This article has been accepted for publication in BMJPH following peer review.
The definitive copyedited, typeset version is available online at
10.1136/bmjph-2024-001289

Impact of inappropriate empirical antibiotic therapy on in-hospital mortality: A retrospective multicentre cohort study of patients with bloodstream infections in Chile, 2018-2022

Kasim Allel PhD[1,2,3], Anne Peters MS[4], Luis Furuya-Kanamori PhD[5], Maria Spencer-Sandino PhD(c)[4], Emma Pitchforth PhD[6], Laith Yakob PhD[7], Jose M. Munita MD[4,8*], Eduardo A. Undurraga PhD[9,10*]

[1] *Health Economics Research Centre, Nuffield Department of Population Health, University of Oxford, Oxfordshire, United Kingdom*

[2] *Department of Infectious Diseases, School of Medicine, Pontificia Universidad Católica de Chile, Santiago, Región Metropolitana, Chile*

[3] *Institute for Global Health, University College London, London, United Kingdom*

[4] *Genomics and Resistant Microbes (GeRM), Instituto de Ciencias e Innovación en Medicina (ICIM), Facultad de Medicina Clínica Alemana, Universidad del Desarrollo, Santiago, Región Metropolitana, Chile*

[5] *UQ Centre for Clinical Research, Faculty of Medicine, The University of Queensland, Brisbane, Australia*

[6] *Exeter Collaboration for Academic Primary Care, Department of Health and Community Health Sciences, University of Exeter, Exeter, UK*

[7] *Department of Disease Control, Faculty of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, London, UK*

[8] *Hospital Padre Hurtado, Santiago, Región Metropolitana, Chile*

[9] *Escuela de Gobierno, Pontificia Universidad Católica de Chile, Santiago, Región Metropolitana, Chile*

[10] *Centro de Investigación para la Gestión Integrada del Riesgo de Desastres (CIGIDEN), Región Metropolitana, Chile*

Word count

Main text: 3712/5000; Abstract: 269/300; Tables: 3; Figures: 2; References: 45/100.

*Corresponding author: Eduardo A. Undurraga, PhD, Escuela de Gobierno, Pontificia Universidad Católica de Chile, Av. Vicuña Mackenna 4860, Macul, Santiago, 7820436, Región Metropolitana, Chile. Email: eundurra@uc.cl;

Alternate corresponding author: Jose M. Munita, MD, Genomics & Resistant Microbes (GeRM), Instituto de Ciencias e Innovación en Medicina (ICIM), Facultad de Medicina Clínica Alemana, Universidad del Desarrollo, Av. Plaza 680, Las Condes, 7610658, Santiago, Chile. Email: josemunita@udd.cl.

Author emails and ORCID IDs: Kasim.Allel1@lshtm.ac.uk, 0000-0002-2144-7181; apeters@udd.cl; l.furuya@uq.edu.au, 0000-0002-4337-9757; mspencers@udd.cl; E.Pitchforth@exeter.ac.uk, 0000-0001-9055-9331; Laith.Yakob@lshtm.ac.uk, 0000-0001-8639-4511; josemunita@udd.cl, 0000-0002-7870-1056; eundurra@uc.cl, 0000-0002-4425-1253.

ABSTRACT

Introduction. Empirical antibiotic therapy is essential for treating bloodstream infections (BSI), yet there is limited evidence from resource-limited settings. We quantified the association of inappropriate empirical antibiotic therapy (IEAT) with in-hospital mortality and the associated burden on BSI patients in Chile.

Methods. We used a retrospective multicentre cohort study of BSI cases in three Chilean tertiary hospitals (2018-2022) to assess the impact of IEAT on 30-day and overall in-hospital mortality and quantify excess disease and economic burdens associated with IEAT. We determined the appropriateness of pathogen-antimicrobial pairings based on in-vitro susceptibilities and pathogen-corresponding antibiotic treatment, allowing a 48-hour window after the initial blood culture. We addressed confounding using propensity scores and inverse probability weights (IPW). We used IPW-weighted logistic competing-risk survival models, including time-varying independent variables after blood tests as controls.

