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Original article

Effect of adequacy of empirical antibiotic therapy for hospital-acquired bloodstream infections on intensive care unit patient prognosis: a causal inference approach using data from the Eurobact2 study

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A B S T R A C T

Objectives: Hospital-acquired bloodstream infections (HA-BSI) in the intensive care unit (ICU) are common life-threatening events. We aimed to investigate the association between early adequate antibiotic therapy and 28-day mortality in ICU patients who survived at least 1 day after the onset of HA-BSI.

Methods: We used individual data from a prospective, observational, multicentre, and intercontinental cohort study (Eurobact2). We included patients who were followed for ≥1 day and for whom time-to-appropriate treatment was available. We used an adjusted frailty Cox proportional-hazard model to assess the effect of time-to-treatment-adequacy on 28-day mortality. Infection- and patient-related variables identified as confounders by the Directed Acyclic Graph were used for adjustment. Adequate therapy within 24 hours was used for the primary analysis. Secondary analyses were performed for adequate therapy within 48 and 72 hours and for identified patient subgroups.

Results: Among the 2418 patients included in 330 centres worldwide, 28-day mortality was 32.8% ($n = 402/1226$) in patients who were adequately treated within 24 hours after HA-BSI onset and 40% ($n = 477/1192$) in inadequately treated patients ($p < 0.01$). Adequacy within 24 hours was more common in young, immunosuppressed patients, and with HA-BSI due to Gram-negative pathogens. Antimicrobial adequacy was significantly associated with 28-day survival (adjusted Hazard Ratio (aHR), 0.83; 95% CI, 0.72–0.96; p 0.01). The estimated population attributable fraction of 28-day mortality of inadequate therapy was 9.15% (95% CI, 1.9–16.2%).

Discussion: In patients with HA-BSI admitted to the ICU, the population attributable fraction of 28-day mortality of inadequate therapy within 24 hours was 9.15%. This estimate should be used when

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hypothesizing the possible benefit of any intervention aiming at reducing the time-to-appropriate antimicrobial therapy in HA-BSI. **Ambre Loiodice, Clin Microbiol Infect 2024;30:1559**

Introduction

Hospital-acquired bloodstream infections (HA-BSI) have an increasing incidence worldwide and are associated with high morbidity and mortality rates [1–3]. Delays in their appropriate treatment may negatively affect the outcome, especially in critically ill patients with sepsis or shock [4]. However, the estimated impact of the adequacy of empirical antimicrobial therapy varies widely across studies [5–8].

We designed this study to investigate the association between adequate antimicrobial therapy within 24 hours after the blood culture collection and 28-day mortality in critically ill patients with HA-BSI. Data from the multicentre, multinational, prospective Eurobact2 study were used [2], with Directed Acyclic Graph (DAG) method to optimally select the measured confounders and causal inference models.

Methods

Eurobact2 study design

Eurobact2 was a prospective international cohort study registered in ClinicalTrials.org (NCT03937245).

It was conducted from August 2019 to June 2021. Comprehensive details on the methodology used can be found elsewhere [2] and in Supplementary data. Briefly, centres were recruited on a voluntary basis to include 10 consecutive cases for a maximal period of 3 consecutive months. We included adult ($\geq$18 years of age) patients with HA-BSI treated in the intensive care unit (ICU). HA-BSI was defined as a positive blood culture sampled more than 48 hours after hospital admission. Treatment in the ICU was defined as the blood culture having been either sampled in the ICU or the patient having been transferred to the ICU for the treatment of the HA-BSI.

ICU and patient selection

We included 2418 ICU patients with HA-BSI from 330 centres of the Eurobact2 study; 182 (7%) patients with <1 day of follow-up after HA-BSI onset and those with missing data on time-to-treatment adequacy were excluded (see Fig. 1, Fig. S1, and Table S1).

Data collection and definitions

Data collection is described in detail elsewhere (see Supplementary data) [2]. The primary outcome was 28-day patient survival status (data always available).

For the study, the time of collection of the first positive blood culture defined the time zero. The time-to-treatment adequacy was treated as a binary variable, specifically evaluating adequacy within the first 24 hours as a primary variable of exposure. Difficult-to-treat resistance (DTR) definition is detailed in Supplementary data [9].

The selected variable of interest was adequate antimicrobial therapy within the first 24 hours. The therapy adequacy was defined as at least one antimicrobial with *in vitro* activity for the pathogen at the considered timepoint, with adequacy of antimicrobial selection, dosing, and administration, and was manually reviewed before database lock by one of the three experts (A.T., F.B., and N.B.).

