**Title**

Mortality in intensive care – the impact of bacteremia and the utility of SIRS.

## Abstract

*Objective*

To determine the impact of bacteraemia on ICU mortality and develop a bacteremia prediction tool using Systemic Inflammatory Response Syndrome (SIRS) criteria.

*Participants*

Patients aged >18 who had blood cultures taken in the ICU 1st January 2011-31st December 2013.

*Design*

All patients meeting the above criteria were identified from microbiology department records of Glasgow Royal Infirmary, Scotland. Clinical and outcome data were gathered from ICU records. Patients with clinically significant bacteraemia were matched to controls using propensity scores. SIRS criteria were gathered and used to create decision rules to predict the absence of bacteraemia.

*Main outcome measures*

Mortality at ICU discharge. Sensitivity and accuracy of prediction of blood culture status by SIRS decision rule.

Results

One hundred patients had a clinically significant positive blood culture and were matched to 100 controls. Bacteraemic patients had higher ICU mortality (OR 2.35 p=0.001) and longer ICU stay (17.0 vs. 7.8 days, p=<0.001). Of 1548 blood culture episodes, 1274 met ≥2 SIRS criteria (106 significant positive cultures, 1168 negative cultures). There was no association between SIRS criteria and positive blood cultures (p=0.11). A decision rule using three SIRS criteria had optimal predictive performance (sensitivity 56%; specificity 50%) but had low accuracy.

*Conclusion*

ICU patients with bacteraemia have increased mortality and length of ICU stay. SIRS criteria cannot be used to identify patients at low risk of bacteraemia.

## Keywords

Intensive care; Bacteraemia; Mortality; Length of Stay; SIRS; Decision Support Techniques.

## Introduction

Bacteraemia accounts for around 15% of all intensive care unit (ICU) infections [1]. Its most serious manifestation, septic shock, has a mortality of up to 70% [2]. There are conflicting reports in the literature concerning the outcomes of ICU patients with bacteraemia; for example, a Canadian study demonstrated that patients presenting to the ICU with bacteraemia did not have increased mortality compared to those without (OR 1.1 95% CI 0.7-1.8) [3]. This contrasts with studies by Prowle et al and Lambert et al which found that bacteraemia was independently associated with an increase in mortality rate in ICU patients of three and two-four fold respectively [4,5]. Accurate diagnosis and management of a sepsis episode is vital in order to reduce mortality and improve antimicrobial stewardship efforts.

Blood cultures are the current gold-standard for detecting bacteraemia [2]. Collection of diagnostic information from blood cultures must be balanced with appropriate testing intervals and frequency to maximize the accuracy and usefulness of the procedure [6]. Obtaining and processing blood cultures that are frequently negative increases the risk of false-positive results, which may lead to increased patient length of stay, exposure to inappropriate antimicrobials and increased laboratory time and costs [6,7]. Untreated bacteraemia, however, leads to septic shock and positive blood cultures allow rationalization of empiric antimicrobial therapy [8]. The ability to simply and accurately assess the risk of bacteraemia would be useful when deciding whether to take blood cultures. Previous work has indicated that the Systemic Inflammatory Response Syndrome (SIRS) is a sensitive indicator of the presence of bacteraemia in general medical patients [3,9,10].

The aim of this study was to investigate the mortality of ICU patients with bacteraemia and the relationship between SIRS status and blood culture status in ICU patients.

## Materials and methods

### Study setting and population

This study was conducted in Glasgow Royal Infirmary, a tertiary referral hospital Scotland with a 20 bed mixed medical/surgical ICU that admits approximately 1,200 patients annually. All blood cultures taken in patients aged ≥18 years old between 1st January 2011 and 31st December 2013 were included. Eligible patients were identified from microbiology laboratory records. The retrospective, non-interventional nature of this study meant that Research Ethics approval was not required.

#### Data analysis

##### ICU based data

The following variables were collected about patients: age, gender, APACHE II score, admitting specialty (medical vs. surgical), result of blood culture, organism(s) isolated and length of ICU and total hospital stay.

