population should be discussed As this occurred at just one hospital were there any changing re admission protocols, other hospitals from where maybe transfer or increased resources for admissions elsewhere? -In discussing MRSA there should be a discussion of whether the MRSA seen here is hospital or community acquired and whether any genetic testing was done on the isolates as the two strains behave quite differently. Those who were operated on potentially could have been healthier (as determined suitable/fit for surgery)
Reviewer 3	
Name	Gilca Rodica
Position	
Institution	
Competing interests	
Date review returned	31-Mar-2014
General comments	General comment: Given the important cost and resource use associated with MRSA, more details describing patients with MRSA would be useful for the readers. Specific comments: Page 8, Study design and outcomes - Definition of overall mortality, particularly its post-discharge component, should be clarified. How long after discharge patients were followed-up? Was the follow-up available for all patients? These details are especially important for the 110 patients who deceased beyond 90 days of discharge. - Since requirement for prolonged MV and length of hospital stay are only presented as variables included in regression models, authors might want deleting them from the list of secondary outcomes. Page 9, statistical analysis - One may presume that patients were followed-up until the last day of the study (December 31, 2012), although this is not clear from the paper. If so, those admitted in the later period of the study had a shorter time of follow-up after discharge compared to patients admitted earlier. Consequently, patients who have the propensity to die earlier may be overrepresented. In addition, I am not sure patients who die at home or in other settings are accounted for. Survival analysis taking into account contribution of each patient to the time at risk for dying might be more appropriate for properly identifying factors associated with post-discharge mortality. - Some variables included in the multivariable models (such as hepatic failure, liver disease, hepatitis C infection, table 3) might be correlated. Was the collinearity verified? - Because of the substantial number of variables included in

	multivariate models, I am no sure all strata had sufficient observations. Presenting odds ratios for not significant variables in table 3 and 4 might reassure the reader. Results Table 1: Hepatitis B/C co-infection is listed under characteristic column; there is no separate row for hepatitis C and hepatitis B infection, although in table 3 hepatitis C and hepatitis B are presented as separate variables. This should be clarified. Page 10, 1st paragraph Suggest using the term "proportion" instead of "incidence" in relation to MRSA and to sepsis. Page 10, last paragraph In addition to proportions, the reader might be interested to see trends in terms of incidence (per admissions or per patient-days, if available) of SAB, MRSA and MSSA. Page 11, 1st paragraph The text suggests that methicillin resistance is independently associated both with overall mortality and with in-hospital mortality. However, methicillin resistance is not listed in Table 4 presenting multivariable analysis of in-hospital mortality. Interpretation, 1st paragraph - Use of wording "incidence" in the context of the study is questionable. Page 12, first line: mentioning implementation of infection control strategies to prevent the spread of SAB is confusing when the paper reports increase in MRSA proportion and does not mention SAB incidence. Page 12, lines 40-47: Post-discharge mortality, particularly beyond 90 days and in patients admitted in 2008 may add up to almost 5 years of follow-up. It is hard to believe that in a population with an important proportion of comorbidities mortality is attributable only to long-term consequences from SAB. Page 13, lines 42-44: Diabetes and malignancy (cancer) are given as examples for differences between comorbidities associated with mortality and with the acquisition of SAB. However, they are listed under both mortality and acquisition of SAB risk factors. Page 13, lines 47-49: the statement about interaction between patient-specific factors and pathogen virulence should be clarified.
Author response	1. The rationale for your study is unclear. Please explain why you chose to describe SAB in this particular cohort. Please clearly articulate any pre-specified hypotheses. Rationale: Thank you for this comment. We have revised the last paragraph of our introduction to carefully outline our study rationale and the reasons for describing SAB in our particular cohort (to describe the current clinical burden of disease and to determine predictors of mortality). 2. Please describe your data source and comment on the quality and quantity of the data (i.e., Do you have data for all of the key variables?).