Statistical analysis

Median with interquartile range (IQR) was used for continuous variables and number of patients (n) and percentage (%) for categorical variables. Comparisons were made using parametric or non-parametric tests, as appropriate.

First, we identified confounders based on existing literature and expertise (A.T., J.F.-T., N.B., and F.B.) [10] and reported them visually in a DAG [11,12] (Fig. 2). Patient-related independent confounding variables were age, sex, delay between hospitalization and HA-BSI, time-to-positivity of the blood culture, pathogen species, comorbidities, immunosuppression, source of infection, and the Sequential Organ Failure Assessment score at HA-BSI onset.

The availability of infectious diseases (ID) physicians 24/7 and of written procedures for antimicrobial therapy were considered as two independent centre-based surrogates for prescriber quality.

The association between therapy adequacy and 28-day mortality was evaluated using a frailty Cox proportional-hazard model with a centre random effect. All analyses were adjusted for all selected patient- and centre-related confounders. The e-value was used to assess the association robustness with potential unmeasured confounding factors [13,14].

The same model was used considering adequate treatment time within 48 hours and 72 hours after blood culture collection, on patients with $\geq$ 2 days and $\geq$ 3 days of follow-up after HA-BSI, respectively.

Using the same method, sub-analyses were conducted to assess specific subgroups of patients according to microorganisms, resistance profile, and presence of septic shock. We performed various post hoc analyses based on reviewers' suggestions.

The population attributable fraction (PAF) of 28-day mortality associated with inappropriate therapy was estimated using hazard ratio [15,16].

A sample of 2418 patients was calculated as sufficient to detect a benefit of 4.8% in 28-day mortality with adequate therapy if the 28-day mortality of inadequately treated patients is 40%, the proportion of adequate therapy is 50%, with a power of 80% and a type one error of 5% (unilateral formulation).

We used SAS software version 9.4 (SAS Institute) and R software, version 3.3.1 (R Foundation for Statistical Computing).

Results

Patients' characteristics

A total of 1226 patients with adequate treatment within the first 24 hours of HA-BSI and 1192 patients with inadequate treatment were included in the analysis (main patients characteristics, Tables 1 and 2); 28-day mortality was 36.4% (n = 879). Excluded patient characteristics are shown in Table S1.

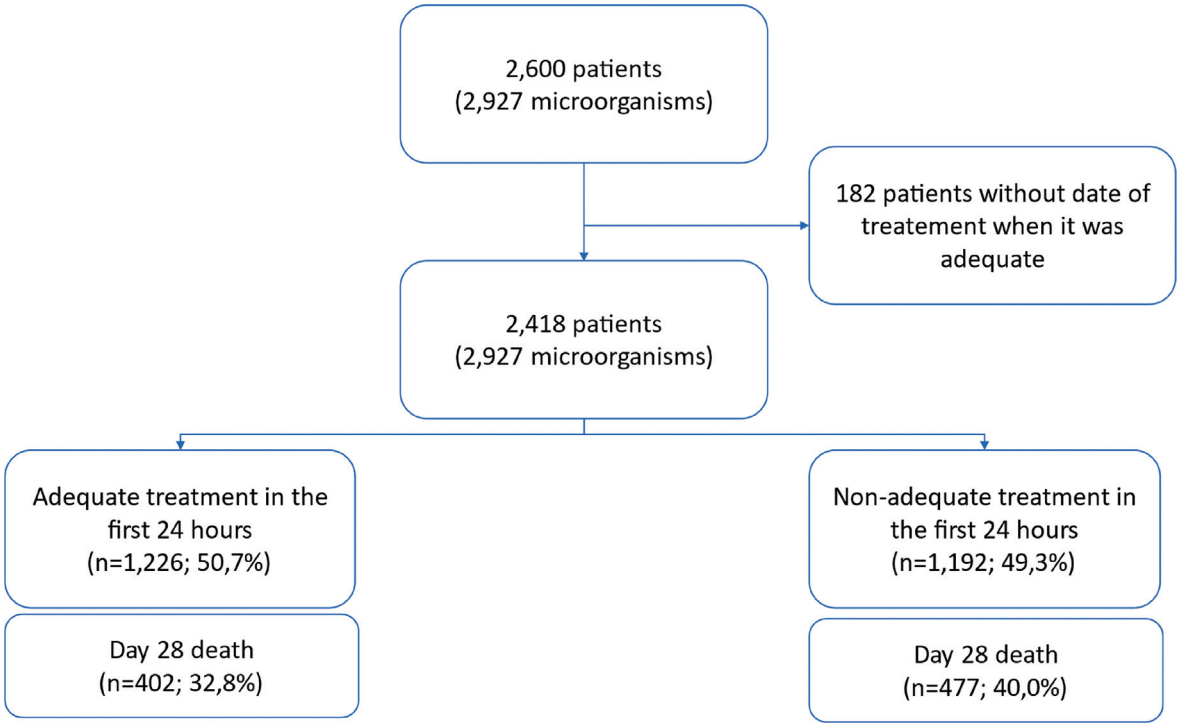

Fig. 1. Flow chart of patients with HA-BSI with or without adequate treatment within the first 24 hours after the positive blood culture. HA-BSI, hospital-acquired bloodstream infection.

