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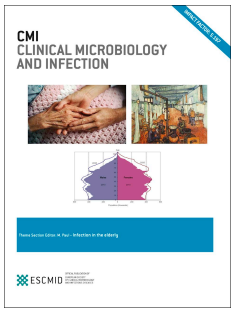

Effect of adequacy of empirical antibiotic therapy for hospital-acquired bloodstream infections on ICU patient prognosis: a causal inference approach using data from the Eurobact2 study

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Title page – Original article

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

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Abstract

Objectives. Hospital-acquired bloodstream infections (HA-BSI) in the intensive care unit (ICU) are common life-threatening events.

We wanted to investigate the association between early adequate antibiotic therapy and 28-day mortality in ICU patients surviving for at least 1 day after the onset of HA-BSI.

Methods We used individual data from a prospective, observational, multicenter, intercontinental cohort study (Eurobact2).

We included patients followed for ≥1 day 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 primary analysis. Secondary analyses were performed for adequate therapy within 48 and 72 hours and for identified patient subgroups.

Results. Among the 2,418 patients included in 330 centers 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 (aHR 0.83, 95% CI 0.72-0.96, p=0.01). The estimated population attributable fraction (PAF) of 28-day mortality of inadequate therapy was 9.15% (95% CI 1.9%-16.2%).

Conclusions. In patients with HA-BSI admitted in ICU, the PAF of 28-day mortality of inadequate therapy within 24 hours was 9.15%. This estimate should be used when

hypothesizing the possible benefit of any intervention aiming at reducing the time-to-appropriate antimicrobial therapy in HA-BSI.

Key words: time-to-antibiotic therapy, sepsis, hospital-acquired bloodstream infection, critically ill, adequacy, Directed Acyclic Graph, mediation analysis.

Text

1. 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 multicenter multinational prospective Eurobact2 study were used[2], with direct acyclic graph method to optimally select the measured confounders, and causal inference models.

2. 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 employed can be found elsewhere[2] and in supplementary material. Briefly, centers were recruited on a voluntary basis to include 10 consecutive cases for a maximal period of 3 consecutive months. We included adult (≥ 18 years of age) patients with a HA-BSI treated in the ICU. HA-BSI was defined as a positive blood culture sampled more than 48 h 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.

Intensive care unit and patient selection:

We included 2,418 ICU patients with HA-BSI from 330 centers 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 Figure 1, electronic supplement Figure E1,Table E1).

Data collection and definitions:

Data collection is detailed elsewhere (see ESM)[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 ESM[9].

The selected variable of interest was an 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 (AT,FB and NB).

Statistical analysis:

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

First, we identify confounders based on existing literature and experts (AT,JFT,NB,FB) [10] and reported it visually in a Directed Acyclic Graph (DAG)[11, 12] (Figure 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 SOFA 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 center-based surrogates of prescriber quality.

The association between therapy adequacy and 28-day mortality was evaluated using a frailty Cox proportional-hazard model with a center random effect. All analyses were adjusted on all selected patient- and center-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 bloodculture collection, on patients with ≥2 days and ≥3 days of follow-up after the 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.

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

A sample of 2,418 patients was calculated as sufficient to detect a benefit of 4.8% in 28-day mortality of 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).

3. Results

Patients' characteristics

A total of 1,226 patients with adequate treatment within the first 24 hours of HA-BSI and 1,192 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 patients characteristics are in Table E1.

The main antimicrobials included are carbapenems, piperacillin-tazobactam, colistin, vancomycin and echinocandins(Table E2). The median delay of 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 with 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% *versus* 81.4%, p<0.01). The cause of infection was more frequently a Gram-negative pathogen (66.4% *versus* 58.5%, p<0.01)(Table 2); fungal HA-BSI were less frequent (3.9% *versus* 13.6%, p<0.01). They had a lower overall prevalence of multidrug-

resistant Gram-negative infections (13% *versus* 30%, p<0.01) and *Acinetobacter* spp. infections (13.9% *versus* 28.4%, p<0.01).

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

The percentage of adequate treatment within 24h per center was higher for centers 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 of the frailty Cox models are those associated with both adequate treatment and mortality (Figure 2). The variables used for adjustment were hospital stay duration before HA-BSI, pathogen category, time-to-blood culture positivity, age, sex, comorbidities, SOFA 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 it influenced the promptness of antimicrobial therapy and acted as confounders. Pathogen resistance was not used for adjustment as considered causally associated with early adequate treatment but not *per se* causally associated with death[6, 17]. Prescriber quality was assumed as represented by 2 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 center-based variable, as recently evaluated by another analysis[19]. Available financial resources, hospital quality, and the socio-economic situation of the hospital, are latent variables, not included in the adjustment but were considered introducing a random center effect in all models.

Survival analyses

After accounting for all measured confounders and incorporating the random center effect, the adequacy of antimicrobial therapy within the first 24 hours was significantly associated with 28-day survival (HR 0.83, 95%CI 0.72-0.96, p=0.01)(Figure 2 and Table E3). The e-value was 1.53 for the estimate and 1.19 for the confidence interval, indicating an acceptable risk of not taking into account unmeasured confounders (see ESM). Based on the adjusted hazard ratio of 28-day mortality and the observed mortality of 32.8% (402/1226) among adequately treated patients, the estimated 28-day population attributable fraction (PAF) of death due to inadequate therapy within 24 hours was 9.15% (95% CI 1.9%-16.2%).

Subgroup analyses

Using Frailty Cox proportional-hazard model with center random effect adjusted on the same confounding variables, subgroup analyses were conducted on selected subgroups including Gram-positive pathogens, *Staphylococcus aureus*, Gram-negative pathogens, Difficult-to-Treat Resistant Gram-negative pathogens (DTR), non-DTR Gram-negative pathogens, carbapenem-resistant Gram-negative pathogens, *Klebsiella* spp., A*cinetobacter* spp., fungi, anaerobes, and patients with and without septic shock (Figures 3a,b). We did not unmask subgroups of patients with a significantly higher impact of adequate therapy on mortality. In patients with septic

shock, the 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 frailty Cox proportional-hazard model with a center random effect in patients still alive at 48 and 72 hours, sensitivity analyses were conducted defining an adequacy time within 48h or within 72h, 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%); (Figure E2, Tables E4 & E5); 72-hour threshold: HR=0.863 [0.729-1.02], p=0.085,PAF 3.95% (8.12%;-0.55%) (Figure E3, Tables E6 & E7). 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.

