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Short Communication

Quantifying the importance of active antimicrobial therapy among patients with Gram-negative bloodstream infections: Cefepime as a representative agent

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ABSTRACT

The quantitative importance of active antimicrobial treatment relative to other modifiable and non-modifiable risk factors for mortality has not been well defined in the literature. Here we quantify the impact of active antimicrobial treatment on mortality relative to other disease modifiers in patients with Gram-negative bloodstream infection (GNBSI). Patients with at least one positive blood culture who were treated with ≥24 h of cefepime for GNBSI were included in the study. To examine in-hospital survival, a full primary model and a base model with the least significant covariate from the primary model were established. Relative importance of covariates was calculated using percentages of difference in log-likelihood values when each covariate was iteratively added to the base model. A total of 154 unique patients with GNBSI were included. The primary model included active cefepime therapy ($P=0.004$), normalised days to positive culture ($P=0.091$), intensive care unit (ICU) at time of treatment ($P=0.001$), modified Acute Physiology and Chronic Health Evaluation (APACHE) II score on day zero ($P=0.025$), history of leukaemia ($P=0.008$) and prior immunosuppressive therapy ($P=0.088$). Active antimicrobial therapy displayed a relative importance of 32.2%, which was second to ICU residence at the time of culture. Amongst all covariates in the model, active antimicrobial therapy was the only modifiable variable and contributed significantly to in-hospital survival in acutely ill patients with GNBSI.

1. Introduction

Timely initiation of effective antimicrobial therapy is associated with reduced mortality and improved outcomes in patients with Gram-negative bloodstream infections (GNBSIs) [1]. Even with administration of appropriate antimicrobial therapy in a timely manner, mortality due to GNBSI is driven by a multitude of factors, such as severity of illness [2–5]. Whilst previous studies have associated timely administration of active antimicrobial therapy with improved outcomes, to our knowledge the relative importance of active therapy has not yet been quantified. In addition, it is important to examine the modifiable factors. This paper aimed to quantify the relative importance of active antimicrobial therapy in patients with GNBSI in relation to severity of illness and other significant covariates.

2. Materials and methods

To investigate and quantify the importance of active antimicrobial therapy in patients with GNBSI, data available from patients treated for GNBSI with well-characterised antibiotic exposures and outcomes were retrospectively probed [6]. To focus on patients most likely to benefit from active antibiotic therapy, patients with modified Acute Physiology and Chronic Health Evaluation (APACHE) II scores ≥10 and with at least one positive blood culture who were treated with ≥24 h of cefepime for GNBSI were included [1,7,8]. Active antimicrobial therapy was defined as treatment with cefepime for GNBSI with an infecting pathogen with a minimum inhibition concentration (MIC) of ≤2 mg/L. Patients were excluded if: (i) no cefepime MIC was documented for the infecting pathogen; (ii) only one dose was administered and amounted to <24 h of therapy (or renally adjusted equivalence dosing); or (iii)

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Table 1
Baseline characteristics of the included population ($n = 154$).

Parameter	No. (%) of patients[a]
Age (years) (mean ± S.D.)	58.9 ± 14.7
Male sex	88 (57.1)
Race	
White	97 (63.0)
Black	32 (20.8)
Asian	4 (2.6)
Hispanic	14 (9.1)
Other	7 (4.5)
Modified APACHE II on day zero (mean ± S.D.)	15.9 ± 4.0
Admission from:	
Outpatient clinic	10 (6.5)
Direct	42 (27.3)
Emergency department	81 (52.6)
Outside hospital	21 (13.6)
ICU admission	32 (20.8)
Mechanical ventilation within past year	35 (22.7)
Neutropenia during admission[b]	81 (52.6)
History of haematological malignancy[c]	62 (40.3)
Receipt of immunosuppressant therapy within 12 months	114 (74.0)
Concurrent co-morbid conditions	
Lymphoma	19 (12.3)
Leukaemia	32 (20.8)
Multiple myeloma	17 (11.0)
Hospitalisation within past year	130 (84.4)

S.D., standard deviation; APACHE, Acute Physiology and Chronic Health Evaluation; ICU, intensive care unit.
[a] Data are *n* (%) unless otherwise stated.
[b] Absolute neutrophil count <500 cells/mm^3.
[c] Includes leukaemia, lymphoma or multiple myeloma.

the blood culture result was polymicrobial. Two sensitivity analyses were performed. In the first analysis, patients with a modified APACHE II score between 10 and 23 were included ($n = 152$). This range was chosen as it was previously found to represent an important window for impact on mortality and provides an upper bound for APACHE II [7]. In the second analysis, the patient population was restricted to those who received active cefepime treatment within 24 h of blood culture ($n = 128$).