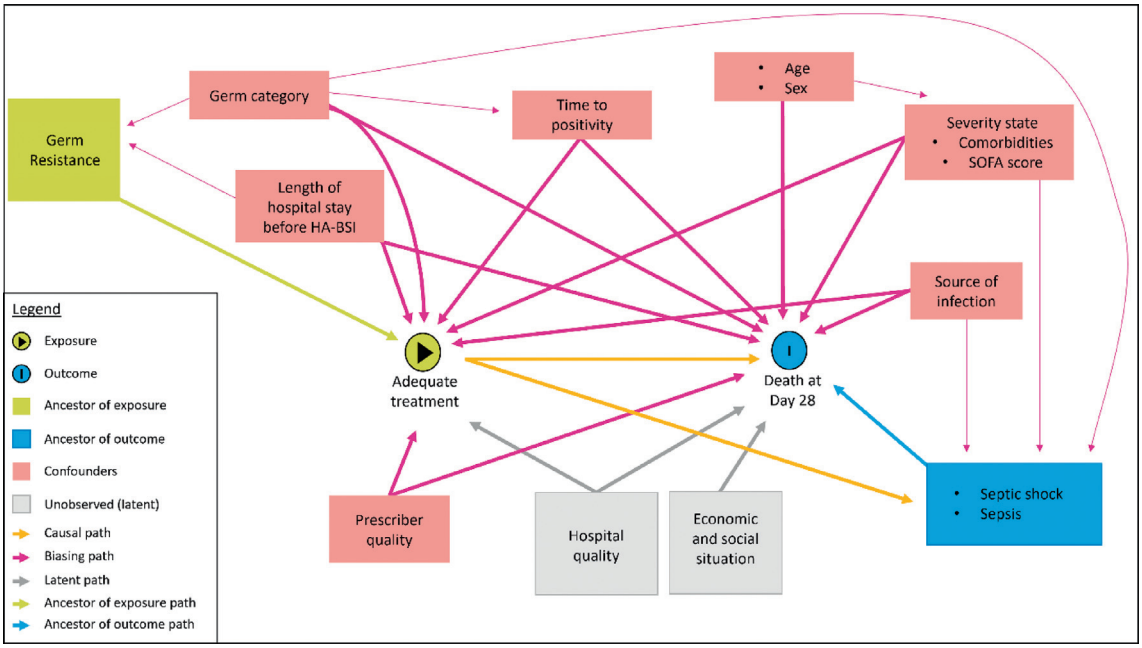

Fig. 2. Confounding variables selection using a Directed Acyclic Graph (DAG). The DAG is a graphical representation of the potential causal relationships between variables, with arrows used to denote the direction of causality. Collider bias occurs when two arrows collide on a variable that has been controlled for. DAG was performed using the DAGitty v3.1 software (https://dagitty.net/dags.html). *Nota bene*: Each arrow represents a causal effect. The purple arrows represent an open back-door path. For example, 'prescriber quality' is linked to early adequate treatment and 28-day death. Controlling for prescriber quality will close the backdoor path. Delayed adequate treatment may promote sepsis and septic shock occurrence. Consequently, 'sepsis and septic shock' partially mediate the association between adequate treatment and death. Control of 'sepsis and septic shock' would be inappropriate, because it would partially close the causal path, attenuating the observed association between adequate treatment and death (see text for further discussion). The ancestors of exposure and outcome are confounders. Biases can be reduced by adjusting or controlling for confounders (see text for details). *Nota bene*2: DAG is a visual representation of the potential interplay among variables. All variables in pink were considered as confounders and included in the final model as adjustment factors. HA-BSI, hospital-acquired bloodstream infection; SOFA, Sequential Organ Failure Assessment.