##### SIRS data collection

The number of SIRS criteria a patient met at the time of each blood culture episode was recorded and episodes were assigned a score from 0-4 depending of the number of criteria met. SIRS criteria were defined as those established by Bone et al for the Society of Critical Care Medicine/American College of Chest Physicians (see Table 1) [11]. Patients were also classified by severity of infection at the time of their first positive blood culture according to the criteria in Table 1. Each blood culture episode was defined as a 48-hour period beginning when a blood culture was drawn. Additional blood cultures drawn within these 48 hours were considered part of the initial episode. If additional cultures were drawn after 48 hours had passed, this was considered a new episode and the number of SIRS criteria met was recorded again.

*Table I: Details of the systemic inflammatory response syndrome criteria and different severity of infection based on this, as described by Bone et al. [11]*

| **Syndrome** | **Clinical signs** |
|---|---|
| SIRS | *Two or more of the following:* |
| | Heart rate >90 bpm |
| | Respiratory rate >20 breaths per minute *or* $PaCO_2$ <4.3kPa. |
| | Temperature <36°C/>38°C |
| | White cell count $<4x10^9$/L/$>12x10^9$/L |
| Sepsis | Two SIRS criteria due to infection |
| Severe sepsis | Sepsis with evidence of organ dysfunction |
| Septic shock | Severe sepsis with hypotension not responsive to fluid resuscitation |

Mortality data

The mortality difference between bacteraemic and non-bacteraemic patients was analysed at ICU discharge, hospital discharge and 90 days post ICU admission. Length of stay comparison was done using only surviving patients and calculated for ICU stay and total hospital stay.

Microbiology laboratory data

Positive blood cultures were assessed for clinical significance by the researcher collecting the data. In line with previous studies, gram-negative organisms were considered to represent clinically significant infection [12] and single isolates of coagulase-negative staphylococci*, Propionibacterium acnes* and *Corynebacterium* species were classified as contaminants [13–15]. Multiple isolates of these organisms or other common skin commensals were reviewed by a clinical microbiologist and, taking into account diagnosis and clinical course, were subsequently classified as representing contamination or clinically significant infection. Generally, isolates commonly representing contamination were only considered significant if isolated from two or more consecutive cultures taken on

different days and with a clinical history consistent with infection. A patient who had a true positive blood culture at any point in their ICU stay was classified as bacteraemic.

Statistical analysis

Two-sided p-values of <0.05 were considered significant for all comparisons. Calculations were done using *SPSS* version 22.0 (IBM, New York, United States). Bacteraemic patients were matched to negative controls on a one-to-one ratio using propensity scoring in R *(*R Foundation for Statistical Computing, Vienna, Austria) with the optimal matching method. Propensity scoring is a method whereby baseline covariates are assigned a numerical value with the summation of the values of all baseline covariates being the propensity score for a given individual. Thus a set of subjects with the same propensity score will have equal distribution of baseline coavariates [16,17]. Controls were matched to positive patients based on who had the closest propensity score. In the optimal match method, this is done so as to produce the smallest total difference of propensity scores between the entire matched and control cohorts [17]. Controls were matched based on four variables identified from a Delphi process of intensive care consultants: age, APACHE II score, gender and admitting specialty. Continuous variables were compared using Student's *t*-test or the Mann-Whitney U test. Categorical variables were compared using the chi-square test. The odds ratio (OR) of death in bacteraemic compared to negative patients was calculated using logistic regression. Survival at 90 days post ICU admission was also compared using Kaplan-Meier curves. The chi-square test was used to test for association between meeting the criteria for SIRS and positive blood culture episodes. To

assess the ability of SIRS status to predict blood culture outcome, a series of decision rules were created with each sequential level of SIRS criteria bring set in turn as a cut-off point to consider that episode as 'likely to be positive' or 'unlikely to be positive' with these classifications subsequently compared to actual blood culture results for each level of SIRS criteria. Sensitivity and specificity of each level of SIRS criteria were calculated.