4. Discussion

In a prospective multinational cohort study of 2,418 ICU patients with HA-BSI, approximately half of ICU patients received adequate antimicrobial therapy within the first 24 hours of 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 previous 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 one 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, the 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 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 ($p<0.001$, $I2=72\%$) regarding the impact of inappropriate therapy on the prognosis of BSIs in adults[5]. The adjusted multivariable analysis performed on 125 studies concluded that early adequate therapy influences the prognosis of BSI (aOR 2.02 (95%CI, 1.86-2.49), but again with considerable heterogeneity ($I2=92\%$, $p<0.001$) and large discrepancies between the adjustment factors considered. In 14 studies performed in ICU, the aOR 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 antimicrobial stewardship studies associated with rapid molecular

tests allow a dramatic decrease in the time-to-appropriate therapy, but are underpowered to detect 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 bacteremia, but it is associated with a 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 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 of 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 a high inoculum and poor outcome[32], and is associated with more rapid appropriate antibiotic therapy. We therefore considered, if time zero 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 ID physician and of written antibiotic protocols in a center 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 subjects to limitations[10, 11]: it does not indicate the magnitude of biases or their interplay with random errors. The causal DAGs 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 an 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(Figure 2) as confounding variables provided similar results.

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 using 24,48 and 72 hours as time thresholds for adequate therapy.

We only included patients who were still alive one 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, since it represented only 7% of the patients (table E1), and the impact of antibiotic therapy was shown to increase with time-to-antibiotic therapy threshold in a study using a landmark approach[33].

The follow-up was limited to 28 days following 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 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 (for more than half, broad spectrum beta-lactams).

Indeed, in culture-proven sepsis, unnecessarily broad-spectrum antimicrobials have been associated with an increased in-hospital mortality compared to that associated with narrow spectrum adequate antimicrobials[29, 34].

Finally, the administration of an antimicrobial for which the strain is susceptible *in vitro* may be suboptimal. As an example, colistin may be considered suboptimal for DTR Gram-negative bacteria compared to new betalactam-betalactamases inhibitors (BL-BLI)[35-40]. However, these agents are not available in many countries, 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 PK/PD targets. However, the adequacy of the dose administered was considered appropriate during the quality control checking.

5. Conclusions

After carefully adjustment for all measured patients- and center-related confounders, the adequacy of antimicrobial therapy within the first 24 hours of HA-BSI was significantly associated with a decreased 28-day mortality. The resulting population-attributable-fraction of mortality attributable to inadequate therapy within the first 24 hours was 9.15%. This point should be considered when designing 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]

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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.

Availability of data and materials:

The datasets used and/or analyzed during the current study are available from

the OUTCOMEREA organization upon reasonable request.

Competing interests:

FB reported consulting and lecture fees, conference invitation from MSD and lecture fees from BioMérieux. J-FT reported advisory boards participation for Merck, Gilead, Beckton-Dickinson, Pfizer, Shionogi, Medimmune, Advanz, Roche diagnostic, Biomerieux research grants from Merck, Pfizer, Thermofischer. The other authors have nothing to disclose.

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SR, SB, JFT, FB, AT and NB designed and conducted the study. AL, SB, SR, QS performed the statistical analyses. AL wrote the first draft of the manuscript. All authors performed critical review of the manuscript. JFT supervised the writing process.

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Figure 1: Flow Chart of patients with HA-BSI with or without adequate treatment within the first 24 hours after the positive blood culture.