Table 1
Patients' characteristics at HA-BSI time and outcome

Variables	All HA-BSI (n = 2418)	Adequate treatment H24 (n = 1226)	Inadequate treatment H24 (n = 1192)	p[a]	p[b]
Patients' characteristics on HA-BSI onset					
Age (y)	64 (51–73)	63 (50–73)	65 (53–74)	<0.01	0.02
Male gender	1542 (63.8)	795 (64.8)	747 (62.7)	0.27	0.81
Comorbid conditions					
Respiratory	391 (16.2)	197 (16.1)	194 (16.3)	0.89	0.83
Cardio-vascular	548 (22.7)	265 (21.6)	283 (23.7)	0.21	0.67
Neurological	351 (14.5)	151 (12.3)	200 (16.8)	<0.01	0.53
Immunosuppression	464 (19.2)	249 (20.3)	215 (18)	0.16	0.77
Malignancy	529 (21.9)	292 (23.8)	237 (19.9)	0.02	0.22
Septic shock	783 (32.4)	438 (35.7)	345 (28.9)	<0.01	0.07
Without septic shock	1635 (67.6)	788 (64.3)	847 (71.1)	<0.01	0.07
Length of hospital stay before HA-BSI	13 (8–24)	13 (7–23)	14 (8–25)	0.02	0.03
ICU-acquired BSI	1886 (78)	916 (74.7)	970 (81.4)	<0.01	<0.01
SOFA score at HA-BSI onset	8 (5–11)	8 (6–11)	8 (5–11)	0.9	0.40
Epinephrine/norepineprine[c]	1314 (54.3)	718 (58.6)	596 (50)	<0.01	0.04
28-d mortality[d]	879 (36.4)	402 (32.8)	477 (40.0)	<0.01	<0.01

Results were reported as n (%) for categorical variables and median (IQR) for continuous variables. There were no missing values. HA-BSI, hospital-acquired bloodstream infection; ICU, intensive care unit; IQR, interquartile range; SOFA, Sequential Organ Failure Assessment.

[a] To assess differences in categorical variables, chi-square or Fisher's exact tests were used as appropriate. Additionally, t-test or Wilcoxon rank sum test were used as appropriate for continuous variables.

[b] To assess differences in categorical variables stratified by centre, Cochran–Mantel–Haenszel test was used. Additionally, the Van Elteren test was used for continuous variables.

[c] For some patients, vasopressor was started before the new sepsis without dose increase and is not included in the definition of septic shock.

[d] Day 28 vital status was available for all patients.

Table 2
Hospital-acquired bloodstream infection characteristics

Variables	All HA-BS (n = 2418)	Adequate treatment H24 (n = 1226)	Inadequate treatment H24 (n = 1192)	p[a]
Time-to-positivity of blood culture (h)[b]	21 (12–46)	18 (11–35.5)	24 (12–48)	<0.01
Most likely source of infection				<0.01
Catheter	619 (25.6)	305 (24.9)	314 (26.3)	
Intra-abdominal	375 (15.5)	208 (17)	167 (14)	
Primary	374 (15.5)	160 (13.1)	214 (18)	
Respiratory	663 (27.4)	353 (28.8)	310 (26)	
Urinary	182 (7.5)	98 (8)	84 (7)	
Other	205 (8.5)	102 (8.3)	103 (8.6)	
Gram-positive pathogens	798 (33)	387 (31.6)	411 (34.5)	0.13
S. aureus	231 (28.9)	144 (37.2)	87 (21.2)	<0.01
Coagulase-negative staphylococci	236 (29.6)	83 (21.4)	153 (37.2)	<0.01
Enterococcus spp.[c]	290 (36.3)	126 (32.6)	164 (39.9)	0.03
Gram-negative pathogens	1511 (62.5)	814 (66.4)	697 (58.5)	<0.01
Nonfermentative GNB	572 (37.9)	249 (30.6)	323 (46.3)	<0.01
Acinetobacter spp.	311 (20.6)	113 (13.9)	198 (28.4)	<0.01
Pseudomonas aeruginosa	211 (14)	121 (14.9)	90 (12.9)	0.28
Klebsiella spp.	451 (29.8)	259 (31.8)	192 (27.5)	0.07
Enterobacter spp.	133 (8.8)	70 (8.6)	63 (9)	0.76
DTR[d] pathogen	315 (22.1)	106 (13.6)	209 (32.3)	<0.01
PDR pathogen	44 (2.9)	0 (0)	44 (6.3)	<0.01
Anaerobes	56 (2.3)	30 (2.4)	26 (2.2)	0.66
Fungi	210 (8.7)	48 (3.9)	162 (13.6)	<0.01
Source control				0.08
Not required	1139 (47.1)	576 (47)	563 (47.2)	
Required and complete	1050 (43.4)	550 (44.9)	500 (41.9)	
Required but partial	229 (9.5)	100 (8.2)	129 (10.8)	

Results were reported as n (%) for categorical variables and median (IQR) for continuous variables. DTR, difficult-to-treat resistant; GNB, Gram-negative bacteria; HA-BSI, hospital-acquired bloodstream infection; IQR, interquartile range; PDR, pan-drug resistant.

