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Intensive care unit (ICU)-acquired bacteraemia and ICU mortality and discharge: addressing time-varying confounding using appropriate methodology

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SUMMARY

Background: Studies often ignore time-varying confounding or may use inappropriate methodology to adjust for time-varying confounding.

Aim: To estimate the effect of intensive care unit (ICU)-acquired bacteraemia on ICU mortality and discharge using appropriate methodology.

Methods: Marginal structural models with inverse probability weighting were used to estimate the ICU mortality and discharge associated with ICU-acquired bacteraemia among patients who stayed more than two days at the general ICU of a London teaching hospital and remained bacteraemia-free during those first two days. For comparison, the same associations were evaluated with (i) a conventional Cox model, adjusting only for baseline confounders and (ii) a Cox model adjusting for baseline and time-varying confounders.

Findings: Using the marginal structural model with inverse probability weighting, bacteraemia was associated with an increase in ICU mortality (cause-specific hazard ratio (CSHR): 1.29; 95% confidence interval (CI): 1.02–1.63) and a decrease in discharge (CSHR: 0.52; 95% CI: 0.45–0.60). By 60 days, among patients still in the ICU after two days and without prior bacteraemia, 8.0% of ICU deaths could be prevented by preventing all ICU-acquired bacteraemia cases. The conventional Cox model adjusting for time-varying confounders gave substantially different results [for ICU mortality, CSHR: 1.08 (95% CI: 0.88–1.32); for discharge, CSHR: 0.68 (95% CI: 0.60–0.77)].

Conclusion: In this study, even after adjusting for the timing of acquiring bacteraemia and time-varying confounding using inverse probability weighting for marginal structural

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models, ICU-acquired bacteraemia was associated with a decreased daily ICU discharge risk and an increased risk of ICU mortality.

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Introduction

Nosocomial bacteraemia is a potentially life-threatening condition that is estimated to affect 240,000 people in Europe annually [1]. Patients in intensive care units (ICUs) are at especially high risk of acquiring bacteraemia due to frequent invasive healthcare interventions [2].

Estimating the health impact and cost per case is essential to enable health economic evaluations comparing different interventions, to determine cost-effective options and to determine justified level of investment in control. Many studies have estimated the potential impact of ICU-acquired bacteraemia on mortality and discharge [2–12]. Nevertheless, the effect of ICU-acquired bacteraemia on mortality and length of stay is still uncertain [11]. Part of the variation in estimates may be explained by differences in case-mix, quality of care and antimicrobial resistance rates. However, there are also various methodological issues that may impact estimates and are often overlooked. The fact that ICU-acquired infections have a time-dependent nature has often been ignored. For instance, comparisons of ever-infected versus never-infected patients may ignore that patients need to survive long enough in order to acquire infection, thus giving an apparent survival benefit to the ever-infected patients [13]. Time-dependent exposures may be modelled using time-dynamic models, such as time-dependent survival or multi-state models [13].

However, even when using time-dependent survival or multi-state models, assessment of the infection effect may be biased due to confounding by severity of illness. Adjusting for all confounders measured at the time of ICU admission may not be sufficient, as patients who develop bacteraemia may deteriorate further, prior to bacteraemia, than patients who stay bacteraemia-free. The aforementioned techniques for time-dependent exposures fail to adjust correctly for such time-dependent confounding [14,15]. They eliminate the effect of infection that is mediated through later severity of illness, thus potentially wiping out all of the infection's effect. Moreover, they induce a so-called collider-stratification bias which may induce artificial correlations between infection and mortality, even in the absence of an effect (Appendix 1) [16]. To accommodate this, our study has made use of inverse probability-weighted methods for marginal structural models [17].

A further factor that may complicate interpretation occurs due to the fact that patients who stay longer in the ICU are at greater cumulative risk of death. For example, even if bacteraemia does not influence the daily risk of dying, one may still observe an apparent increase in cumulative mortality if infection increases length of stay. This issue can be solved by estimating the effect on the cumulative incidence of ICU death [18,19].