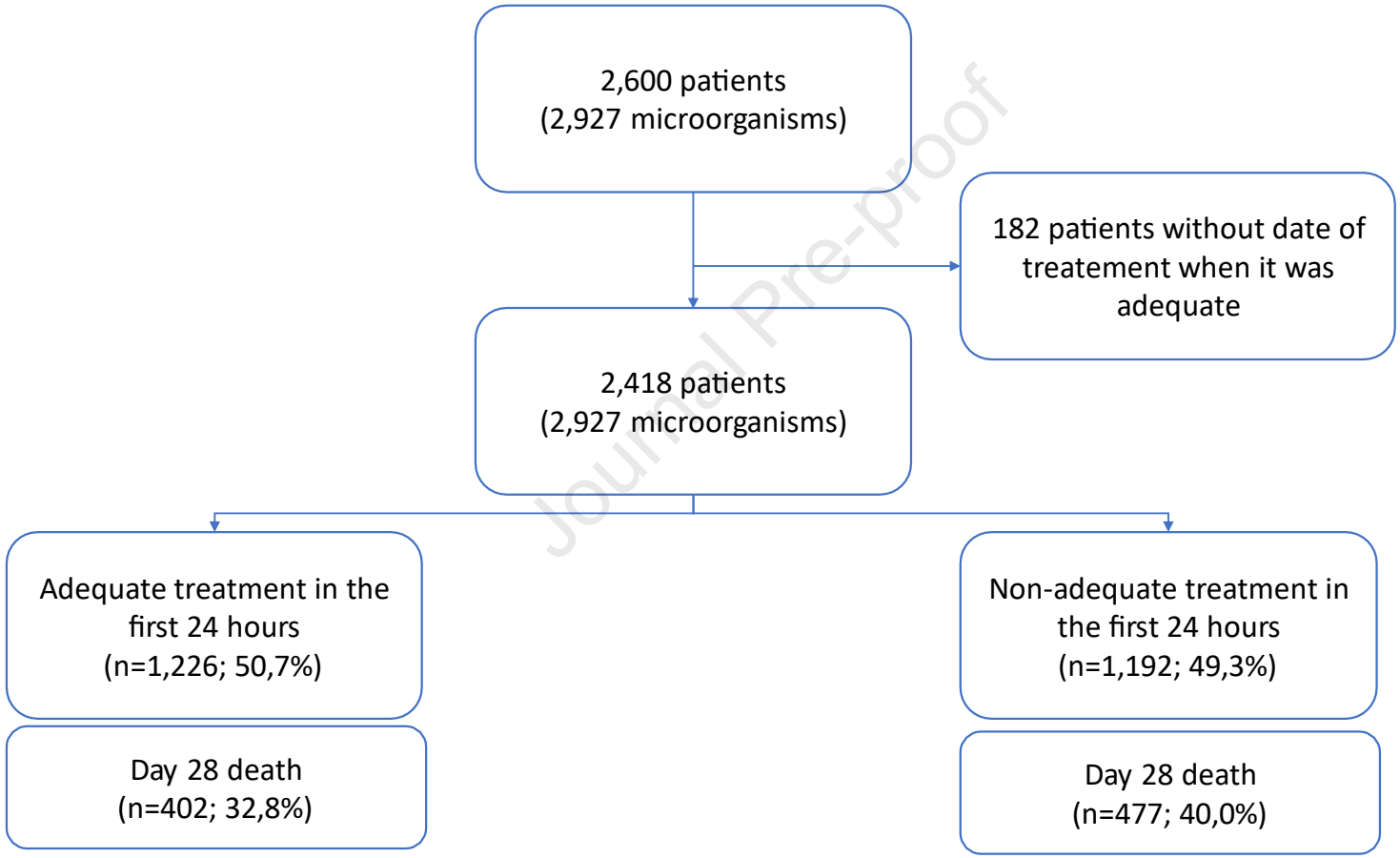
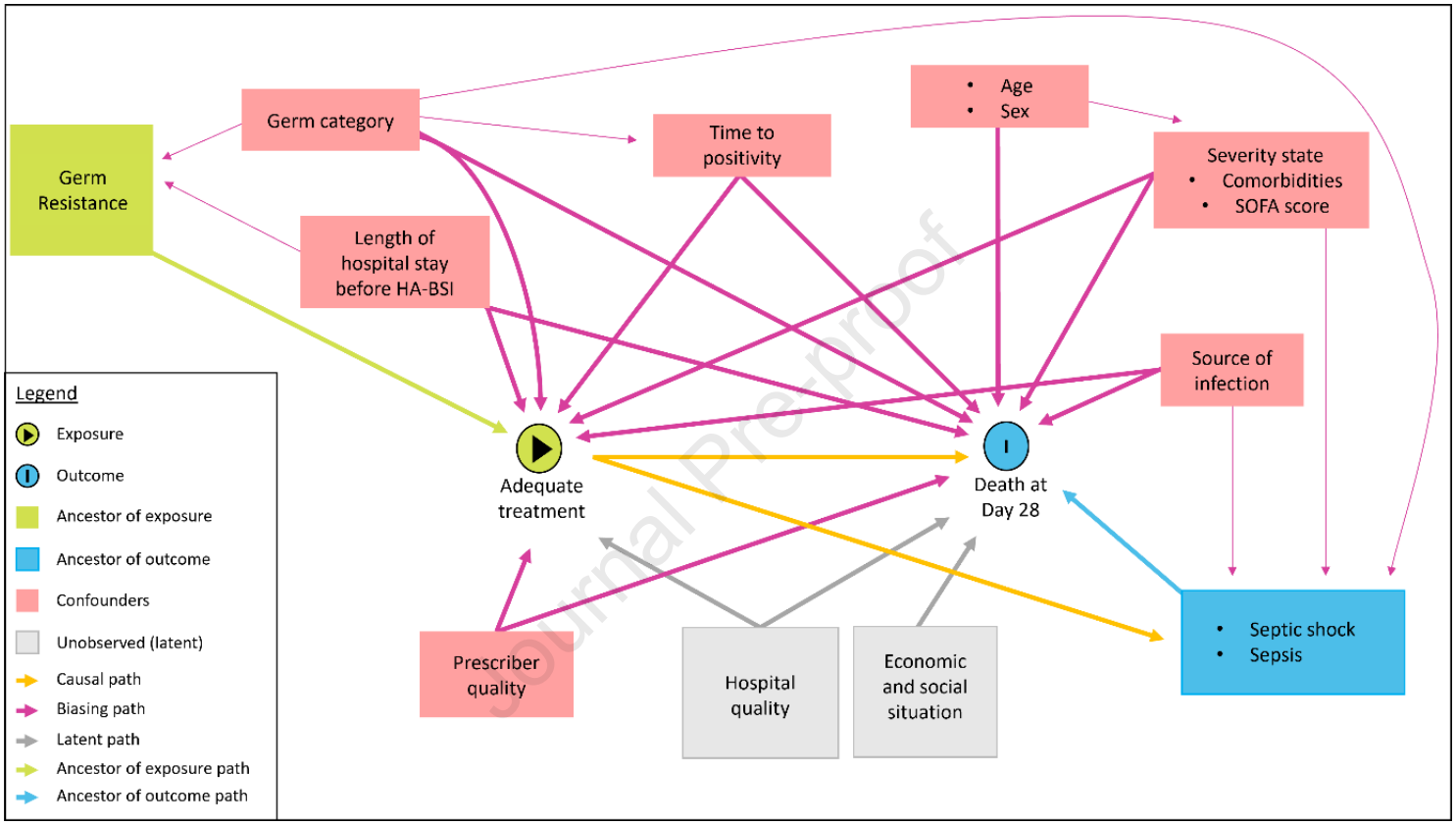


Figure 2. Confounding variables selection using a Directed Acyclic Graph (DAG).



Legend. SOFA score: Sequential Organ Failure Assessment score.