[a] To assess differences in categorical variables, chi-square or Fisher's exact tests were used as appropriate. Additionally, t-test or Wilcoxon rank sum test were used as appropriate for continuous variables.

[b] Time-to-positivity: 822 missing data recorded using the median value for multivariate analyses and.

[c] *E. faecalis*, n = 132; *E. faecium*, n = 143; other enterococci, n = 15; vancomycin-resistant enterococci were only reported in 36/290 cases.

[d] DTR: 86 missing data because antibiotic susceptibility testing was not completed for all the drugs required to meet the DTR definition.

The main antimicrobials included are carbapenems, piperacillin-tazobactam, colistin, vancomycin, and echinocandins (Table S2). The median delay in therapy was 1 hour (IQR, 0–8) for the adequate therapeutic group $\leq$ 24 hours and 57 hours (IQR, 38–91) for the >24 hours group.

Patients who received adequate treatment within the first 24 hours were younger, had more often prior malignancy or immunosuppression, and were more frequently in septic shock. These patients acquired less frequently their HA-BSI in the ICU (74.7% vs. 81.4%, $p < 0.01$). The cause of infection was more

frequently a Gram-negative pathogen (66.4% vs. 58.5%, p < 0.01) (Table 2); fungal HA-BSI was less frequent (3.9% vs. 13.6%, p < 0.01). They had a lower overall prevalence of multidrug-resistant Gram-negative infections (13% vs. 30%, p < 0.01) and *Acinetobacter* spp. infections (13.9% vs. 28.4%, p < 0.01).

In adequately and inadequately treated patients, 28-day mortality was 32.8% ($n = 402$) and 40% ($n = 477$) (p < 0.01), respectively.

The percentage of adequate treatment within 24 hours per centre was higher for centres having declared local written infection control guidelines (56.7% vs. 41.5%, p < 0.0001) and with ID physician available within the ICU staff or under consultancy 24/7 (52.2% vs. 48.4%, p 0.23).

Mediation assumptions for selecting confounders for the multivariate models

The variables chosen for adjustment in the frailty Cox models are those associated with both adequate treatment and mortality (Fig. 2). The variables used for adjustment were hospital stay duration before HA-BSI, pathogen category, time-to-blood culture positivity, age, sex, comorbidities, Sequential Organ Failure Assessment score, and source of infection. Septic shock and sepsis were not included in the model as they are considered solely related to mortality, and a mediator in the relationship between early adequate therapy and prognosis; however, a sub-analysis was rerun including septic shock as a confounder. Pathogen category and source of infection were causally linked with death. We assumed that they influenced the promptness of antimicrobial therapy and acted as confounders. Pathogen resistance was not used for adjustment as it is considered to be causally associated with early adequate treatment but not per se causally associated with death [6,17]. Prescriber quality was assumed as represented by two variables: 'ID specialists or clinical microbiologists are consulted or available as part of the permanent staff of the ICU,' or 'at least one member of the ICU staff is an ID specialist,' and 'the availability of local written infection treatment guidelines' [18]. A post hoc analysis used the availability of a pharmacist as a centre-based variable, as recently evaluated in another analysis [19]. Available financial resources, hospital quality, and the socio-economic situation of the hospital are latent variables that were not included in the adjustment but were considered introducing a random centre effect in all models.

Survival analyses

After accounting for all measured confounders and incorporating the random centre effect, adequacy of antimicrobial therapy within the first 24 hours was significantly associated with 28-day survival (Hazard ratio (HR), 0.83; 95% CI, 0.72–0.96; p 0.01) (Fig. 2 and Table S3). The e-value was 1.53 for the estimate and 1.19 for the CI, indicating an acceptable risk of not taking into account unmeasured confounders (see Supplementary data). Based on the adjusted hazard ratio for 28-day mortality and the observed mortality of 32.8% (402/1226) among adequately treated patients, the estimated 28-day PAF of death due to inadequate therapy within 24 hours was 9.15% (95% CI, 1.9–16.2%).

Subgroup analyses

Using the frailty Cox proportional-hazard model with centre random effect adjusted for the same confounding variables, subgroup analyses were conducted on selected subgroups including Gram-positive pathogens, *Staphylococcus aureus*, Gram-negative pathogens, DTR Gram-negative pathogens, non-DTR Gram-negative pathogens, carbapenem-resistant Gram-negative pathogens, *Klebsiella* spp., *Acinetobacter* spp., fungi, anaerobes, and patients with and without septic shock (Figs. 3(a) and (b)). We did not unmask subgroups of patients with a significantly higher impact of adequate therapy on mortality. In patients with septic shock, adequacy of antimicrobial therapy within the first 24 hours showed an adjusted HR of 0.86 (95% CI, 0.68–1.09) for 28-day mortality. The result was similar excluding fungemia (HR, 0.83; [0.72–0.96]).