**Results**

Between January 1st 2011 and December 31st 2013, 2819 patients were admitted to the ICU of which 813 had at least one blood culture taken.

One or more microorganisms were isolated from the cultures of 165 patients (20.3%), of which 100 (12.3%) were determined to be clinically significant. Clinical and demographic characteristics of patients are detailed in Table 1. Compared to patients with negative blood cultures, patients with clinically significant bacteraemia were more likely to have been admitted to the ICU from a surgical specialty and had a higher mean APACHE II score.

*Table II: Comparison of demographic and clinical data between bacteraemia-positive and bacteraemia-negative patients*

| **Variable** | **Bacteraemic patients n=100** | **Negative patients n=713** | **P-value** |
|---|---|---|---|
| | | | |
| Male sex | 58 (58%) | 420 (58.3%) | 0.863 |
| Mean age | 56.2±14.6 | 57.6±15.9 | 0.429 |
| Medical admission | 33 (33%) | 343 (48.1%) | 0.006 |
| APACHE II score | 22.1±8.2 | 19.9±7.4 | 0.006 |
| *Infective status* * | | | |
| Infected | 1 (0.9%) | - | - |
| Sepsis | 14 (14%) | - | - |

| | | | |
|---|---|---|---|
| Severe sepsis | 50 (50%) | - | - |
| Septic shock | 40 (40%) | - | - |

*At time of index positive blood culture according to criteria defined by Bone et al [11]

Details of microorganisms isolated from positive blood cultures are summarised in Table 2. The most common isolates were *Enterococcus* species (n=49, 23%), *Escherichia coli* (n=46, 21%) and clinically significant coagulase-negative staphylococci, where it represented clinically significant infection (n=24, 11%).

*Table III: Clinically significant microorganisms isolated from positive blood cultures*

| | |
|---|---|
| **Gram Positive** (n=110) | |
| *Staphylococcus aureus* | 31 |
| Coagulase-negative staphylococci | 24 |
| *Enterococcus* spp. | 49 |
| *Streptococcus pneumoniae* | 1 |
| | |
| *Streptococcus* spp. (*S. anginosus* & *S. mitis* groups) | 2 |
| *Clostridium* spp. | 2 |
| *Bacillus* spp. | 1 |
| | |
| **Gram negative** (n=89) | |
| *Escherichia coli* | 46 |
| *Klebsiella* spp. | 12 |
| Other enteric gram-negative rods | 25 |
| Gram-negative anaerobes | 6 |
| | |
| **Yeasts** (n=18) | |
| *Candida albicans* | 12 |
| Other Candida species | 5 |
| Other yeasts | 1 |