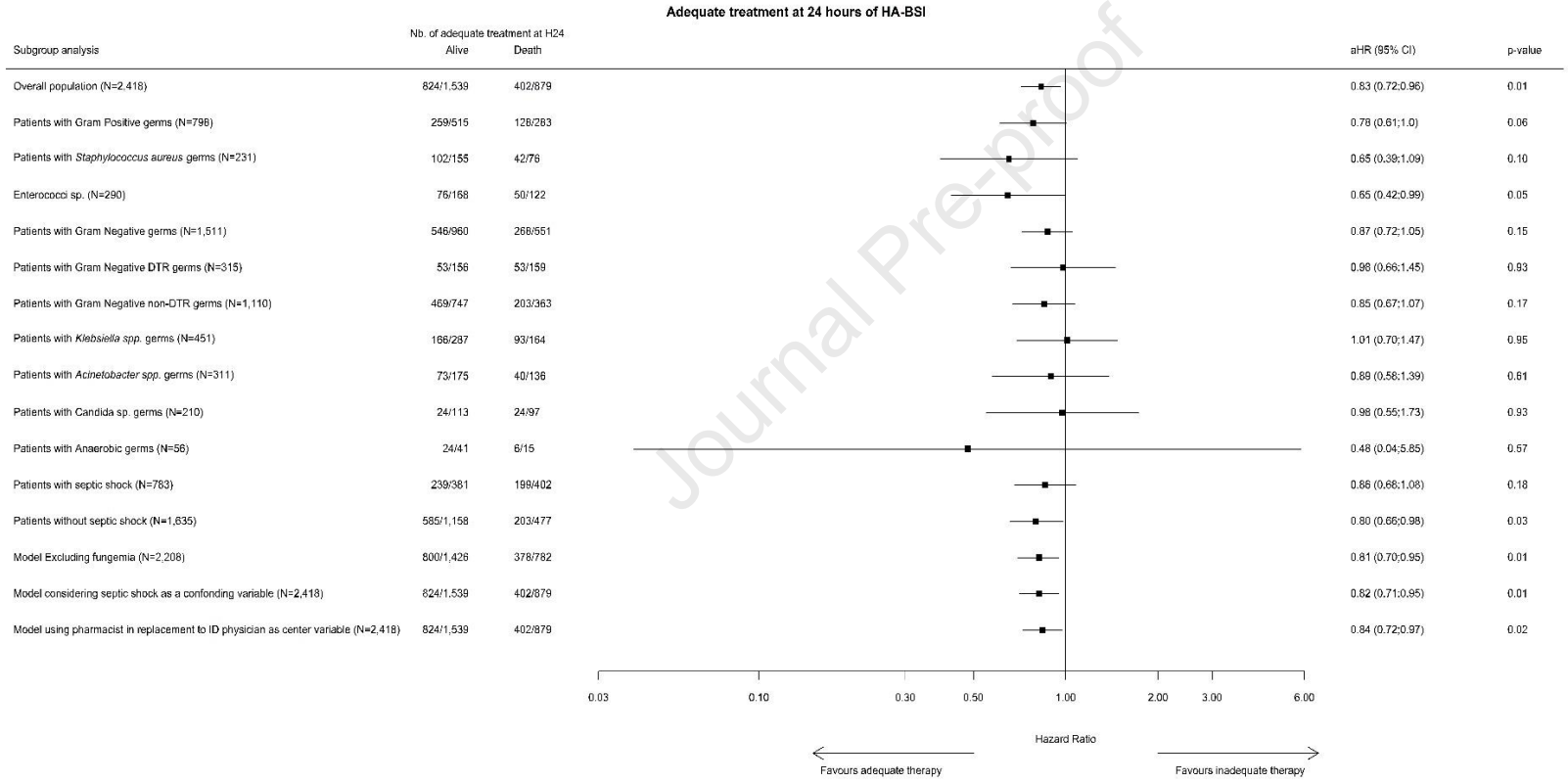
The DAG is a graphical representation of the potential causal relationships between variables, with arrows used to denote the direction of causality. Collider bias occurs when 2 arrows collide on a variable that has been controlled for. DAG was performed using the DAGitty v3.1 software (https://dagitty.net/dags.html).

NB: 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 mediates 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).

NB2: 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.

716 **Figure 3. Forest plot: Adjusted hazard of 28-Day death (panel A) and population attributable fractions (panel B) according**
717 **to adequacy of therapy within the first 24 hours in the primary analysis and subgroups analyses. (Frailty Cox proportional-**
718 **hazard model adjusted on all the confounders described in figure 2).**



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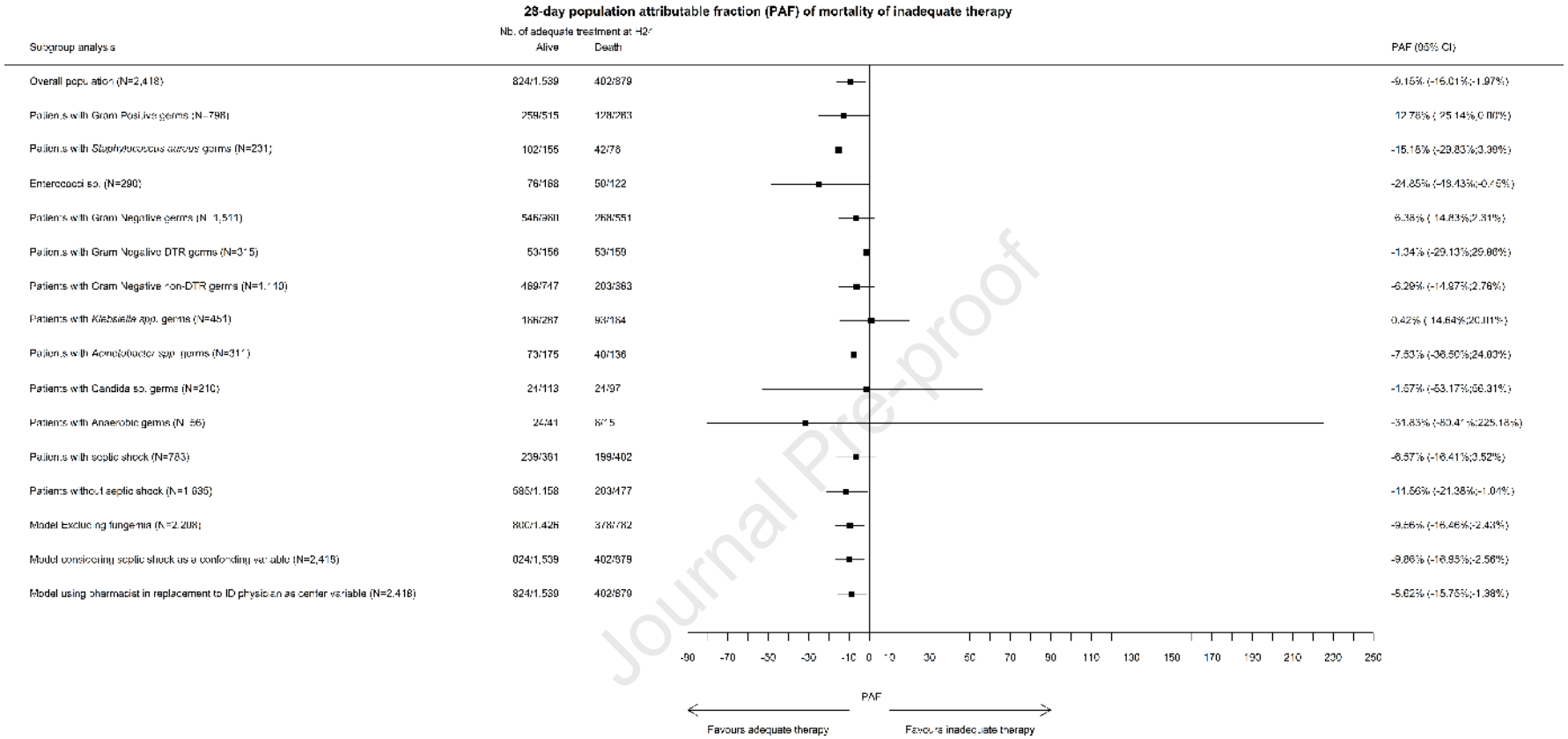

Legend. HA-Legends of the figure 2: BSI: Hospital-acquired bloodstream infection. ICU: Intensive care unit. DTR: Difficult to Treat Resistance.