Sensitivity analyses

Using the frailty Cox proportional-hazard model with a centre random effect in patients still alive at 48 and 72 hours, sensitivity analyses were conducted defining an adequacy time within 48 hours or within 72 hours, respectively, and showed similar results (48-hour threshold: HR, 0.847; 95% CI, 0.726–0.988; p 0.034; PAF, 5.85% (0.81–10.98%); (Fig. S2, Tables S4 and S5); 72-hour threshold: HR, 0.863; [0.729–1.02]; p 0.085; PAF, 3.95% (8.12–0.55%) (Fig. S3, Tables S6 and S7). The inclusion of septic shock (HR, 0.82; [0.71–0.95]) and of the clinical pharmacist availability (HR, 0.84; [0.72–0.97]) yielded similar conclusions.

Discussion

In a prospective multinational cohort study of 2418 ICU patients with HA-BSI, approximately half of ICU patients received adequate antimicrobial therapy within the first 24 hours after blood culture collection. Treatment was more likely to be adequate in the most severely ill patients, those with *S. aureus* HA-BSI, and those with prior immunosuppression or cancer, and less likely to be adequate in patients with enterococcal or non-fermentative Gram-negative HA-BSI, candidemia, and HA-BSI due to microorganisms that were resistant to antimicrobials. The proportion of patients still in the ICU at day 28 and 28-day mortality were numerically lower in patients treated adequately within 24 hours.

After careful adjustment for measured confounders using DAG and causal inference models, we observed a significant association between adequate antimicrobial therapy within the first 24 hours and 28-day mortality in patients with HA-BSI hospitalized for more than 1 day. The results remained similar when using 48 and 72 hours as thresholds for adequate therapy. Although the results were not significantly different between subgroups that considered the microorganism type, resistance profile, and presence of septic shock, PAF was qualitatively higher for Gram-positive HA-BSIs (mainly *S. aureus* and Enterococci).

The benefit of early appropriate empirical antimicrobial therapy has been suggested by many cohort studies and systematic reviews [6,20–24]. Despite some negative findings [25], early adequate therapy sounds like the necessary first step to ensure good outcomes in patients with septic shock [26,27].

The most recent systematic review highlighted a substantial between-study heterogeneity (p < 0.001, $I^2 = 72\%$) regarding the impact of inappropriate therapy on the prognosis of bloodstream infections in adults [5]. The adjusted multivariable analysis performed on 125 studies concluded that early adequate therapy influences the prognosis of bloodstream infections (adjusted OR, 2.02; 95% CI, 1.86–2.49), but again with considerable heterogeneity ($I^2 = 92\%$, p < 0.001) and large discrepancies between the adjustment factors considered. In 14 studies performed in the ICU, the adjusted OR was 2.26, again with considerable heterogeneity ($I^2 = 91\%$, p < 0.001).

With the current analysis, we made huge efforts to adjust for all possible confounders using DAG, which substantially strengthened our final results.

We found that the benefit of adequate therapy within the first 24 hours was significant. It equated to a 20% decrease in the risk of mortality and a PAF of 9.15%. This finding may explain why

