Does appropriate empiric antibiotic therapy modify ICU-acquired Enterobacteriaceae bacteraemia mortality and discharge?

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Running title: ICU-acquired bacteraemia and antibiotics

Background: Conflicting results have been found regarding outcomes of intensive care unit (ICU)-acquired Enterobacteriaceae bacteraemia and the potentially modifying effect of appropriate empiric antibiotic therapy.

Aim: We therefore evaluate these associations while adjusting for potential time-varying confounding using methods from the causal inference literature.

Methods: Patients who stayed >2 days in 2 general ICUs in England between 2002 and 2006 were included in this cohort study. Marginal structural models with inverse probability weighting were used to estimate the mortality and discharge associated with Enterobacteriaceae bacteraemia and the impact of appropriate empiric antibiotic therapy on these outcomes.

Findings: Among 3,411 ICU admissions, 195 (5.7%) ICU-acquired Enterobacteriaceae bacteraemia occurred. Enterobacteriaceae bacteraemia was associated with an increased daily risk of ICU death (cause-specific hazard ratio [HR], 1.48; 95% confidence interval [CI], 1.10-1.99) and a reduced daily risk of ICU discharge (HR, 0.66; 95% CI, 0.54-0.80). Appropriate empiric antibiotic therapy did not significantly modify ICU mortality (HR 1.08; 95% CI, 0.59-1.97) or discharge (HR 0.91; 95% CI, 0.63-1.32).

Conclusion: ICU-acquired Enterobacteriaceae bacteraemia was associated with an increased daily risk of ICU mortality. Furthermore, the daily discharge rate was also lower after acquiring infection, even when adjusting for time-varying confounding using appropriate methodology. We found no evidence for a beneficial modifying effect of appropriate empiric antibiotic therapy on ICU mortality and discharge.

Introduction

Bacteraemia is estimated to affect approximately 1.2 million people in Europe each year, of which up to 35% have a nosocomial-onset.[1] Particularly in intensive care unit (ICU) settings, patients have an elevated risk of acquiring bacteraemia due to the severity of their illness and frequent use of invasive procedures, such as central line catheterisation.[2]

Enterobacteriaceae are common causative pathogens of bacteraemia.[3] None of the studies that evaluated ICU-acquired Enterobacteriaceae bacteraemia outcomes[2,4,5] have addressed potential confounding by time-varying factors using appropriate methodology. The severity of illness of patients may be both a cause and effect of acquiring Enterobacteriaceae. Standard regression methods have been shown to be inadequate to account for such complex patterns of time-varying confounding by severity of illness; alternative solutions have been proposed instead, such as inverse probability weighting.[6-10] Because of the lack of studies that make use of such methods, it is not clear to what extent patients die due to or only with ICU-acquired Enterobacteriaceae bacteraemia.

While several studies indicate that, especially among critically ill patients, appropriate empiric treatment for bacteraemia is associated with reduced mortality,[11-19] many other studies did not find a protective effect.[20-30] Several analyses combined community- and hospital-acquired bacteraemia, adjusting for potential confounders measured at admission and/or at the day of bacteraemia onset, but did not use all available daily information about patients between admission and acquiring the bacteraemia.

Here, we evaluate the impact of Enterobacteriaceae bacteraemia on ICU discharge and mortality, adjusting for potential time-varying confounding using inverse probability weighting. In addition, we

86 estimate the influence of appropriate empiric antibiotic treatment on these outcomes using the
87 same methodology.
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Methods

Patient data

Clinical records of all patients admitted to one of two general ICUs at Guy's and St Thomas' Hospitals (London, UK) between 2002 and 2006 were obtained. Patients with an ICU length of stay of less than 3 days were excluded. From the remaining cohort, we excluded patients with a blood culture positive for Enterobacteriaceae during the first 2 days in the ICU, to exclude community-acquired cases. Age, gender, type of admission (surgical or medical), and ICU ward were recorded at ICU admission. The following variables were recorded at baseline and subsequently on a daily basis: Acute Physiology and Chronic Health Evaluation (APACHE) II score, receipt of systemic antimicrobials, mechanical ventilation, central lines, and renal replacement therapy. In addition, we obtained admission, discharge and mortality data, and microbial culture and sensitivity test results. The effect of the first ICU-acquired microbiological proven Enterobacteriaceae bacteraemia was modelled. Patients were considered to have received appropriate empiric treatment if they were prescribed one or more systemic doses of one or more antibiotics to which the organism cultured was sensitive *in vitro* on the day the blood culture was taken.[20]

Marginal structural model

Marginal structural models along with inverse probability weighting were used to adjust for confounding by severity of illness.