NB: PAF is the fraction of death that would have not occurred if inadequate therapy had been eliminated.

NB: 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.

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

Variables	All HA-BSI	Adequate treatment H24	Inadequate treatment H24	P value[1]	P value[2]
	(n=2,418)	(n=1,226)	(n=1,192)		
Patients' characteristics on HA-BSI onset					
Age, years	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
Co-morbid 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*	1314 (54.3)	718 (58.6)	596 (50)	<0.01	0.04
28-Day mortality**	879 (36.4)	402 (32.8)	477 (40.0)	<0.01	<0.01

730
731 Legend: HA-BSI: Hospital-acquired bloodstream infection. ICU: Intensive care unit. SOFA: Sequential
732 organ failure assessment score.
733 *: for some patients, vasopressor was started before the new sepsis without dose increase and are not
734 included in the definition of septic shock.
735 **: day 28 vital status was available for all patients.
736 [1]To assess differences in categorical variables, chi-square or Fisher's exact tests were used as
737 appropriate. Additionally, t-test or Wilcoxon rank sum test were used as appropriate for continuous
738 variables.
739 [2]To assess differences in categorical variables stratified by center, Cochran-Mantel-Haenszel test was
740 used. Additionally, Van Elteren test was used for continuous variables.
741 Footnotes: Results reported as n (%) for categorical variables and median [IQR] for continuous
742 variables. There were no missing values.

Table 2: Hospital-acquired bloodstream infection characteristics

Variables	All HA-BSI	Adequate treatment H24	Inadequate treatment H24	P value[1]
	(n=2,418)	(n=1,226)	(n=1,192)	
Time-to-positivity of blood culture (hours)[2]	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.[4]	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
Non fermentative 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[3] 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)	

Legend: HA-BSI: Hospital-acquired bloodstream infection. GNB: Gram negative bacteria, DTR: Difficult to Treat Resistant. PDR: Pan-Drug Resistant.
[1]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.
[2]Time-to-positivity: 822 missing data recoded using the median value for multivariate analyses and
[3]DTR: 86 missing data because antibiotic susceptibility testing was not completed for all the drugs required to meet the DTR definition.
[4]*E faecalis* n=132, *E faecium* n=143, other enterococci n=15, vancomycin-resistant enterococci were only reported in 36/290 cases.
Footnotes: Results reported as n (%) for categorical variables and median [IQR] for continuous variables.

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Participating ICUs: Avicenne Military Hospital, Icu: Dr Issam Serghini, Pr Rachid Seddiki. CHU Hassan II Fès, Intensive Care Unit A4: Dr Brahim Boukatta, Dr Nabil Kanjaa. Hospital Of Specialties, Critical Care Unit of Neurology and Neurosurgery: Prof Doumiri Mouhssine, Prof Maazouzi Ahmed Wajdi. Ibn Sina University Hospital, faculty of Medicine and Pharmacy, Mohammed V University in Rabat, Medical Icu: Pr Tarek Dendane, Pr Amine Ali Zeggwagh. Mohammed VI University Hospital of Oujda, Faculty Of Medicine and Pharmacy Oujda, Mohammed Premier University, Anesthesia and Resuscitation Department: Prof Brahim Housni, Dr Oujidi Younes. Mohammed VI University Hospital, Medical Icu, Marrakech: Prof Abdelhamid Hachimi. National Institute of Oncology of Rabat, Intensive Care Unit: Prof A Ghannam, Prof Z Belkhadir.
Palestine
Participating ICUs: ICU, Alia governmental hospital, Hebron / West Bank, Palestine: Dr. Sarah Amro. Gaza city, Alshifaa hospital, Gaza, Palestine: DR. Mustafa Abu Jayyab.
Qatar
National Coordinator: Dr Ali Aithssain
Participating ICUs: Hamad General Hospital, Medical Icu: Dr Ali Ait Hssain, Dr Abdurahaman Elbuzidi. Al Wakrah Hospital, Critical Care: Dr Edin Karic. Hamad General Hospital, Sicu: Dr Marcus Lance, Dr Shaikh Nissar.
Saudi Arabia
Participating ICUs: King Faisal Specialist Hospital &Research Center, Adult Critical Care Medicine: Dr Hend Sallam. Prince Sultan Medical Military Center, Intensive Care Unit: Dr Omar Elrabi, Dr Ghaleb A Almekhlafi. Security Force Hospital - Riyadh, Critical Care Unit: Dr Maher Awad, Dr Ahmed Aljabbary.
Syria
Participating ICUs: Al Mouwasat University Hospital, Icu: Dr Mohammad Karam Chaaban. Assad University Hospital, Neurological Intensive Care Unit: Dr Natalia Abu-Sayf. Damascus University Cardiac Surgery Hospital Near Al-Mouwasat University Hospital, Mazzeh Kiwan, Cardiac Surgery Icu: Dr Mohammad Al-Jadaan, Miss Lubna Bakr.
Tunisia
National Coordinator: Dr Mounir Bouaziz
Participating ICUs: Habib Bourguiba University Hospital, Department of Intensive Care: Dr Mounir Bouaziz, Dr Olfa Turki. Military Hospital of Tunis, Department of Anesthesiology And Intensive Care Unit, Lr12dn01: Pr Walid Sellami.

Latin America and The Caribbean

Argentina

National Coordinator: Dr. Gabriela Vidal

Participating ICUs: Hcas Cuenca Alta, Terapia Intensiva: Dr Pablo Centeno, Lic Natalia Morvillo. Hospital Central De Formosa, Servicio De Terapia Intensiva: Dr José Oscar Acevedo, Dr Patricia Mabel Lopez. Hospital Español De Mendoza, Terapia Intensiva De Adultos: Dr Rubén Fernández, Dr Matías Segura. Hospital Zatti, Ucia: Dra Marta Aparicio, Microbiologa Irene Alonzo. Instituto De Diagnostico De La Plata, Unidad De Terapia Intensiva: Dr Yanina Nuccetelli, Dr Pablo Montefiore.