Aforementioned methodological challenges are rarely addressed simultaneously in published studies [3]. We will add

to the literature by simultaneously controlling for all three factors that complicate analysis: (i) the time-varying nature of the exposure; (ii) potential time-varying confounding; (iii) the presence of competing risks. We evaluate the effect of ICU-acquired bacteraemia on mortality and discharge using the R statistical package 'ipw' under marginal structural models and compare our results with estimates obtained using traditional regression methodology that ignores complicating factors.

The UK government recently published its ambition to reduce the incidence of healthcare-associated Gram-negative bacteraemia by 50% by 2020 [20]. It is important to quantify the health and economic burden of Gram-negatives to estimate justified levels of investment in their control, allowing cost-effectiveness evaluations of local and national interventions.

Hence, we also evaluated the effect of bacteraemia involving Gram-negatives.

Methods

Electronic clinical records of all patients admitted to two general ICU wards at Guy's and St Thomas' hospitals, London, between 2002 and 2006 were obtained [12,21].

All patients with an ICU length of stay of more than two days were included. From this cohort, we excluded patients with bacteraemia occurring during the first two days in the ICU, as these were assumed not to be ICU-acquired [2–12].

The following variables were recorded at ICU admission: age, gender, type of admission (surgical or medical), and ICU ward. The Acute Physiology And Chronic Health Evaluation (APACHE) II score, administration of antibiotics, mechanical ventilation, central lines, and renal replacement therapy were recorded on a daily basis during the entire ICU stay. All these variables were considered potential confounders based on clinical considerations and the literature.

Marginal structural model with ipw

Cause-specific hazard ratios (CSHRs) for ICU mortality and discharge were obtained using marginal structural Cox regression models, fitted using ipw to adequately take into account that the history of severity of illness may be different between patients who do and do not acquire bacteraemia. To adjust for confounders, a pseudo-population was constructed in which there was no longer confounding by the considered time-dependent variables. This was achieved by reweighting patients in the risk set (those who were still present in the ICU and were bacteraemia-free) on each day [17]. Hence, by giving more weight to patients that do acquire bacteraemia on a specific day despite being unlikely to acquire bacteraemia due to their history of severity of illness and vice versa, an artificial population is created in which the measured confounders (severity of illness) are independent of bacteraemia. The conditional probabilities used in the construction of the weights were set to 1 from the time of bacteraemia and

onwards, and were otherwise estimated based on a pooled logistic regression model for the probability of acquiring bacteraemia in the ICU (Appendix 2).

The obtained probabilities were used to generate daily patient-specific weights. When using these weights, the analysis can become heavily dependent on a single or few individuals who acquire bacteraemia despite having a very low predicted probability to acquire bacteraemia or vice versa, thereby resulting in very large standard errors. To overcome this problem, stabilized weights were calculated by multiplying the generated weights by the product of the conditional probability of the observed infection status before that day, as obtained from a similar pooled logistic regression model that included only baseline covariates; these same covariates were included in the marginal structural model [22].

The marginal structural models were fitted using weighted Cox regression with robust standard errors. To evaluate the effect of ICU-acquired bacteraemia a time-varying binary indicator was included whether or not bacteraemia was acquired at or before the considered time, as well as the baseline covariates used for stabilization of the weights [21]. The latter is necessary, because the stabilized weights create a pseudo-population in which there may still be confounding by the variables used for stabilization [22].

In the marginal structural model for ICU death (ICU discharge), the competing event ICU discharge (ICU death) was handled as a censoring event, resulting in CSHRs. The two cause-specific models for ICU discharge and ICU death were subsequently combined to estimate, for each patient at each time, the cumulative incidence of ICU death in the absence of bacteraemia (R code in Appendix 3). By comparing this cumulative incidence with the observed incidence, the number of ICU deaths that could be prevented was estimated. Our approach is different from multi-state approaches that ignore (time-dependent) confounding, and therefore is less biased when such confounding is present [23].

Although there were no missing values at baseline, in 3.8% of the following days missing values for the APACHE II score were imputed using the last observation carried forward.