	Response: Thank you for this comment. We have revised our methods section to carefully describe the data sources (electronic and paper charts) and the quality and quantity of the data. We manually reviewed electronic and paper charts, and recorded data using a standard extraction form. We collected information about demographic characteristics, source of infection, baseline comorbidities, course of illness, and outcomes including mortality. Chart abstraction was performed separately by three reviewers, who each reviewed 40% of the charts: the Cohen's kappa (κ) statistic for the coding of categorical and qualitative variables was 0.82, indicating excellent inter-rater reliability. All available data were recorded. This is explained in the Study Design portion of the Methods section. We also emphasize that missing data for key variables were coded explicitly as missing and excluded from the analysis. 3. What was the follow-up period? How was this period of follow up determined? Patient charts were reviewed in August 2013, 6 months after the conclusion of the study period (January 1 2008 to December 31, 2012). For the purposes of survival analyses (Kaplan Meier and Cox proportional hazards analysis) and multivariable logistic regression analysis, we elected to censor the data at 90 days. This was because mortality due to S. aureus bacteremia could be reasonably attributed to have contributed to mortality up to 90 days post-discharge. Beyond 90 days, we could not truly ascertain whether mortality was secondary to the patient's admission for S. aureus bacteremia. Consequently, our data was censored at 90 days. However, because our followup was 6 months after the conclusion of the study period, we have elected to show the number of patients who died beyond 90 days post-discharge. The Kaplan-Meier survival analysis for the study population (in-hospital length of stay and post-discharge survival to 90 days) is therefore right-censored. We describe this in our Methods section, as well as in our Interpretation. 4. Your primary outcome of overall mortality may have been better described using survival analysis methods (see also Dr. Gilca's comments). Please re-analyze accordingly. Response: Thank you for the feedback. In the context of this study, we were analyzing all patients with S. aureus bacteremia as a single population. We have performed a survival analysis of our study population using a Cox proportional-hazards analysis to identify risk factors associated with mortality from S. aureus bacteremia. We have provided the univariable and multivariable logistic regression analysis as supplemental tables to demonstrate that we considered as many statistically and clinically-significant variables in our analyses. Moreover, both the hazard ratios and odds ratios show similar direction and strengths of association. We hope this is acceptable to the editorial board and the reviewers of the study. Other points:

	1. For only the most standard abbreviations (i.e., 95% CI, SD, OR, RR, HR), please spell out at first mention and include the abbreviation in parentheses. The abbreviations may be used throughout the remainder of the manuscript. Please remove all other abbreviations. Response: Thank you for this point. We have removed all non-standard abbreviations in our manuscript. 2. Please include up to 1 academic and 1 professional degree after each author's name. Response: We have included an academic and professional degree for each author. 3. Please provide a funding statement (which includes a comment on the role of the funder) at the end of your manuscript. Response: We have provided a funding statement at the end of our manuscript to acknowledge our funding agencies, and have included a comment on the role (or lack thereof) of the funding agencies. 4. Please structure the Interpretation section (discussion) into the following 4 main categories: main findings; explanation and comparison with other studies; limitations; and conclusions and implications for practice and future research. Response: Thank you for this feedback. We have restructured our interpretation section into the 4 main categories as requested. Moreover, we have included limitations and conclusions as separate subheadings within the Interpretation section. 5. Please use plain numbers in brackets for your references and do not use automatic numbering of field codes as these do not carry over well into our publishing software. Response: We have removed the use of automatic numbering of field codes, and have maintained the CMAJ reference format for the manuscript. 6. Please include a completed STROBE checklist. Response: Thank you for this comment. We have attached our completed STROBE checklist to the manuscript submission as a separate document. Reviewers' Comments to Author: Reviewer: Dr. Jane A Buxton, UBC Comments to the Author This paper is interesting and although not unique, does have information which may be of interest to the journal readers. However we suggest a number of changes to improve clarity especially in the method section before it should be published. Title and Abstract: 1. Title should reflect study design and where occurred- currently could be interpreted as a national study.