| | |
|---|---|
| Total | 217 |

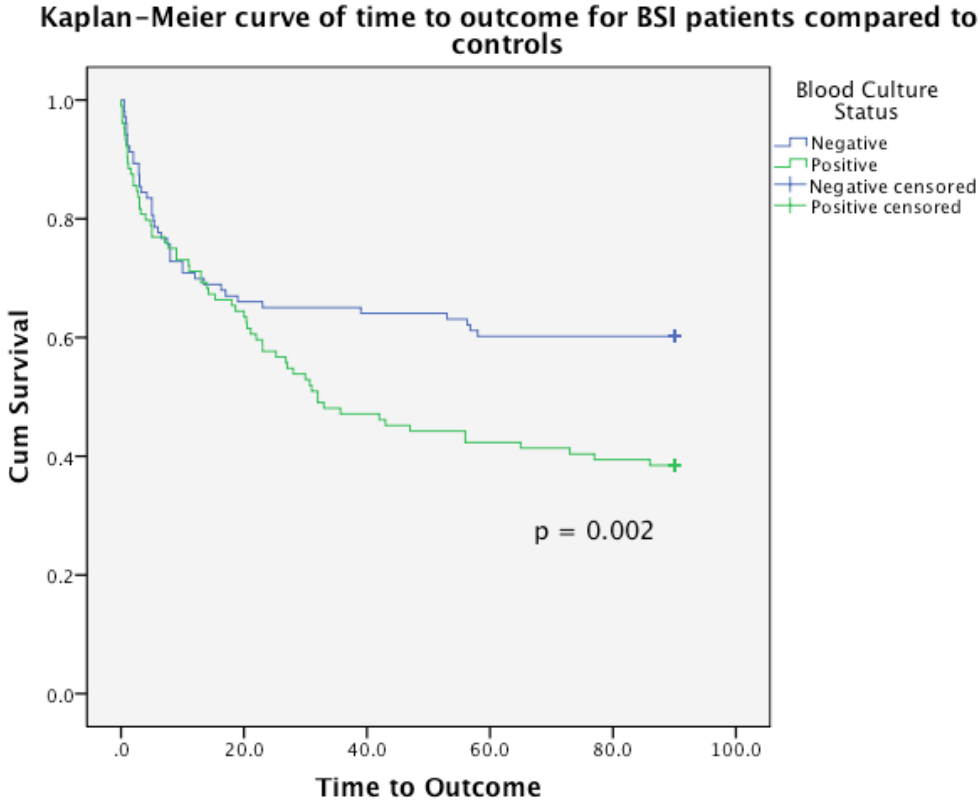
Patients with a significant bacteraemia were assigned and matched to 100 negative controls. The data in Table 3 details the mortality and length of stay for all patients in the study. After excluding patients who died, those with bacteraemia had a longer ICU stay than controls (median time 17.0 vs. 7.8 days, p=<0.001) as well as a longer total hospital stay (median time 49.5 vs. 22.1 days, p=0.05). Compared to matched controls, bacteraemic patients had a higher risk of mortality at ICU discharge (OR 2.35 (95% CI 1.45-3.83), p=0.001) and at hospital discharge (OR 2.70 (95% CI 1.67-4.34), p=<0.001). Seven patients (3.5%) had an ICU stay longer than 90 days of which two (both bacteraemic) were discharged alive. Fifteen patients (7.5%) had a total hospital stay longer than 90 days of which 11 were discharged alive (two negative, nine bacteraemic). At 90 days follow-up, patients with bacteraemia had reduced survival with analysis using Kaplan-Meier curves (figure I) demonstrating this difference occurs primarily between 20 and 40 days post ICU admission. An analysis with bacteraemic patients stratified into Gram positive, Gram negative, polymicrobial and fungal cohorts did not demonstrate increased mortality at any point compared to controls for any of these individual groups.

| | All patients n=813 | Bacteraemic patients n=100 | All negative patients n=713 | P-value |
|---|---|---|---|---|
| **Mortality** | | | | |
| At ICU discharge | 215 (26.4%) | 42 (42.0%) | 173 (24.3%) | <0.001 |
| At hospital discharge | 262 (32.2%) | 52 (52.0%) | 210 (29.5%) | <0.001 |
| 90 days | - | 64 (64.0%) | 41 (41.0%)* | <0.001* |
| **Median length of stay (days)** | | | | |

| | | | | |
|---|---|---|---|---|
| ICU | 7 (3-14) | 17 (5.7-30.8) | 6.8 (3-13) | <0.001 |
| Total hospital | 20 (11-46) | 49.5 (33.3-75.2) | 20 (11-36.5) | 0.004 |
| *only negative patients selected as matched to positives | | | | |

*Table IV: Comparison of mortality and length of stay between bacteraemia-positive patients and matched controls*

*Figure I: Kaplan-Meier curve comparing survival analysis to 90 days in patients with bacteraemia to matched controls*




Descriptive data for blood cultures and relationship to SIRS status is detailed in Table 4. A total of 1548 blood culture episodes were recorded in the study period: 124 (8.1%) were true positive, leaving 1424 (including contaminants; 91.9%) classified as negative. One-hundred-and-six (84.8%) positive episodes met at least two SIRS criteria as did 1168 (81.2%) negative episodes. There was no association

between meeting ≥2 SIRS criteria and the result of a blood culture episode (p=0.109).