All models were built using R version 3.2.1 (packages ‘ipw’, ‘splines’, ‘survival’) [24].

Comparison with conventional Cox models

In subsequent analyses a comparison was made with two frequently applied, but potentially biased, approaches: (i) a Cox model ignoring potential confounding by risk factors that change over the course of the ICU stay, thus only adjusting for baseline confounders; and (ii) a Cox model regressing on baseline and time-varying factors (Appendix 4).

Comparison of Gram-negative and -positive bacteraemia

The effect of bacteraemia involving Gram-negatives was also evaluated. To obtain such estimates, without having to condition on a time-varying factor that is measured after the start of follow-up, we jointly modelled the probability of bacteraemia and the probability that the bacteraemia involved Gram-negatives.

Table I
Baseline patient characteristics and crude length of stay and mortality rates for admissions during which ICU-acquired bacteraemia developed vs did not develop

Variable	Admissions during which bacteraemia developed (N = 671)	Admissions during which bacteraemia did not develop (N = 2488)
Male sex	434 (64.7%)	1483 (59.6%)
Age (years), mean (SD)	61.8 (15.52)	60.8 (17.30)
APACHE II score, mean (SD)	19.1 (6.42)	18.0 (6.45)
Admission type		
Medicine	402 (59.9%)	1521 (61.1%)
Surgery	269 (40.1%)	967 (38.9%)
ICU length of stay, median (Q1, Q3)	21 (13, 34)	6 (4, 9)
ICU mortality	208 (31.0%)	444 (17.8%)

ICU, intensive care unit; SD, standard deviation; APACHE II, Acute Physiology And Chronic Health Evaluation II.

To obtain the inverse probability weights for this analysis, the weights previously estimated for any bacteraemia were multiplied, from the time of acquiring bacteraemia onwards, by the stabilized inverse conditional probability that the bacteraemia involved Gram-negative bacteria, given the time-varying confounders on the previous day (Appendix 2).

The CSHR for ICU mortality and discharge were subsequently obtained using marginal structural Cox regression models. Compared to the analysis modelling ‘any bacteraemia’, an additional interaction between the indicator for bacteraemia and a binary indicator for the type of pathogen involved (Gram-negative set to 1) was incorporated. To obtain the effect of Gram-negative or -positive bacteraemia, these parameter estimates were combined and confidence intervals were calculated using the Delta method.

To further investigate whether potential differences between bacteraemia caused by Gram-negative or Gram-positive bacteria would be likely due to the inclusion of contaminated blood samples, particularly relevant for coagulase-negative staphylococci (CNS), we further stratified the analyses for Gram-positive bacteria into three groups: *Staphylococcus aureus*, CNS, and other Gram-positives [3].

Results

Between 2002 and 2006, 2914 patients were admitted to either ICU, contributing 3159 ICU admissions. In 21.2% of admissions (N = 671), a first blood culture positive for any bacteria was obtained from the patient more than two days after ICU admission. Of those ICU-acquired bacteraemia cases, 218 (32.5%) involved Gram-negative bacteria, whereas 493 (73.5%) involved Gram-positive bacteria.

The main isolated Gram-negative bacteria were *Pseudomonas* spp. (N = 68), *Escherichia coli* (N = 43), *Enterobacter*

Table II

Association between ICU-acquired bacteraemia and ICU mortality and discharge

Adjustment	ICU mortality CSHR (95% CI)	ICU discharge CSHR (95% CI)
Adjustment for baseline variables only	1.28 (1.04–1.57)	0.51 (0.45–0.58)
Adjustment for baseline and time-varying variables using conventional Cox model	1.08 (0.88–1.32)	0.68 (0.60–0.77)
Adjustment for baseline and time-varying variables using marginal structural model with inverse probability weighting	1.29 (1.02–1.63)	0.52 (0.45–0.60)

CI, confidence interval; CSHR, cause-specific hazard ratio; ICU, intensive care unit.

spp. ($N = 41$), *Klebsiella* spp. ($N = 26$), and *Proteus* spp. ($N = 17$). Isolated Gram-positive bacteria were mainly CNS ($N = 370$), *S. aureus* ($N = 69$) and *Enterococcus* spp. ($N = 52$). Median time from ICU admission to bacteraemia onset was eight days (25th–75th percentile: 6–13).