In particular, a pseudo-population was constructed by reweighting patients in the risk set on each day (all patients who did not acquire Enterobacteriaceae bacteraemia in one of the previous days) by the inverse of the product of the conditional probabilities of the observed infection status before that day, given the history of time-varying confounders.[7-9] After weighting, a pseudo-population remains in which there is no further time-varying confounding by the considered confounders. To additionally estimate the effect of appropriate empiric antibiotic therapy on ICU mortality and

discharge, we multiplied the obtained weights for infected patients, from the time of infection onwards, by the reciprocal of the conditional probability that their bacteraemia was appropriately treated or not, given time-varying confounders on the previous day. These weights were calculated as described in Appendix 1.

The marginal structural model was fitted using weighted Cox proportional hazard regression with robust standard errors, thereby accounting for ICU mortality and discharge being competing events. We included the baseline variables used for stabilization of the weights in the final model, to take into account possible residual confounding by those variables.[31] To evaluate the effect of Enterobacteriaceae bacteraemia, we included a time-varying indicator which was zero before infection and one from the time of infection onwards. The model that was used to estimate the effect of appropriate empiric treatment additionally included an indicator for appropriate treatment, which equalled one if a patient received appropriate empiric antibiotic treatment and zero if the patient either received inappropriate empiric treatment or not (yet) acquired Enterobacteriaceae bacteraemia.

Although there were no missing values at baseline, there were missing values for the APACHE II score in 3.7% of the subsequent days. Those missing values were imputed using the last observation carried forward method.

All models were built using R version 3.2.1 (R Foundation for Statistical Computing, Vienna, Austria; packages “ipw”, “splines”, ”survival”, ”zoo”). The proportional hazard assumption was evaluated graphically by plotting weighted Schoenfeld residuals for all proportional hazards models.

Scenario analysis

Despite extensive confounding adjustment, appropriate treatment may still be a marker of more-severe infection. To assess whether this may, indeed, be the case, we evaluated whether patients with more severe infections were more likely to receive appropriate empiric antibiotic treatment. Severe Enterobacteriaceae bacteraemia was defined by the clinical presence of at least three of the following indicators: i) respiratory rate of 22/min or greater; ii) systolic blood pressure of 100mm Hg or less; iii) temperature >38.5°C; iv) white blood cell count >15,000/mm^3. Further adjustment for the severity of infection measured on the day the blood culture was taken could also bias the results, as severity markers may actually be measured after initiation of – and hence affected by – (in)appropriate empiric antibiotic therapy. Therefore, we fitted a logistic regression model among patients with Enterobacteriaceae bacteraemia and compared the odds of receiving appropriate treatment for severe versus non-severe Enterobacteriaceae bacteraemia, while adjusting for covariates measured the day before acquiring the bacteraemia.