Colombia

National Coordinator: Mario Arias

Participating ICUs: Clinica Universidad De La Sabana, Critical Care Unit : Dr Luis Felipe Reyes. Universidad De La Sabana, Infectious Diseases Department: Dr Luis Felipe Reyes.

Mexico

National Coordinator: Dr Silvio A. Ñamendys-Silva

Participating ICUs: Hospital Medica Sur, Department of Critical Care Medicine: Dr Silvio A. Ñamendys-Silva, Dr Juan P. Romero-Gonzalez. Centenario Hospital Miguel Hidalgo, Centenario Hospital Miguel Hidalgo: Dr Mariana Hermosillo, Dr Roberto Alejandro Castillo. Hospital General De Zona 14, Intensive Care Unit: Dr Jesús Nicolás Pantoja Leal, Dr Candy Garcia Aguilar. Hospital General Regional No.1, IMSS Tlaxcala: Dr Mara Ocotlan Gonzalez Herrera, Dr Missael Vladimir Espinoza Villafuerte. Hospital H+ Queretaro, Unidad De Terapia Intensiva Adultos: Dr Manuel Lomeli-Teran. Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Division of Pulmonary, Anesthesia and Critical Care Medicine: Dr Jose G. Dominguez-Cherit, Dr Adrian Davalos-Alvarez, Dr Silvio A. Ñamendys-Silva. UMAE Hospital de Especialidades Antonio Fraga Mouret, Centro Médico Nacional La RazaIMSS, Terapia Intensiva Hospital de Especialidades CMN La Raza: Dr Luis Sánchez-Hurtado, Dr Brigitte Tejeda-Huezo. Hospital General San Juan del Rio, Querétaro, , Unidad de Terapia Intensiva de Adultos: Dr Orlando R Perez-Nieto, Dr Ernesto Deloya Tomas.

Europe And Central Asia

Belgium

National Coordinator: Dr. Liesbet De Bus

Scientific Committee: Prof. Jan De Waele

Recruitment of participating ICUs worldwide: Mr. Guy Francois

Participating ICUs: Ghent University Hospital, Intensive Care Unit: Dr Liesbet De Bus, Dr Jan De Waele. A.S.Z., Iz: Dr Isabelle Hollevoet. Az Nikolaas, Icu: Dr Wouter Denys. Az Sint-Jan Av Brugge - Oostende Campus Brugge, Icu: Dr Marc Bourgeois. Az Sint-Lucas, Department of Intensive Care: Dr Sofie F.M. Vanderhaeghen. Centre Hospitalier De Jolimont, Soins Intensifs : Dr Jean-Baptiste Mesland, Dr Pierre Henin. Chu Ambroise Paré, Unité Des Soins Intensifs : Dr Lionel Haentjens. Chu Charleroi, Medico-Surgical Icu: Dr Patrick Biston, Mrs Cindérella Noel. Chu Liège, Soins Intensifs : Dr Nathalie Layos, Dr Benoît Misset. Clinique Saint-Pierre, Intensive Care Unit : Dr Nicolas De Schryver, Dr Nicolas Serck. Cliniques Universitaires Saint-Luc, UCLouvain, Soins Intensifs : Dr Xavier Wittebole. Uzbrussel, Intensieve Zorgen: Prof Elisabeth De Waele, Mrs Godelive Opdenacker.

Bosnia And Herzegovina

National Coordinator: Dr Pedja Kovacevic

Participating ICUs: University Clinical Centre of The Republic Of Srpska, Medical Intensive Care Unit: Dr Pedja Kovacevic, Dr Biljana Zlojutro.

Croatia

National Coordinator: Dr Ina Filipovic-Grcic

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Hospital Dubrava, Clinical Department of Anesthesiology, Reanimatology and Intensive Care: Prof Jasminka Persec, Dr Sanja Sakan, Dr Mario Nikolic, Dr Hrvoje Lasic.

France

National Coordinator: Prof. Marc Leone

Scientific Committee: Prof. Jean-François Timsit, Prof. Etienne Ruppe, Mr. Stephane Ruckly, Prof. Philippe Montravers

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Germany

National Coordinator: Prof. Hendrik Bracht

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Kazakhstan

National Coordinator: Dr. Dmitriy Viderman

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Greece

National Coordinator: Dr. Kostoula Arvaniti

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Italy

National Coordinator: Prof. Matteo Bassetti and Dr. Daniele Giacobbe

Participating ICUs: Città Della Salute E Della Scienza - Molinette, Anestesia E Rianimazione Universitaria: Dr Giorgia Montrucchio, Dr Gabriele Sales. Fondazione Policlinico Universitario A. Gemelli Irccs. Universita Cattolica Del Sacro Cuore. Italy, Uoc Di Anestesia, Rianimazione, Terpia Intensiva E Tossicologia Clinica: Dr Gennaro De Pascale, Dr Luca Maria Montini, Dr Simone Carelli, Dr Joel Vargas, Ms Valentina Di Gravio. Irccs Ospedale Policlinico San Martino, U.O. Anestesia E Rianimazione: Prof Daniele Roberto Giacobbe, Dr Angelo Gratarola, Dr Elisa Porcile, Dr Michele Mirabella. Irccs Sacro Cuore Don Calabria, Terapia Intensiva: Dr Ivan Daroui, Dr Giovanni Lodi. Madonna Delle Grazie, U.O.C. Anestesia E Rianimazione: Dr Francesco Zuccaro, Dr Maria Grazia Schlevenin. Ospedale Policlinico San Martino, Irccs Per L'oncologia E Le Neuroscienze, Uo Clinica Anestesiologica E Terapia Intensiva: Prof Paolo Pelosi, Dr Denise Battaglini. Policlino Paolo Giaccone, Università Degli Studi Di Palermo, Terapia Intensiva Polivalente: Dr Andrea Cortegiani, Dr Mariachiara Ippolito, Dr Davide Bellina, Dr Andrea Di Guardo. Regina Elena National Cancer Institute of Rome, Anesthesia and Intensive Care Department: Dr Lorella Pelagalli, Dr Marco Covotta. Sant'andrea Hospital Sapienza University of Rome, Department of Medical And Surgical Science And Translational Medicine Intensive Care Unit: Dr Monica Rocco, Dr Silvia Fiorelli. University Hospital O.O.R.R., Department of Anesthesia And Intensive Care: Prof Antonella Cotoia, Dr Anna Chiara Rizzo.