Baseline patient characteristics are shown in Table I. Patients acquiring bacteraemia were more frequently male and had a slightly higher APACHE II score at admission.

Marginal structural model with ipw

To adequately address time-varying confounding, we used marginal structural models fitted using ipw. ICU-acquired bacteraemia was associated with the daily risk of ICU mortality (CSHR: 1.29; 95% confidence interval (CI): 1.02–1.63) (Table II). More detailed descriptions of the models used for each component of the analysis are provided in Appendix 1.

ICU-acquired bacteraemia was associated with a lower daily risk of ICU discharge (CSHR: 0.54; 95% CI: 0.47–0.62).

The inverse probability weights used in these marginal structural models had a median and mean of 0.99 and 1.01, an interquartile range and standard deviation of 0.14 and 0.31 (range: 0.26–4.49). These values raise no concern that our results might be negatively affected by extreme weights [25].

The observed cumulative incidence of ICU death in the patient cohort and the expected cumulative incidence of ICU death if all ICU-acquired bacteraemia episodes would be prevented are shown in Figure 1: by 60 days, among patients still in the ICU after two days and without prior bacteraemia, 8% of ICU deaths could be prevented by preventing all ICU-acquired bacteraemia cases.

Comparison with more conventional Cox models

Using conventional Cox regression, ICU-acquired bacteraemia was associated with ICU mortality (CSHR: 1.28; 95% CI: 1.04–1.57) and discharge (CSHR: 0.51; 95% CI: 0.45–0.58) (Table II), suggesting that bacteraemia is associated with an

increase in cumulative mortality not only because of a higher risk of death, but also because of longer lengths of stay.

Conventional model with adjustment for time-dependent confounders

When adjusting for time-dependent confounders using a conventional Cox model, the hazard ratio for ICU mortality was close to one (CSHR: 1.08; 95% CI: 0.88–1.32). Similarly, the hazard ratio for ICU discharge became weaker (CSHR: 0.68; 95% CI: 0.60–0.77) compared to the marginal structural model fitted using ipw.

Comparison of Gram-negative and -positive bacteraemia

Gram-negative bacteraemia appeared to have a stronger effect on ICU mortality than bacteraemia involving only Gram-positive bacteria (CSHR: 1.66; 95% CI: 1.21–2.28 vs CSHR: 1.15; 95% CI: 0.84–1.58). Similarly, the association with daily ICU discharge rate was slightly stronger for ICU-acquired Gram-negative bacteraemia (CSHR: 0.45; 95% CI: 0.35–0.57 vs CSHR: 0.56; 95% CI: 0.44–0.70). Although based on a limited number of cases, the analysis further stratifying Gram-positive bacteraemia cases suggested that *S. aureus* and 'other Gram-positives' had a stronger association with ICU mortality than CNS (CSHR: 1.35; 95% CI: 0.63–2.85 and CSHR: 1.39; 95% CI: 0.92–2.09 vs CSHR: 1.00; 95% CI: 0.74–1.37). By contrast, *S. aureus* and other Gram-positives did not seem to have a stronger effect on ICU discharge than CNS (*S. aureus* CSHR: 0.65; 95% CI: 0.48–0.87; CNS CSHR: 0.53; 95% CI: 0.45–0.63; other Gram-positives CSHR: 0.63; 95% CI: 0.48–0.83).

Discussion

Intensive care unit-acquired bacteraemia was associated with an increased ICU mortality risk (CSHR: 1.29; 95% CI: 1.02–1.63) and a decreased daily ICU discharge risk (CSHR: 0.54; 95% CI: 0.47–0.62), even after adjusting for potential time-varying confounding and the time-dependent nature of the exposure. Our results suggest that ICU mortality could be noticeably lowered (in our study from 20.3% to 18.6% by 60 days) by preventing ICU-acquired bacteraemia.