Results. Among 1,323 BSI episodes, 432 (33%) received IEAT, with an average time to adequate therapy of 4.6 days. Compared to adequate treatment, IEAT was associated with 30-day and overall mortality risks that were 1.31 and 1.24 times higher, respectively. These risks were further inflated between 2- and 4-fold when ARB was included. Competing-risk models showed associations between IEAT and IEAT-ARB combinations with in-hospital mortality. Accounting for time-varying variables yielded similar results. The economic burden of IEAT resulted in an additional cost of ~$9,900 from premature mortality and 0.46 DALYs per patient with BSI.

Conclusion. Approximately one in three patients received IEAT, often associated with ARB. IEAT was linked to increased mortality risk and higher economic costs. Timely appropriate treatment, early pathogen detection, and resistance profiling are likely to improve health and financial outcomes at the population level.

Keywords: Antibiotic resistance; bloodstream infection; empirical antibiotic treatment; burden of disease; mortality; Latin America.

KEY MESSAGES

What is already known on this topic

Empirical antibiotic therapy, i.e., using antibiotics based on clinical judgment before laboratory tests are available, is pivotal in optimizing patient outcomes, especially in life-threatening conditions such as bloodstream infections (BSIs). Existing studies from the United States and Europe have underscored the consequences of inappropriate empirical antibiotic therapy (IEAT), ranging from prolonged hospital stays to increased mortality rates. However, drawing comprehensive conclusions from existing studies is challenging due to substantial differences in study populations, access to healthcare, resources available, risk adjustment methods, definitions of IEAT, and limited sample sizes. Despite the considerable burden of antibiotic resistance in countries with limited resources, there is a shortage of studies on the effects of IEAT, particularly in Latin America.

What this study adds

Our research quantified the association of IEAT with in-hospital mortality using a retrospective analysis encompassing 1,217 patients (1,323 BSI episodes) from three tertiary hospitals located in the north, centre, and south of Chile. We focused on patient-specific characteristics of BSIs induced by pathogens categorized as critical and high-priority by the World Health Organization (WHO). This study is unique in the region in analysing the prevalence and the disease and economic consequences of IEAT, using hospital mortality as our primary outcome. The results showed that over one-third of the patients experienced IEAT, with Enterobacterales and *Staphylococcus aureus* resistant to empirical treatment being the predominant causative agents for BSIs. Episodes associated with resistant bacteria were approximately twice as likely to involve IEAT. On average, IEAT was associated with elevated risks of in-hospital mortality and increased economic costs.

How this study might affect research, practice, or policy

There is an urgent need to enhance national strategies to combat the emergence and spread of antibiotic resistance. Research to uncover the reasons behind lapses in empirical antibiotic coverage across various settings and patient groups is essential. Implementing system-wide measures to refine prescription practices can potentially improve survival rates for patients with BSI. Promptly detecting bloodstream pathogens, particularly Enterobacterales and *S. aureus*, along with their resistance patterns, can substantially improve the prognosis for patients with BSIs.

BACKGROUND

Globally, bloodstream infections (BSIs), especially those attributed to antibiotic-resistant bacteria (ARB), pose a critical public health challenge.[1-4] These infections lead to substantial morbidity and mortality and impose an enormous economic burden on healthcare systems,[5-7] particularly among vulnerable populations.[8] Empirical antibiotic therapy for BSIs is typically prescribed based on clinical judgment, typically before the identification of the causative agent and its corresponding antibiotic susceptibility. This approach is common because of the necessity to initiate treatment promptly, outpacing the time required to await microbiological test results. Unfortunately, empirical antibiotic therapy can result in the use of inappropriate antibiotics, with potentially severe consequences.[9,10]