Poland

National Coordinator: Dr Adam Mikstacki

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Republic Of Ireland

National Coordinator: Prof Ignacio Martin-Loeches

Participating ICUs: St Jame's Hospital, Intensive Care Unit: Prof Ignacio Martin-Loeches, Dr Alessandra Bisanti.

Portugal
National Coordinator: Prof. José Artur Paiva
Scientific Committee: Prof. Pedro Póvoa
Participating Icus: Centro Hospitalar Medio Tejo - Unidade Abrantes, Ucip: Dr Nuno Cartoze, Dr Tiago Pereira. Centro Hospitalar Universitário do Porto, Sci 1: Dr Nádia Guimarães, Dr Madalena Alves. Centro Hospitalar Vila Nova De Gaia/Espinho, Unidade De Cuidados Intensivos Polivalente: Dr Ana Josefina Pinheiro Marques, Dr Ana Rios Pinto. CHUA Faro, Smi-1 : Dr Andriy Krystopchuk, Dr Ana Teresa. Hospital De Cascais Dr Jose De Almeida, Unidade de Cuidados Intensivos: Dr António Manuel Pereira de Figueiredo, Dr Isabel Botelho. Hospital Curry Cabral, Intensive Care Medicine Department: Dr Tiago Duarte. Hospital Sao Francisco Xavier, CHLO, Unidade De Cuidados Intensivos Polivalente: Dr Vasco Costa, Dr Rui Pedro Cunha. Hospital Pedro Hispano, Serviço De Medicina Intensiva: Dr Elena Molinos, Dr Tito da Costa. CHULC, Hospital Sao José, Unidade de Urgência Médica: Dr Sara Ledo, Dr Joana Queiró. ULS Litoral Alentejano, Serviço de Medicina Intensiva: Dr Dulce Pascoalinho. ULS Nordeste, Unidade de Cuidados Intensivost: Dr Cristina Nunes. ULSAM, UCI: Dr José Pedro Moura, Dr Énio Pereira. ULS Baixo Alentejo, Unidade Cuidados Intensivos Polivalente: Dr António Carvalho Mendes.

Romania
National Coordinator: Dr Liana Valeanu
Participating ICUs: Emergency Institute for Cardiovascular Diseases Prof. Dr. C. C. Iliescu, 1st Anesthesia and Intensive Care Department: Dr Liana Valeanu, Prof Serban Bubenek-Turconi. Clinical Emergency Hospital Bucharest, Anesthesia and Intensive Care Department: Prof Ioana Marina Grintescu, Dr Cristian Cobilinschi. Emergency Institute for Cardiovascular Diseases Prof. Dr. C. C. Iliescu, 2nd Anesthesia and Intensive Care Department: Prof Daniela Carmen Filipescu, Dr Cornelia Elena Predoi. Fundeni Clinical Institute, 3rd Department of Anesthesia and Intensive Care: Prof Dana Tomescu, Dr Mihai Popescu, Dr Alexandra Marcu. University Of Medicine and Pharmacy "Grigore T Popa", Anesthesia and Intensive Care Department: Prof Ioana Grigoras, Dr Olguta Lungu.

Russian Federation
National Coordinator: Prof. Alexey Gritsan
Participating ICUs: V.F. Voino-Yasenetsky Krasnoyarsk State Medical University, Krasnoyarsk Regional Clinical Hospital, Dep. Anaesthesiology and Intensive Care #3: Prof Alexey Gritsan. City Clinical N.I.Pirogov Hospital, Clinical Pharmacology: Dr Anastasia Anderzhanova, Dr Yulia Meleshkina. City Clinical N.I.Pirogov Hospital, Icu: Dr Marat Magomedov. E.A. Vagner Perm State Medical University, Intensive Care Unit: Prof Nadezhda Zubareva, Dr Maksim Tribulev. Krasnoyarsk Regional Clinical Hospital, Dep. Anaesthesiology and Intensive Care #3: Dr Denis Gaigolnik. Petrovsky National Research Centre of Surgery, Intensive Care: Dr Aleksandr Eremenko, Dr Natala Vistovskaya, Dr Maria Chukina. Privolzhskiy District Medical Center, Department Anesthesiology and Intensive Care: Dr Vladislav Belskiy, Dr Mikhail Furman.