We applied various modelling strategies to our data that are applied in the literature. Substantially different results were obtained when conditioning on time-varying factors instead of using techniques such as marginal structural models with ipw. Using this former modelling strategy, bias may be introduced due to adjustment for factors that are likely affected by bacteraemia itself and due to collider-stratification bias [15,17]. Although the estimates obtained using the analysis completely ignoring time-varying confounding were very similar to the results obtained using the marginal structural model with ipw, this should not be assumed always to be the case without testing [3,17]. Both simulation studies and studies using real data, including a recent study assessing the effect of ICU-acquired enterococcal bacteraemia, showed that marginal structural models with inverse probability weighting are often necessary to adjust for time-dependent confounders that are affected by exposure [3,14,17,26,27]. For example, the effect of enterococcal bacteraemia was overestimated using a

Figure 1. Observed intensive care unit (ICU) mortality vs expected ICU mortality without ICU-acquired bacteraemia. The solid line represents the observed ICU mortality in the patient cohort and the dashed line the expected mortality if all ICU-acquired bacteraemia in the same cohort would have been prevented.

conventional Cox model adjusting only for baseline confounders [3].

An important strength of this study is that it is one of the first to assess the effects of ICU-acquired bacteraemia while addressing simultaneously the time-varying nature of this type of exposure, potential time-varying confounding and competing risks. One study has been published that used similar methodology to estimate cumulative mortality incidence associated with, specifically, enterococcal bacteraemia [3]. Unfortunately, in our study, a separate estimate for enterococci resulted in very wide confidence intervals, prohibiting a meaningful comparison.

Time-varying confounders should not be modelled using conventional regression techniques that condition on time-varying factors that may be affected by exposure. Instead marginal structural models with ipw, such as applied in the current study, could be used. When extreme weights are generated, fitting marginal structural models with ipw is not reliable [22]. In that regard, it is a pity that researchers often fail to report the distribution of the estimated weights including maximum and minimum values [3,25]. The estimated weights in our study are not considered extreme weights.

However, despite marginal structural models with ipw being able to adequately adjust for time-varying confounding, these techniques remain vulnerable to unmeasured confounding. Deterioration prior to acquiring bacteraemia may have been insufficiently captured by measuring the daily APACHE II score, administration of antibiotics, mechanical ventilation, central lines, and renal replacement therapy. In a study that focused on the effect of ICU-acquired enterococcal bacteraemia, using similar methodology, adjustment for time-varying sequential organ failure assessment (SOFA) score, prior antibiotic use, and abdominal perforation or surgery resulted in more moderate effect estimates compared to a Cox model with adjustment for baseline confounders [3]. Hence, in our study, the effect of ICU-acquired bacteraemia may have been overestimated.

Some of the samples classified as bacteraemia may have been contaminated blood samples. Particularly, blood cultures positive for CNS may be contaminated blood samples, instead

of true infections [3]. The stronger associations observed for ICU-acquired Gram-negative bacteraemia are therefore in line with expectations, although the difference between both groups could not be completely explained by the inclusion of CNS.

Due to data limitations in records from recent years, we necessarily had to restrict our analysis to the years 2002–2006. Since then, the number of Gram-negative bacteraemia cases resistant to the most widely used antibiotics has increased [28]. Therefore, the current impact of ICU-acquired bacteraemia caused by Gram-negative bacteraemia may be even higher than the estimates in this study. Especially the impact on ICU discharge may have been underestimated, since a recent English study found that antibiotic resistance among *E. coli* increases length of stay, but did not seem to have a significant impact on in-hospital mortality [29].

In our study, even after adjusting for the timing of acquiring bacteraemia and time-varying confounding using ipw for marginal structural models, ICU-acquired bacteraemia was associated with a substantial increased daily risk of ICU mortality and decreased daily ICU discharge risk.

Conflict of interest statement

None declared.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.jhin.2017.11.011>.

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