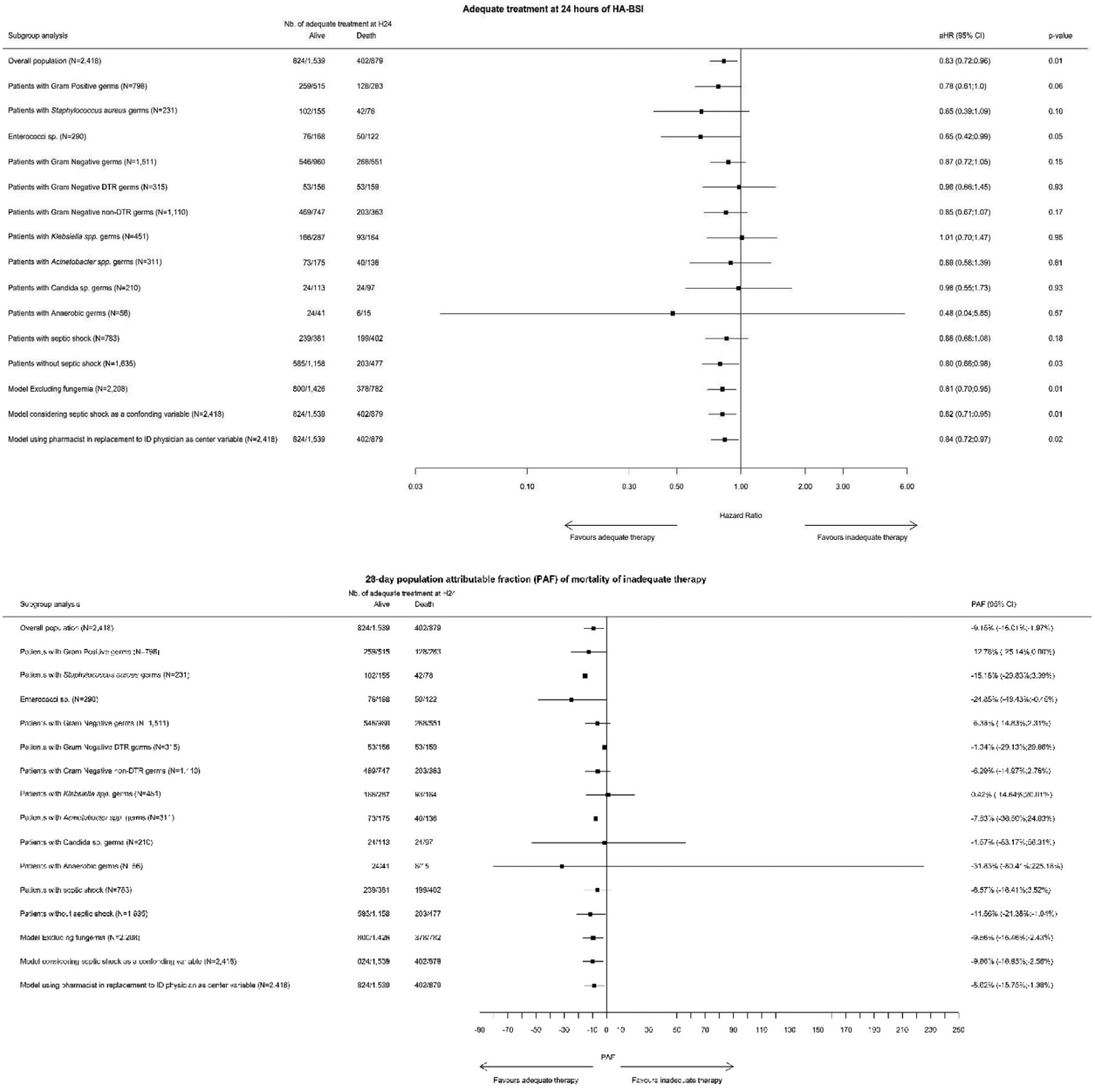

Fig. 3. Forest plot: adjusted hazard of 28-day death (panel a) and population attributable fractions (panel b) according to the adequacy of therapy within the first 24 hours in the primary analysis and subgroups analyses (frailty Cox proportional-hazard model adjusted on all the confounders described in Fig. 2). *Nota bene*: PAF is the fraction of death that would have not occurred if inadequate therapy had been eliminated. *Nota bene*: Interactions between septic shock and non-septic shock effect as well as interactions between Gram-negative DTR and Gram-negative non-DTR, Carbapenem susceptible Gram-negative and Carbapenem-resistant Gram-negative were non-significant, indicating the absence of heterogeneity of effect size between subgroups. DTR, difficult-to-treat resistance; HA-BSI, hospital-acquired bloodstream infections; ICU, intensive care unit; ID, infectious disease.

antimicrobial stewardship studies associated with rapid molecular tests allow a dramatic decrease in the time-to-appropriate therapy but are underpowered to detect a significant improvement in mortality risk in ICU patients [28,29].

The hypotheses of our mediation analysis could be questioned. Many studies adjusted for the severity of bacteraemia, but it is associated with delayed adequate treatment of an infectious process. It acts as a mediator in the analysis and should not be considered. On the other hand, almost half of the studies did not adjust for comorbidities [30], source of infection, or place of acquisition [31]. We considered that these variables were the reasons for an early prescription of broad-spectrum antimicrobials and risk factors for death, and therefore acted as confounders in estimating the causal path between adequate therapy and death.

We opted to use the time of collection of the first positive blood culture as time zero. A short time-to-blood culture positivity correlates with high inoculum and poor outcome [32] and is associated with more rapid appropriate antibiotic therapy. We therefore considered, if time 0 is the time the blood culture was obtained, that time-to-positivity is an ancestor of both time-to-adequate treatment and death (i.e. a confounder) and controlled our analysis for time-to-blood culture positivity.