Spain
National Coordinator: Dr. Ricard Ferrer Rocca
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Sweden
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Switzerland
National Coordinator: Dr. Josef Prazak
Scientific Committee: Dr. Niccolò Buetti
Participating ICUs: Inselspital, Bern University Hospital, Department of Intensive Care Medicine: Dr Josef Prazak, Dr Stephan Jakob. Chuv, Service De Médecine Intensive Adulte : Dr Jl Pagani, Mrs S Abed-Maillard.
Turkey
National Coordinator: Prof. Murat Akova, Dr. Abdullah Tarık Aslan
Participating ICUs: Hacettepe University of Faculty of Medicine, Intensive Care Unit(ICU): Dr Murat Akova, Dr Abdullah Tarik Aslan, Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, Department of Anesthesiology: Dr Arif Timuroglu. Acibadem Fulya Hospital, Infectious Diseases: Dr Sesin Kocagoz, Dr Hulya Kusoglu. Acibadem Kadikoy Hospital, ICU: Dr Selcuk Mehtap, Dr Solakoğlu Ceyhun. Ankara University Faculty Medicine Ibni Sina Hospital, Medical ICU: Prof. Dr. Neriman Defne Altintas, Dr Leyla Talan. Ankara Yildirim Beyazit University, Ankara City Hospital, Infectious Diseases and Clinical Microbiology: Dr Bircan Kayaaslan, Dr Ayşe Kaya Kalem. Aydin Adnan Menderes University Research Hospital, Anesthesia and Reanimation ICU: Prof. Dr. Ibrahim Kurt, Dr (Professor) Murat Telli, Dr (Associate Professor) Barcin Ozturk. Baskent University Hospital, Infectious Diseases and Clinical Microbiology: Dr Çiğdem Erol. Bitlis Goverment Central Hospital, Bitlis Icu: Dr Emine Kubra Dindar Demiray, Dr Sait Çolak. Duzce University Hospital, Medical ICU: Dr Türkay Akbas. Erciyes University, ICU: Prof. Dr. Kursat Gundogan, Dr Ali Sari. Fatih Sultan Mehmet Research and Training Hospital, Infection Diseases: Dr Canan Agalar, Dr Onur Çolak. Hitit University Erol Olcok Education and Research Hospital, Infectious Diseases and Clinical Microbiology: Prof. Dr. Nurcan (N) Baykam, Assistant Prof. Dr Ozlem (O) Akdogan. Istanbul Medipol University, Kosuyolu Hospital, Infectious Diseases and Clinical Microbiology: Dr Mesut Yilmaz, Dr Burcu Tunay, Dr Rumeysa Cakmak. Istanbul University-Cerrahpasa, Cerrahpasa Medical Faculty, Sadi Sun ICU: Prof.Dr. Nese Saltoglu, Ass Prof.Dr. Ridvan Karaali. Karadeniz Technical University Faculty of Medicine, Infectious Disease and Clinical Microbiology: Prof Dr. Iftihar Koksal, Assist. Prof. Firdevs Aksoy. Karadeniz Technical University Farabi Hospital, Anesthesia ICU 1: Dr Ahmet Eroglu. Kartal Dr. Lutfi Kirdar Training and Research Hospital, ICU: Dr Kemal Tolga Saracoglu, Dr Yeliz Bilir. Kayseri City Hospital, ICU: Dr Seda Guzeldag. Mersin University Hospital, Department of Infectious Diseases and Clinical Microbiology: Dr Gulden Ersoz, Dr Guliz Evik. Pamukkale Univ, Anesthesiology and Reanimation: Prof Hulya Sungurtekin, Dr Cansu Ozgen. School Of Medicine, Medipol Mega University Hospitals Complex, Department of Anesthesiology and Reanimation: Dr Cem Erdoğan. University of Health Sciences Diskapi Yildirim Beyazit Training and Research Hospital, The Department of Infectious Diseases and Clinical Microbiology and ICU: Dr Yunus Gürbüz, Dr Nilgün Altin. Turgut Ozal Medical Center, Department of Infectious Diseases and Clinical Microbiology: Dr Yasar Bayindir, Dr Yasemin Ersoy. University of Health Sciences Istanbul Umraniye Training and Research Hospital, Anaestesia and Reanimation: Dr Senay Goksu, Dr Ahmet Akyol. University of Health Sciences, Kartal Dr. Lutfi Kirdar Training and Research Hospital, Infectious Diseases and Clinical Microbiology: Prof Ayse Batirel, Dr Sabahat Cagan Aktas.

The United Kingdom
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Ukraine
Participating ICUs: Kharkiv Clinical Infectious Diseases Hospital, Intensive Care: Prof Anton Sokhan, Dr Yaroslava Burma.

North America
Canada
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South Asia

Bangladesh

National Coordinator: Dr Raihan Rabbani

Participating ICUs: General Icu, Dhaka: Dr Raihan Rabbani, Dr Shihan Mahmud Redwanul Huq. Asgar Ali Hospital, Critical Care Medicine: Dr Rajib Hasan, Dr Mohammad Motiul Islam.

India

National Coordinator: Prof. Mohan Gurjar

Participating ICUs: Sanjay Gandhi Postgraduate Institute of Medical Sciences (SGPGIMS), Lucknow, Department of Critical Care Medicine: Dr Mohan Gurjar, Dr Arvind Baronia. All India Institute of Medical Sciences (AIIMS) Jodhpur, Department of Anaesthesiology & Critical Care Medicine: Dr Nikhil Kothari, Dr Ankur Sharma. All India Institute of Medical Sciences (AIIMS), Pulmonary Medicine ICU, Department of Pulmonary Medicine: Dr Saurabh Karmakar, Dr Priya Sharma. Breach Candy Hospital Trust, SICU: Dr Janardan Nimbolkar, Dr Pratit Samdani. Cauvery Heart And Multi-Speciality Hospital, MICU: Dr Vaidyanathan R, Dr Noor Ahmedi Rubina. CHL Hospitals, Dept of Critical Care Services: Dr Nikhilesh Jain, Dr Madhumati Pahuja. Indira Gandhi Institute of Medical Sciences, Trauma & Emergency: Dr Ritu Singh, Dr Saurav Shekhar. King George's Medical University, Department of Critical Care Medicine: Dr Syed Nabeel Muzaffar, Dr Ahmad Ozair, Dr Suhail Sarwar Siddiqui. Medica Superspecialty Hospital, Medica Institute of Critical Care: Dr Payel Bose, Dr Avijatri Datta. Sir H N Reliance Foundation Hospital, Critical Care Unit: Dr Darshana Rathod, Dr Mayur Patel. Sri Ramachandra Institute of Higher Education and Research, Department of Critical Care Medicine: Prof MK Renuka, Dr Sailaja K Baby. St Johns Medical College Hospital, Department of Critical Care Medicine, MICU: Dr Carol Dsilva, Dr Jagadish Chandran. Tata Medical Center, Critical Care Medicine: Dr Pralay Ghosh, Dr Sudipta Mukherjee. Yashoda Hospital, Somajiguda, Hyderabad: Dr Kaladhar Sheshala, Dr Krushna Chandra Misra.

Sub-Saharan Africa

Nigeria

National Coordinator: Dr. Oyebola O. Adekola

Participating ICUs: Ahmadu Bello University Teaching Hospital Shika Zaria Abuth Zari, Icu Abuth Zaria: Dr Saidu Yusuf Yakubu, Dr Euphemia Mgbosoro Ugwu. Lagos University Teaching Hospital, Department of Anaesthesia And Intensive Care: Dr John (O) Olatosi, Dr Ibironke Desalu. One Life Hospital, One Life Intensive Care Unit: Dr Gabriel Asiyanbi, Dr Motunrayo Oladimeji. University College Hospital, Anaesthesia: Dr Olusola Idowu, Dr Fowotade Adeola.

South Africa

National Coordinator: Prof. Mervyn Mer

Participating ICUs: Charlotte Maxeke Johannesburg Academic Hospital, Ward 576: Prof Mervyn Mer, Mrs Melanie Mc Cree.

Sudan

National Coordinator: Dr. Bashir El Sanousi

*Participating ICUs:*Al-Rajhi Hospital, Medicine: Dr Ali Adil Ali Karar. East Nile Hospital, Intensive Care Unit: Dr Elfayadh Saidahmed, Dr Hytham K.S. Hamid.