	Response: Thank you for the feedback. We have changed our title to reflect the retrospective, single-centre nature of our study. 2. Abstract should be tightened up. There are a lot of vague descriptions used eg "SAB is a persistent and challenging disease". In this example perhaps the author's meant to say that either that SAB has a high incidence, or perhaps that it imposes substantial morbidity and mortality. When reporting statistical results both the test statistic and the p value should be reported eg (chisquare= X; p=Y) Response: Thank you for this valuable feedback. We have revised our abstract for clarity, and have included both the test statistic and the p value for our logistic regression analyses in the results section of the abstract. As the reviewer has accurately pointed out, we have changed the abstract to particularly describe that SAB imposes substantial morbidity and mortality, and remains an infection with a high incidence. 3. Uses term intravenous drug users- this has been common practice in past but it is stigmatizing to identify someone by an action rather than as a person. People who inject drugs (PWID) is used fairly commonly now. IDU is fine as an action. Response: Thank you for this important point. We agree with the reviewer, and have changed the term intravenous drug users to people who inject drugs. We have retained intravenous drug use as an action, as suggested by the reviewer. Introduction: 4. The readability of the paper would be improved by tightening the language. Several sentences have too many clauses, and there is an overuse of non-specific adjectives and adverbs. It is not what is meant by Not all concurrent co-morbidities "are alike in effect". Furthermore a significant majority of post discharge mortalities occurred beyond 90 days. Does significant refer to statistical test if not please use a different term. Response: Thank you for the feedback. We have revised the paper to improve readability, as suggested by the reviewer. In agreement with the reviewer, we have removed the term significant when referring to post discharge mortalities. 5. The objective of the study should be stated more clearly. Perhaps the authors intended to say something like: "This retrospective cohort study describes the incidence of SAB and its corresponding morbidity and mortality in a tertiary care hospital in Ontario. It also describes risk factors associated with all-cause mortality, in hospital and post-discharge (30, and 90 day) in this population." Response: Thank you for this feedback. We have sought to more clearly define the objectives of our study to reflect the valuable suggestion of the reviewer. Methods:

	6. The source of data is unclear. Was it pulled from electronic medical records (EMR) or an administrative data set e.g. provincial discharge abstract database? Were cases identified by the lab only? How was in hospital mortality ascertained eg via hospital database or via vital statistics? How was mortality after discharge ascertained? Presumably this came from vital stats, how was this linked to the EMR or hospital records? How complete were the data, when was the linkage performed i.e. was there issues of truncation if insufficient follow up time post discharge? Response: Thank you for the feedback and the questions. We have revised our methods section, particularly the study design portion to more accurately describe the source of the data (manual chart and electronic record abstraction). Cases were identified by the clinical microbiology laboratory. Patient information was linked to the vital statistics information from the Ministry of Ontario, using the provincial health card number and/or name and date of birth. 7. Description of inclusion and inclusion criteria are inconsistent throughout the paper. Were patients eligible if they were >18 yo or ≥18 yo? Response: Thank you for this feedback. We have carefully revised our description of inclusion criteria (all adult patients ≥18 yo with ≥1 positive blood culture for S. aureus based on the clinical laboratory result). Patients were eligible for this study if they were ≥18 yo. We have made this change to achieve consistency in the manuscript. 8. When "overall mortality" is discussed do the authors mean "all-cause mortality"? Why was a Cochrane-Armitage chi-square test used instead of a pearson chi-square test? Please explain reasons for choosing. Response: We have revised "overall mortality" to "all-cause mortality," as pointed out by the reviewer. We used the Cochrane-armitage chi-square test for trend because it specifically examines changes over time to determine if there is a statistically significant trend. The Pearson chi-square test only compares differences between two sets of values, and is not as accurate as the Cochrane-Armitage test when examining changes over time. Results: 9. See previous comment about reporting statistical tests. Results: We have revised our manuscript to make the statistical changes. 10. In table 2 post –discharge mortality unclear as this 0-30 days, 30-90 all <90 days or 90+ days, etc. Please be specific in the table Response: Thank you for this comment. We have adjusted our description of the post-discharge mortality to 0-30 days, 31-90 days, and after 90 days. 11. States some were excluded as were discharged against medical advice but not clear how many this was and how fit into Figure 1.