*Table V: Breakdown of the number of blood culture episodes and the performance the decision rule by different levels of SIRS criteria for all blood culture episodes*

| | | | |
|---|---|---|---|
| Blood culture episodes | | 1548 | |
| Blood cultures | | 2738 | |
| True positive | | 242/2738 (8.8%) | |
| Contaminant | | 212/2738 (7.7%) | |
| Negative | | 2284/2738 (83.4%) | |
| Blood culture sets/episode | 1 | 807 (52.1%) | |
| | 2 | 347 (22.4%) | |
| | 3 | 342 (22.1%) | |
| | >4 | 53 (3.4%) | |
| Indication | Pyrexia | 786 (50.8%) | |
| | Inflammation* | 180 (11.6%) | |
| | Sepsis† | 303 (19.6%) | |
| | Other | 77 (5%) | |
| | Unclear | 197 (12.7%) | |
| | | | |
| SIRS criteria by episode type | | Positive | Negative |
| SIRS | 4 | 17 (13.6%) | 208 (14.6%) |
| | 3 | 51 (40.8%) | 505 (35.5%) |
| | 2 | 38 (30.4%) | 455 (32.0%) |
| Non-SIRS | 1 | 11 (8.8%) | 191 (13.4%) |
| | 0 | 7 (5.6%) | 65 (4.6%) |

* Defined as raised C-reactive protein or white cell count.

† Includes suspected sepsis or focal infection

Using a decision rule that required two SIRS criteria to be present before ordering blood cultures in order to model prediction of positive blood culture status created an 'unlikely to be positive' cohort of 274 (17.7%) episodes. This rule had a sensitivity of 87%, a specificity of 18% and would have prevented 256 (18%) negative episodes (272 blood cultures) but missed 18 (13%) positive episodes (31 blood cultures, 18 patients). A decision rule requiring three SIRS criteria was identified from a ROC curve as providing optimal trade-off between sensitivity (56%) and specificity (50%) and created an 'unlikely' cohort of 767 (49%) episodes. This would have prevented 708 (49.7%) negative episodes (1172 blood cultures) with 59 (47%) positive episodes (108 blood cultures, 52 patients) missed. One and four criteria rules had a sensitivity of 95% and 15%, prevented 65 (4%) (90 cultures) and 1208 (78%) (2064 cultures) and missed 7 negative episodes (0.4%) (15 cultures, 7 patients) and 115 (92%) (229 cultures, 90 patients) positive episodes respectively. No level of SIRS criteria significantly increased the odds of a blood culture episode being positive.

## Discussion

This study has demonstrated that bacteraemia increases mortality and length of stay among survivors compared to matched controls in a general ICU population. Several other authors have also investigated this, with some finding that bacteraemia does not increase mortality [3,14,18] and others concluding it does [4,5,19]. This may be because the observed impact of bacteraemia varies with study population and setting. By using propensity scoring to assign controls and by including all patients with bacteraemia, we tried to avoid these limitations. Due to the difficulty in establishing where an infection was acquired, we did not stratify analysis by community and nosocomial acquired infection. The use of propensity scores helped account for likely confounders of mortality differences between cohorts. Our primary aim was to determine whether bacteraemia, specifically, increases ICU patient mortality after controlling for confounders, not to identify predictors of mortality

amongst patients who have blood cultures taken. For these reasons a multivariate analysis to identify independent predictors of mortality was not done.

Subgroup analysis of mortality by gram stain result or specific organisms would be desirable to show that some bacteraemias are likely more severe than others. When bacteraemic patients were divided into sub-cohorts based on gram stain results, no cohort demonstrated a statistically significant increase in mortality compared to controls. This is probably because there were not sufficient numbers in each cohort to allow a small increase in mortality to be demonstrated. Because of this, analysis by individual organism was not performed.

Survival analysis showed that survival in the two cohorts was similar until the 20$^{th}$ day of ICU stay. In our analysis we did not match controls based on length of stay prior to bacteraemia. This was because matching factors were identified prospectively using a Delphi process, in which length of stay prior to infection was not identified. Furthermore, we were careful to avoid 'overmatching'; trying to match controls based on too many variables, as this runs the risk of not being able to match controls for all cases. Length of stay prior to infection however, may be an important confounder to our results as it is possible that patients with increased length of stay are more severely ill and this puts them at increased both of acquiring nosocomial bacteraemia and death.