158 **Results**

159 In total, 3,121 patients were included in the study, contributing 3,411 ICU admissions with a length
160 of stay of at least 3 days and without having a blood culture positive for Enterobacteriaceae during
161 the first two days in the ICU. Among those 3,411 ICU admissions, 195 (5.7%) ICU-acquired
162 Enterobacteriaceae bloodstream infections occurred. In 173 (88.7%) cases, only one type of
163 Enterobacteriaceae was isolated from the blood, while for 20 cases 2 (10.3%), and for 2 cases 3 (1%)
164 different types were isolated. The isolated microorganisms were *Escherichia coli* (n=63),
165 *Enterobacter* spp. (n=57), *Klebsiella* spp. (n=50), *Proteus* spp. (n=23), *Serratia* spp. (n=19) and
166 *Citrobacter* spp. (n=7). Median time from ICU admission to bacteraemia onset was 10 (25th – 75th
167 percentile, 7-17) days.
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169 Patient characteristics on admission are shown in Table I. The crude ICU mortality risk of patients
170 that acquired Enterobacteriaceae bacteraemia was 40.0% compared to 19.5% for patients who did
171 not. Median unadjusted length of stay in the ICU was 22 days (25th-75th percentile, 14-40) for
172 patients acquiring bacteraemia and 7 days (25th – 75th percentile, 4-13) for patients who remained
173 bacteraemia-free.
174
175 Using a marginal structural model, ICU-acquired Enterobacteriaceae bacteraemia was associated
176 with an increased daily risk of death in the ICU (cause-specific hazard ratio [HR], 1.48; 95%
177 confidence interval [CI], 1.10-1.99) (Table II). The daily risk of ICU discharge was reduced (cause-
178 specific HR, 0.66; 95% CI, 0.54-0.80), thereby increasing the length of stay and therefore the overall
179 number of ICU deaths.
180 When extreme weights are generated, inference using marginal structural models is less reliable.[6,7]
181 The inverse probability weights used in our marginal structural models had a median and mean of
182 0.99 and 0.99, an interquartile range and standard deviation of 0.03 and 0.19, a minimum of 0.13

and maximum of 3.24. These values indicate that our analyses are not negatively affected by extreme weights.

Appropriate empiric antibiotic treatment

Of all bacteraemia cases caused by Enterobacteriaceae (n=195), 74 (38%) received appropriate empiric antibiotic treatment at the day the blood sample was taken. Of those appropriate empiric antibiotic treatment courses, 92% were with at least one of six antibiotics (gentamicin, ceftazidime, ciprofloxacin, piperacillin/tazobactam, meropenem and amikacin) recommended in local guidelines (Appendix 2).[32] Of all patients who did not receive appropriate empiric treatment on the day of infection (n=121), 73 (60%) did receive appropriate treatment at some point during their stay. A switch to appropriate antibiotic treatment occurred for 79% of these patients within 2 days, indicating that if a change was made, it was usually done based on clinical symptoms and before the full microbiological test results, particularly susceptibility test results, were available. In our analysis we only took into account whether treatment was appropriate on the day the sample was taken.

Appropriate treatment was not significantly associated with the daily risk of ICU mortality (cause-specific HR 1.08; 95% CI, 0.59-1.97) or ICU discharge (cause-specific HR 0.91; 95% CI, 0.63-1.32). The weights used to reweight the patient population had a median and mean of 0.99 and 1.00, an interquartile range and standard deviation of 0.03 and 0.24 (min. 0.14, max. 5.21).

Secondary analysis showed that severe infections were not associated with an increased odds of receiving appropriate empiric antibiotics (adjusted odds ratio, 1.09; 95% CI, 0.59-2.01).

Discussion

In this study, ICU-acquired Enterobacteriaceae bacteraemia had a substantial impact on ICU mortality. Moreover, the daily discharge rate was also substantially lower among patients that acquired such an infection, even after adjusting for time-varying confounding using a marginal structural model. Additional length of stay and ICU mortality associated with ICU-acquired Enterobacteriaceae bacteraemia was irrespective of initial empiric treatment, i.e. whether this was appropriate or inappropriate.

When interpreting the results, it should be noted that our analysis assessed the influence of acquiring Enterobacteriaceae bacteraemia versus not acquiring it on clinical outcomes. Information about bacteraemia caused by other pathogens was ignored. A direct comparison of effect estimates with other studies evaluating the effect of ICU-acquired Enterobacteriaceae bacteraemia is difficult due to different clinical settings, focus on specific bacteria belonging to the Enterobacteriaceae family, and different methodology.