	Response: Thank you for the comment. We had included patients discharged against medical advice together with patients with incomplete/missing information. In going through our records, we have re-identified and reclassified a portion of these patients as being discharged against medical advice. Discussion: 12. In discussions of mortality it is unclear how long after discharge mortality was analyzed. -Potential sources of bias in this study or this population should be discussed Response: We have clarified in the manuscript that, for the purposes of statistical analysis, mortality was defined as occurring in-hospital or within 90 days after discharge. 13. As this occurred at just one hospital were there any changing re admission protocols, other hospitals from where maybe transfer or increased resources for admissions elsewhere? Response: In this timeframe that was studied (2008 to 2012), there were no major changes to admission protocols, or resource re-allocation methods within our tertiary-care centre. We do discuss in our interpretation/limitations that we cannot account for patients who were managed elsewhere. This imposes a selection bias in our analysis, necessitating a larger prospective study for validation. 14. In discussing MRSA there should be a discussion of whether the MRSA seen here is hospital or community acquired and whether any genetic testing was done on the isolates as the two strains behave quite differently. Response: No genetic testing was performed to differentiate between community- and hospital-acquired MRSA. Therefore we were unable to include this as a variable to stratify in our analysis. We do mention that future prospective studies that correlate genetic analyses with clinical outcomes would provide important insight into the pathophysiology of MRSA infections. 15. Those who were operated on potentially could have been healthier (as determined suitable/fit for surgery) Response: Thank you for this feedback. We agree with the reviewer that patients undergoing surgical intervention are likely healthier, and therefore the analysis is at risk for selection bias. We discuss this as a potential limitation that warrants further analysis in the future. Reviewer: Dr. B Foxman, University of Michigan Comments to the Author The authors conducted retrospective cohort study of Staphylococcus aureus bacteremia; mortality was the primary outcome. They have a large data set and the data are important. I would have liked more information on the time of follow-up in the cohort, and to have the analysis take into account time at risk. Response: Thank you for your feedback, and in response to the Reviewers' suggestions, we have included more details

	about the time of follow-up in the cohort and take into account time at risk by using Cox proportional hazards modelling for each of our outcomes. Abstract: 1. The introduction could be more informative, why is it challenging? Some of the information from the introduction of the manuscript might be usefully put here. Response: Thank you for the feedback. We have followed the recommendations of the reviewer and more clearly explained that S. aureus bacteremia is associated with increased morbidity and mortality, leading to the objectives of our current study. 2. The interpretation could be strengthened, what are the key take home messages? Why has mortality decreased with increasing prevalence of MRSA? Response: We have revised our interpretation section in the abstract to focus on the objective. Unfortunately word limits and space constraints prevent us from addressing the issue of decreased mortality within the abstract (although we discuss this in the main body of our manuscript).We hope this is acceptable to the reviewer. Introduction is very clear and informative. Response: Thank you for the feedback. We have made some modest revisions to the introduction to accommodate the valuable feedback from the other reviewers as well. We hope this is acceptable. Methods: 3. It is unclear if a recurrent SAB was included in the analysis more than once, or if only once what episode was selected. (p. 9 first paragraph). Response: Thank you for this comment. We included only the first episode of recurrent infection in the analysis, to preserve the assumption of independence of observations. We have included this statement in the methods section. 4. Please mention the length of follow-up per patient; was this defined? Response: Thank you for the comment. We have clarified that we conducted the chart review 6 months after the conclusion of the study period. Results: 5. P. 10 – First paragraph – did the authors mean that 39% of the SAB cases were caused by MRSA? I'm not clear what they mean by incidence, which would imply the number of new cases caused by MRSA. A similar comment with respect to sepsis. What was the definition of sepsis? In the methods it only refers to septic shock. Response: We have specified that sepsis and severe sepsis were defined according to standard methods, along with septic shock, soft tissue source, and intravascular catheter source. We agree with the reviewer that the term "incidence" may be subject to misinterpretation. Therefore, we have eliminated the term and revised our results to more