Moreover, we used the presence of an ID physician and of written antibiotic protocols in a centre as surrogates of the prescribers' quality, although the prescriber quality was not individually assessed for each antimicrobial treatment. The hospital quality is also another latent confounder. Indeed, mediation analyses using causal DAGs per se are subject to

limitations [10,11]: they do not indicate the magnitude of biases or their interplay with random errors. The causal DAG interpretation may be more complex if there are repeated measures. The severity of organ dysfunction at time 0 might be an indication for an early broad-spectrum adequate therapy (i.e. an ancestor of adequate treatment) and at time 1, the consequence of inadequate treatment at time 0. This could reflect real-world concerns about potential sources of bias. In post hoc analyses, models using septic shock, resistance patterns, and pharmacist availability in the ICU (Fig. 2) as confounding variables provided similar results.

The available studies also differ in the threshold chosen to define early therapy. It varies from before the culture result to 5 days after the culture result, with almost half of the articles not clearly distinguishing between the blood culture collection time and the blood culture positivity time.

Our results remained similar when using 24, 48, and 72 hours as time thresholds for adequate therapy.

We only included patients who were still alive 1 day after the positive blood culture. Consequently, we did not evaluate the impact of treatment adequacy on mortality within the first 24 hours. Results may also have been affected by the immortal time bias introduced by this pre-selection. Indeed, patients who died very early had a higher risk of not receiving appropriate early therapy. Conversely, early death is thought to be related to inflammation and sepsis and is less likely to be reversed by appropriate antibiotic therapy. However, this hypothesis is unlikely because it represented only 7% of the patients (Table S1), and the impact of antibiotic therapy was shown to increase with the time-to-antibiotic therapy threshold in a study using a landmark approach [33].

The follow-up was limited to 28 days after the HA-BSI onset. The long-term effect of adequate therapy could not be evaluated and may have influenced our results [20], especially because half of the patients were still hospitalized at day 28.

The impact of adequate antimicrobial therapy may also vary according to the nature and tolerance of the antimicrobial. In our study, adequate therapy within the first 24 hours was mainly broad-spectrum (in more than half, broad-spectrum beta-lactams). Indeed, in culture-proven sepsis, unnecessarily broad-spectrum antimicrobials have been associated with increased in-hospital mortality compared with that associated with narrow-spectrum adequate antimicrobials [29,34].

Finally, the administration of an antimicrobial to which the strain is susceptible *in vitro* may be suboptimal. As an example, colistin may be considered suboptimal for DTR Gram-negative bacteria compared with new betalactam-betalactamases inhibitors [35–40]. However, these agents are not available in many countries, and thus could not be used against *Acinetobacter baumanni*, which represented a major part of DTR Gram-negative organisms in our study [38]. Furthermore, the Eurobact2 trial did not collect therapeutic drug monitoring data to check whether the antimicrobial was given at a sufficient dose to achieve adequate pharmacokinetic/pharmacodynamic (PK/PD) targets. However, the adequacy of the dose administered was considered appropriate during the quality control checking.

Conclusions

After careful adjustment for all measured patient- and centre-related confounders, the adequacy of antimicrobial therapy within the first 24 hours after HA-BSI was significantly associated with a decreased 28-day mortality. The resulting PAF of mortality attributable to inadequate therapy within the first 24 hours was 9.15%. This point should be considered when designing a superiority trial aiming to demonstrate a benefit in mortality of a strategy or a diagnostic test aiming to shorten the time-to-adequate therapy in bloodstream infections [10].

Author contributions

S.B., S.R., N.B., F.B., A.T., and J.-F.T. designed and conducted the study. A.L., S.B., S.R., and Q.S. performed the statistical analyses. A.L. wrote the first draft of the manuscript. J.-F.T. supervised the writing process. All authors performed critical review of the manuscript.

Transparency declaration

Potential conflict of interest

F.B. reported consulting and lecture fees, conference invitation from MSD, and lecture fees from bioMérieux. J.-F.T. reported advisory board participation for Merck, Gilead, Beckton-Dickinson, Pfizer, Shionogi, Medimmune, Advanz, Roche diagnostic, and bioMérieux research grants from Merck, Pfizer, and Thermofischer. The other authors declare that they have no conflicts of interest.

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Ethics approval and consent to participate

Initial ethical approval as a low-risk research project with waiver of individual consent was granted by the Human Research Ethics Committee of the Royal Brisbane & Women's Hospital, Queensland, Australia (LNR/2019/QRBW/48376). Each study site then obtained ethical and governance approvals according to national and/or local regulations.

Data availability statement

The datasets used and/or analysed during the current study are available from the OUTCOMEREA organization upon reasonable request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2024.09.011.

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