We found no evidence for initial appropriate empiric antibiotic therapy being associated with ICU mortality or length of stay. Our findings are in line with several recent studies that did not find an association between inappropriate antibiotic therapy and mortality.[20-30] A recent prospective evaluation of empiric antibiotic therapy and mortality in ten English acute hospitals did not find an association between inappropriate empiric antibiotic therapy and mortality at 7 or 30 days (adjusted OR 0.82; 95% CI 0.35-1.94 and adjusted OR 0.92; 95% CI 0.50-1.66, respectively).[20] In that study, it was suggested that the contrasting results with the older literature may reflect advances in supportive care, changes in patient mix and differences in the main antibiotic classes used.[20] Another factor that may contribute to the contrasting results in the literature is the substantial variation in methodological quality of different studies.[13]

We evaluated whether more severe infections were more likely to receive appropriate empirical treatment. However, we found no evidence for severe infections being associated with appropriate empiric treatment. Unfortunately, the data were too limited to be able to assess whether appropriate empiric treatment is only effective in severely ill patients or other subgroups.[17]

Another explanation of the absence of a protective effect may be that the majority of switches to appropriate treatment occurred within 2 days after the blood sample was taken. Hence, changes or escalation of therapy, if necessary from a clinical perspective, were typically done without knowledge of microbiological test results and based on clinical assessment. Such switches may have occurred timely enough to prevent potential detrimental effects of initial inappropriate empiric treatment. This has also been observed in a randomized controlled trial evaluating the potential impact of rapid diagnostic tests, where escalation of therapy often happened before the full lab results were available.[33] Although not powered to assess mortality and length of stay, that trial did not observe lower mortality rates or higher discharge rates among patients in the rapid diagnostic test arms, despite a shorter time to first appropriate antibiotic escalation.[33]

Strengths and limitations

This is the first study evaluating the effect of ICU-acquired Enterobacteriaceae bacteraemia on ICU discharge and mortality, while addressing confounding by the evolution of disease prior to infection using appropriate methodology. Data were available for several years, providing sufficient power to focus on Enterobacteriaceae instead of all Gram-negative bacteria grouped together.

Although we took into account as much information as possible and applied advanced statistical methodology to correct for confounding, several limitations must be acknowledged.

Despite marginal structural models allowing appropriate adjustment for time-varying confounding, these techniques remain vulnerable to unmeasured or residual confounding. For example, urinary focus may be associated with more resistance and hence more likely inappropriate treatment and at the same time be associated with less severe outcomes than other foci.[20] This may have resulted in an underestimation of the beneficial effect of appropriate empiric antibiotic therapy.
We evaluated ICU discharge and mortality in the ICU, but follow-up beyond the ICU would have been necessary to fully capture the effect of ICU-acquired Enterobacteriaceae bacteraemia on mortality or total hospital stay.

Appropriateness of empiric antibiotic treatment was determined based on *in vitro* susceptibility tests. However, treatment classified as inappropriate potentially had some activity *in vivo*.[20] Likewise, *in vitro* susceptibility does not guarantee susceptibility *in vivo*.

Due to data limitations in records of more recent years, we had to restrict our analysis to the years 2002-2006. Since then, the number of Enterobacteriaceae bacteraemia cases resistant to the most commonly used antibiotics has increased.[3] Although this might result in selection of appropriate empiric antibiotic therapy being more difficult in recent years compared with our period of study, this would unlikely substantially affect the modifying effect of appropriate empiric antibiotic therapy itself.

Preferably, for future analysis, a large multi-centre prospective study will be performed, collecting information about all potential confounders at baseline and during the ICU-stay. Robust estimates can be obtained by analysing such data using inverse probability weighting for marginal structural models, G-estimation for structural nested models, or G-computation.[6]

ICU-acquired Enterobacteriaceae bacteraemia was associated with an increased daily risk of ICU mortality. Furthermore, the daily discharge rate was also lower after acquiring infection, even when adjusting for time-varying confounding using marginal structural models. When taking into account daily information about patients between ICU admission and acquiring bacteraemia using appropriate methodology, these associations were not modified by appropriate empiric antibiotic treatment. Although our results do not exclude a beneficial impact of empiric antibiotic therapy on ICU mortality and discharge, they suggest the health-economic benefit of rapid diagnostic testing in the ICU setting may be less than initially anticipated and may rely mostly on reductions in antibiotic use and resulting resistance.