	clearly explain that 39% of the SAB cases were caused by MRSA, and that 69% of our study population developed sepsis. 6. p. 10 second paragraph – it might be easier to understand if the authors presented the average number of admissions for SAB per patient (presumably 1114/909?), then noted 205/909 had recurrences. I found the presentation here confusing, as I wasn't sure of either the denominator nor the risk period. Presumably the authors might be able to estimate the risk of adverse outcomes following initial admittance for SAB but that wasn't clear. Since these data are presented in Table 2, it should only be highlighted here. Response: Thank you for the feedback. We have revised our results section for improved clarity. Instead of presenting both the number of admissions and the number of patients, we have focussed only on the number of patients, and presented all the data as percentage of patients in the study. Since we only took the initial admission for patients with recurrent infections, presenting the data as a percentage of total patients in the study would be more accurate. As the reviewer has suggested, we have revised the results section to highlight and complement the results that are found in the Tables. Interpretation: 7. The first paragraph would be usefully revised to summarize major findings. Reponse: Thank you for the feedback. We have revised the first paragraph to summarize the major findings. Tables: 8. The titles of the tables are not complete. They should include the study population and study period. Further, the column headers could be more descriptive rather than 'Value' I would recommend N (%) for table 2, for example. Response: Thank you for the feedback. We have included the study population and study period for the tables. We have changed the column header to N (%) for Table 2. 9. Tables 3 & 4 should state what variables were included in the multivariate analysis. Response: We have revamped Tables 3 and 4 to show our Cox regression analyses for in-hospital, overall, and post-discharge 90-day mortality. The univariable and multivariable analyses for each of these outcomes have been included as Supplementary Tables. 10. Why is methicillin resistance not shown in Table 4? Response: Please see response to Question 9. Thank you. Reviewer: Dr. Rodica Gilca, Système de santé et de services sociaux Comments to the Author General comment: Given the important cost and resource use

	associated with MRSA, more details describing patients with MRSA would be useful for the readers. Response: We thank the reviewer for their comments. We do agree that MRSA is an important pathogen associated with significant cost and resources for its management. However, we feel that the description and analysis of patients with MRSA bacteremia would be beyond the scope of our current study, and would be best answered with a more specific analysis in a future study. Specific comments: Page 8, Study design and outcomes 1. Definition of overall mortality, particularly its post-discharge component, should be clarified. How long after discharge patients were followed-up? Was the follow-up available for all patients? These details are especially important for the 110 patients who deceased beyond 90 days of discharge. Response: Thank you for the comment. We have renamed overall mortality as all-cause mortality following recommendations of the previous reviewers. As per the previous reviewers we have also carefully described the post-discharge mortality component, indicating that all records were reviewed 6 months after the conclusion of the study period. 2. Since requirement for prolonged MV and length of hospital stay are only presented as variables included in regression models, authors might want deleting them from the list of secondary outcomes. Response: Thank you for this feedback. We have removed these from the secondary outcomes, and have left in-hospital, and 90-day post-discharge mortality as the secondary outcomes. 3. One may presume that patients were followed-up until the last day of the study (December 31, 2012), although this is not clear from the paper. If so, those admitted in the later period of the study had a shorter time of follow-up after discharge compared to patients admitted earlier. Consequently, patients who have the propensity to die earlier may be overrepresented. In addition, I am not sure patients who die at home or in other settings are accounted for. Survival analysis taking into account contribution of each patient to the time at risk for dying might be more appropriate for properly identifying factors associated with post-discharge mortality. Response: We have clarified that follow-up was as of August 2013, when the charts were reviewed. Survival analysis was performed by Cox regression analysis to account for the time at risk of dying. 4. Some variables included in the multivariable models (such as hepatic failure, liver disease, hepatitis C infection, table 3) might be correlated. Was the collinearity verified? Response: Only two variables were considered as collinear