The primary outcome for all analyses was in-hospital survival. Stepwise logistic regression and Akaike Information Criterion (AIC) were used for selection of the best and most parsimonious final model ($n+kij$ parameters). Backwards and forwards steps were applied. First, a primary model was created by a backward step procedure that retained variables that predicted mortality at $P < 0.1$. The overall relative importance (%) of each covariate in the model was calculated by removing all predictor variables except for the least significant covariate from the primary model to create the base model for evaluation (model $n+ki$). Each of the covariates identified from the primary model was added iteratively to the base model according to *P*-value significance (from the least to the most significant) to generate log-likelihood values. The relative contribution of each additional covariate was converted into a percentage of the difference between the log-likelihood function values from model $n+ki$ and each iterative model $n+kij$ (i.e. relative importance of each covariate to the final model was calculated). The process was repeated for the sensitivity analysis data sets as described above.

3. Results

In the full data set, a total of 154 adult inpatients with GNBSI were included in the analysis (Table 1). The majority of the patients were male (57.1%) and the overall mean ± standard deviation (S.D.) age was 58.9 ± 14.7 years. The mean ± S.D. modified APACHE II score was 15.9 ± 4.0 on the day of infection (day zero). Infecting organisms were isolated and are shown in Table 2. Of the 154 included patients, 32 were admitted to the intensive care unit (ICU). Patients within the study cohort were highly co-morbid, with 74.0% having received immunosuppressants within 12 months, 44.2% with a current haematological malignancy (leukaemia, lymphoma or multiple myeloma) and 84.4% having been hospitalised in the previous 12 months. In addition, 22.7% were mechanically ventilated within the past year and 52.6% were neutropenic during their admission. A heterogeneous representation of organisms was analysed with cefepime MICs between 1 mg/L and 64 mg/L, and the impact of cefepime MIC was dichotomously classified as active according to Clinical and Laboratory Standards Institute (CLSI) classifications and our previous modelling demonstrating that this breakpoint predicted mortality [9]. The primary model included the following variables: active cefepime therapy ($P = 0.004$); normalised days to positive culture ($P = 0.091$); ICU at time of treatment ($P = 0.001$); modified APACHE II score on day zero ($P = 0.025$); history of leukaemia ($P = 0.008$); and prior immunosuppressive therapy ($P = 0.088$) (log likelihood, –41.8).

Table 2
Number of isolated pathogens stratified by bacterial genus and cefepime minimum inhibitory concentration (MIC) ($n = 154$).

Genus	No. at cefepime MIC (mg/L) of:						
	1	2	4	8	16	32	64
Achromobacter spp.					1		
Acinetobacter spp.		1					2
Aeromonas spp.	1						
Citrobacter spp.	4		1				
Enterobacter spp.	13		1				1
Escherichia coli	37	6	1	2	2	1	3
Klebsiella spp.	19		1	5		1	1
Proteus spp.	2						
Pseudomonas spp.	2	19	6	11	4	1	1
Salmonella spp.	1						
Serratia spp.	3						

4. Discussion

This study to quantified the contribution of active antimicrobial therapy relative to other important predictors of in-hospital survival among patients with GNBSI. This highly co-morbid study cohort had a wide range of cefepime MICs. In the model, active antimicrobial therapy displayed a relative importance of 32.2%, which was second to ICU residence at the time of culture (Table 3). Sensitivity analyses resulted in similar estimates of predictor variable importance. Thus, the importance of highly active and timely therapy underscored as active antimicrobial therapy was the only modifiable variable in the model and contributed significantly to in-hospital survival in acutely ill patients with GNBSI.

The primary analysis included patients with modified APACHE scores ≥10, a score that is predictive of mortality and focuses on patients who most benefit from antimicrobial treatment [7,10]. This study is not without limitations. First, it has a relatively small sample size, but the cohort is representative of those who are often difficult to treat and are underrepresented in clinical trials [11]. Second, whilst all patients received cefepime, other active antibiotics were also sometimes given. However, we have previously shown that cefepime pharmacokinetic/pharmacodynamic exposures independently drove patient outcomes [6]; thus, defining the relative importance of active cefepime therapy holds merit. It is not clear whether these results are generalisable to other drugs, other situations (e.g. single active therapy) or other patient populations.

The methodology of model building and predictor quantification employed here is simple to perform. To our knowledge, this is

Table 3
Overall relative importance of significant clinical covariates.

Covariate	Primary model		Sensitivity model 1 ($n = 152$)		Sensitivity model 2 ($n = 128$)	
	Relative importance (%)	Importance rank	Relative importance (%)	Importance rank	Relative importance (%)	Importance rank
ICU at time of culture	35.58	1	41.35	1	45.83	1
Active antimicrobial therapy	32.15	2	28.15	2	25.24	2
Prior immunosuppressive therapy	12.10	3	11.33	3	5.92	5
APACHE II on day zero	10.79	4	8.00	5	11.66	3
History of leukaemia	9.39	5	11.16	4	11.35	4

ICU, intensive care unit; APACHE, Acute Physiology and Chronic Health Evaluation.

the first study to apply this method to clinical data and to quantify the relative importance of antimicrobials to patient in-hospital survival in those with GNBSI. These data underscore the relative importance of timely and active antimicrobial therapy and thus prompt future studies.

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None.

Competing interests

None declared.

Ethical approval

Institutional review board.

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