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Table I. Baseline characteristics and crude length of stay and ICU-mortality rates for patients with and without ICU-acquired Enterobacteriaceae bacteraemia

	Patients with bacteraemia (n=195)	Patients without bacteraemia (n=3,216)
Male sex, n (%)	131 (67.2)	1,966 (61.1)
Age, mean (SD)	63.1 (14.11)	60.7 (17.11)
APACHE II, mean (SD)	20.1 (6.4)	18.2 (6.5)
Admission type		
Medicine, n (%)	121 (62.1)	1,964 (61.1)
Surgery, n (%)	74 (37.9)	1,252 (38.9)
ICU length of stay, median (Q1, Q3)	22 (14, 40)	7 (4, 13)
ICU mortality, n (%)	78 (40.0)	627 (19.5)

Abbreviations: ICU, intensive care unit; SD, standard deviation.

Table II. ICU-acquired Enterobacteriaceae bacteraemia outcomes and influence of appropriate empiric antibiotic therapy

	ICU mortality CSHR (95% CI)	ICU discharge CSHR (95% CI)
Enterobacteriaceae bacteraemia[a]	1.48 (1.10-1.99)	0.66 (0.54-0.80)
Appropriate empiric antibiotic treatment[b]	1.08 (0.59-1.97)	0.91 (0.63-1.32)

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

[a] The final model estimating the stabilized weights for Enterobacteriaceae bacteraemia at each day included the Acute Physiology and Chronic Health Evaluation (APACHE) II score, the presence of central lines and antibiotic administration as time-varying covariates. These weights were stabilized by including gender as a baseline covariate.

[b] The final model estimating the stabilized inverse probability weights for appropriate empiric antibiotic treatment included the APACHE II score and the presence of central lines as time-varying covariates. These inverse probabilities were stabilized by including the APACHE II score at admission as a baseline covariate. The final stabilized weights were subsequently obtained by multiplying the daily stabilized weights for Enterobacteriaceae bacteraemia with the daily stabilized inverse probabilities for appropriate empiric antibiotic therapy.

Appendix 1. Calculation of the inverse probability weights.

To calculate the inverse probability weights, daily probabilities of acquiring Enterobacteriaceae bacteraemia given baseline and time-varying covariates were estimated by using pooled logistic regression models; these probabilities were set to 1 from the time of bacteraemia onwards. To avoid large weights, we included baseline covariates in the numerator weights and then later also in the marginal structural model.[38] We considered all previously listed variables in the model.

We allowed for a non-linear effect of time by using restricted cubic splines. Non-linear effects of other continuous covariates, i.e. age, APACHE II score and number of systemic antibiotics at each day, were allowed in the model by including quadratic terms. In addition, we allowed for 2-way interactions between (i) APACHE II score at admission and subsequent daily APACHE II score measurements, and (ii) type of admission and daily APACHE II scores. To build parsimonious models, we first added all main effects to the model and sequentially removed them if nonsignificant at the 5% level. Next, the suggested interaction terms and non-linear effects were sequentially added if significant at the 5% level. Similar estimates for the probability that the Enterobacteriaceae bacteraemia of infected patients were appropriately treated were calculated. The obtained probabilities were then used to generate daily patient-specific weighing factors.

Appendix 2. Table I. Appropriate antibiotic therapy for ICU-acquired Enterobacteriaceae bacteraemia

Appropriate empiric antibiotic therapy at day of first positive blood sample taken (n=74)[a]	N (%)
Amikacin	14 (19)
Amikacin + co-amoxiclav	1 (1)
Amikacin + colistin	1 (1)
Ceftazidime	10 (14)
Ceftazidime + gentamicin	3 (4)
Cefuroxime	3 (4)
Ciprofloxacin	8 (11)
Co-amoxiclav	1 (1)
Colistin	2 (3)
Gentamicin	25 (34)
Piperacillin/tazobactam	6 (8)

[a] Only antibiotics shown for which the bacteria were susceptible on the day of the blood sample was taken. E.g. if a patient received both gentamicin and meropenem, but the bacteria were only sensitive to gentamicin, it is shown as monotherapy with gentamicin. At the time of the study local guidelines recommended a single antibiotic course for all ICU-acquired gram-negative infections. All patients with severe sepsis or septic shock were recommended to receive a single dose of gentamicin if a non-aminoglycoside antibiotic course was selected.