	variables: hepatic failure and hepatitis C. However, since we used stepwise models for both the multivariable logistic regression and the proportional-hazards analyses, Hepatitis C was removed from the analyses. 5. Because of the substantial number of variables included in multivariate models, I am not sure all strata had sufficient observations. Presenting odds ratios for not significant variables in table 3 and 4 might reassure the reader. Response: Thank you for the feedback. We have revamped Tables 3 and 4 to reflect our survival analyses and present adjusted hazard ratios. The univariable and multivariable logistic regression models are presented as Supplementary Tables in the manuscript. Results 6. Table 1: Hepatitis B/C co-infection is listed under characteristic column; there is no separate row for hepatitis C and hepatitis B infection, although in table 3 hepatitis C and hepatitis B are presented as separate variables. This should be clarified. Response: Thank you for the feedback. We had combined proven Hepatitis B/C co-infection into one characteristic because of the low frequency of Hepatitis C. We have revised our analysis so that Hepatitis B or C co-infection was considered as one, rather than as separate variables. 7. Page 10, 1st paragraph: Suggest using the term "proportion" instead of "incidence" in relation to MRSA and to sepsis. Response: Thank you for the feedback. We have revised the results and the interpretation to remove the term "incidence." 8. Page 10, last paragraph: In addition to proportions, the reader might be interested to see trends in terms of incidence (per admissions or per patient-days, if available) of SAB, MRSA and MSSA. Response: We are unfortunately unable to ascertain the total number of hospital admissions between 2008 and 2012 because it was beyond the scope of our study. We agree this is a limitation to the data presented in our current manuscript. However, we aim to continue refining and cross-linking our database with other administrative and clinical databases for future studies, and we hope to provide this data in the future. We hope this is acceptable to the reviewer 9. Page 11, 1st paragraph: The text suggests that methicillin resistance is independently associated both with overall mortality and with in-hospital mortality. However, methicillin resistance is not listed in Table 4 presenting multivariable analysis of in-hospital mortality. Response: We have removed the suggestion that methicillin resistance is associated with in-hospital mortality. We also discuss the differences in contribution of MRSA to mortality in-hospital versus post-discharge in our interpretation section. 10. Interpretation, 1st paragraph: Use of wording

	"incidence" in the context of the study is questionable. Response: We agree with the reviewer. As mentioned previously, we have removed the term "incidence" because of the potential for misinterpretation. 11. Page 12, first line: mentioning implementation of infection control strategies to prevent the spread of SAB is confusing when the paper reports increase in MRSA proportion and does not mention SAB incidence. Response: Thank you for the feedback. In our hospital, strategies were implemented to specifically reduce all S. aureus infections (MRSA and MSSA). Since the focus of our study was primarily on bacteremia, we do not have information on outcomes for non-bacteremic S. aureus infections (such as skin infections for example). Consequently, we can only explain the trends we observe with respect to S. aureus bacteremia. Given that we do not have calculated incidences of S. aureus bacteremia during the study period, we are only able to comment on the effect of the infection-control strategies in the context of in-hospital mortality reduction from S. aureus bacteremia. We hope this is acceptable to the reviewer. 12. Page 12, lines 40-47: Post-discharge mortality, particularly beyond 90 days and in patients admitted in 2008 may add up to almost 5 years of follow-up. It is hard to believe that in a population with an important proportion of comorbidities mortality is attributable only to long-term consequences from SAB. Response: We agree with the reviewer. As such, we re-evaluated the risk factors for patients who died within 90 days post-discharge, rather than analyze all patients who died post-discharge. We have accordingly changed our results and interpretation, and we thank the reviewer for their feedback. A future study that uses a propensity-matched analysis across a large provincial clinical and administrative database may provide additional insight into testing the hypothesis that SAB does increase long-term mortality. 13. Page 13, lines 42-44: Diabetes and malignancy (cancer) are given as examples for differences between comorbidities associated with mortality and with the acquisition of SAB. However, they are listed under both mortality and acquisition of SAB risk factors. Response: Thank you for the comment. We have modified our statement to emphasize that, while there are some similarities between risk factors associated with the acquisition and mortality from SAB, the differences suggest that not all comorbidities are alike in their contribution to mortality. Further analyses combined with molecular analyses of the strains may provide additional insight into the pathophysiology of S. aureus. 14. Page 13, lines 47-49: the statement about interaction between patient-specific factors and pathogen virulence should be clarified. Response: Thank you for this comment. We specified that

	future prospective studies that analyze genetic and molecular evaluation of S. aureus, and correlate it with clinical variables and outcomes, would provide additional insight into the pathophysiology of S. aureus and its impact on specific population subgroups.