In the bacteraemic cohort 90 patients (86%) met severe sepsis/septic shock criteria, which are known independent risk factors for death in ICU [20]. Our controls were not matched with respect to sepsis severities; it is possible the increased mortality observed may be due to a greater number of severely septic/shocked patients in the bacteraemic cohort.

Whilst others have also investigated the mortality of ICU bacteraemia, our findings are nonetheless valuable. Because the United Kingdom has the smallest number of

ICU beds/population in developed world [21] a smaller percentage of the hospital population will accommodated there and as such may be sicker at baseline and more susceptible to the effects of bacteraemia. Previous investigations have predominantly taken place outside the UK [7,15,18] or have been limited tonosocomial acquired infection [5,19] or specific organisms [4] and thus their results may not be applicable to this population. These results, including all patients with bacteraemia in a general ICU population provide up-to-date knowledge of the impact bacteraemia. This is crucial to allow better prognostication and highlights bacteraemia treatment as a crucial therapeutic aim.

We also investigated the relationship between SIRS status and blood culture result, as prior work in the non-ICU [3,9,10] setting has suggested that the presence of SIRS is closely linked with bacteraemia and as such might be utilised to be used to predict the presence of bacteraemia and thus avoid unnecessary blood cultures in patients who are unlikely to be bacteraemic [6].

A blood culture decision rule should either be able to identify most negative patients whilst not missing any positives (good sensitivity and high specificity) or be highly sensitive (exclude most negative patients). No decision rule in our results performed adequately for clinical practice: three criteria provided optimal sensitivity and specificity trade-off, but missed too many positives; two criteria had a higher sensitivity (86%) and would have resulted in a respectable reduction in negative blood cultures but still missing 11 bacteraemic patients. Given the consequences of missing a bacteraemic episode we feel this is still too high. Analysing SIRS criteria was a secondary aim of this study and intended to investigate, in ICU patients, specific claims that SIRS criteria can be used as a decision rule about when to order blood cultures. We did not aim to identify all factors predictive of blood culture status and so multivariate analysis was not performed.

The poor ability of SIRS to predict blood culture status in the ICU is probably because ICU patients are exposed to a wider range of SIRS causing stimuli than other patients. The advantages of being able to predict the blood culture status of patients are clear, in particular the ability to reduce the number of ultimately negative cultures drawn would save money and reduce the risks to patients posed to by contaminant blood cultures. SIRS would have provided a simple, well-known basis for such a decision rule to be based upon.

Limitations of this study include the single centre study design – Glasgow Royal Infirmary is a tertiary referral centre for pancreatitis and burns patients, both of which frequently require intensive care admission - therefore our results may not be generalizable to other centres. No data were collected on antimicrobial therapy. Both initially receiving inappropriate antimicrobials and a delay in receiving appropriate antimicrobials have been shown to increase mortality in patients with bacteraemia [15,22] – it is possible this could have confounded our assessment of mortality. Finally, although a small number of initially positive isolates were of questionable clinical significance, no inter-reliability testing was performed between investigators when classifying isolates as contamination vs. clinically significant. It is possible some isolates were thus misclassified, which may have affected the observed impact of bacteraemia in the clinically significant group.

## Conclusions

This study helps clarify the contradictions regarding impact of bacteraemia on mortality and length of stay of ICU patients that exists within the literature by using propensity scoring to provide more evidence that bacteraemia increases mortality in ICU patients. It also refutes the suggestion that SIRS criteria could be used to predict blood culture status.

## Acknowledgements

We gratefully acknowledge the technicians in the microbiology laboratory of Glasgow Royal Infirmary for their help and assistance in gathering data from microbiology records.

## Conflict of interest statement

No conflicts of interest were declared by any of the authors of this manuscript.

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