One of the primary consequences of inappropriate empirical antibiotic therapy (IEAT) is the prolonged duration of infection, which can lead to health complications, including increased mortality. A recent systematic review estimated a pooled adjusted odds ratio (OR) of 2.02 (95% CI: 1.86-2.20) among BSI patients receiving IEAT, compared to appropriate treatment,[10] with Enterobacterales accounting for the highest estimates (OR: 4.35, 95% CI: 1.28–14.76). Additionally, IEAT can extend the length of hospital stays by at least two additional days,[11,12] increasing the risk of nosocomial infections and worsening the patient's overall condition. IEAT BSIs also increase the likelihood of requiring intensive care unit (ICU) admission, significantly increasing the resources and costs associated with patient care.[13,14] The rise in ICU admissions, the need for additional diagnostic tests, and more complex treatment regimens contribute to escalating hospital and patient expenditures. Moreover, ARB, a consequence of inappropriate antibiotic use, necessitates investment in newer, often more expensive antibiotics, further straining healthcare budgets.[15,16] From an economic perspective, IEAT imposes substantial costs on healthcare systems.[15] Some studies have examined the impact of sociodemographic determinants on ARB;[2,17] however, the current understanding of clinically relevant factors, such as empirical antibiotic therapy, remains poor, especially in resource-constrained countries.[10]

Despite the substantial mortality rates associated with ARB in the Americas (56.3 deaths per 100,000 individuals, 95% uncertainty interval UI 40.2-76.3),[4] evidence of IEAT in Latin America remains

sparse and limited to Brazil.[18,19] Understanding IEAT is critical, as it has important implications for patient outcomes and quality of care. Factors such as healthcare practices, access to care, patterns of antibiotic use, healthcare inequalities, pre-existing conditions, and limited resources, including diagnostic capabilities and antibiotics, may amplify the health and economic burden of IEAT in this region. Notably, Chile has the highest estimated proportion of infection deaths associated with ARB (48.2%, 95% UI: 46.0–50.3),[4] and the proportion of critical priority ARB has steadily increased in the past decade.[17,20]

We aimed to quantify the association of IEAT with in-hospital mortality and the economic burden of patients diagnosed with BSIs using a societal perspective. The study was conducted in three tertiary public hospitals in the north, centre, and south of Chile. We hope our results will help inform efforts to mitigate ARB and improve patient outcomes in settings with limited resources.

METHODS

Study design, settings, and participants

We conducted a retrospective cohort study in three tertiary hospitals in Chile from 2018 through 2022. These hospitals, located in northern, central, and southern regions, each have a bed capacity ranging between 400-500, with 25,000-30,000 annual discharges per hospital. Our study focused on adult patients (>15 years of age) with laboratory-confirmed monomicrobial bacterial BSI and corresponding antibiotic susceptibility testing. Patients were recruited from general hospital wards as well as the emergency department. Exclusion criteria applied to pediatric patients and those in maternity or psychiatric wards. The sample focused on patients with BSI (detection of a pathogen of interest in at least one blood culture bottle) caused by *Acinetobacter baumannii, Pseudomonas aeruginosa*, Enterobacteriaceae, *Enterococcus* spp., or *Staphylococcus aureus*. Polymicrobial infections were excluded from the sample (1.9%). All three hospitals had automated blood culture systems, used the automated Phoenix-100 platform (BD Diagnostic) for antimicrobial susceptibility testing, and followed the 2022 Clinical and Laboratory Standards Institute (CLSI) guidance.[21] Isolates recovered from blood cultures obtained more than seven days apart were considered independent BSI episodes.[22] We excluded those occurring before the seven-day gap (1.3%). A total of 1,323 BSI episodes among 1,217 patients were included in our sample (Supplemental Figure S1).

Outcomes and covariates

Inappropriate empirical antibiotic therapy (IEAT)

Empirical antibiotic therapy was considered as the initiation of antibiotics during the period between obtaining the blood cultures and the moment the full microbiology report with species identification and antimicrobial susceptibility was available. Empirical antibiotic therapy was deemed appropriate if at least one antibiotic with *in vitro* activity was administered within the first 48 hours upon blood culture collection, depending on each specific pathogen and phenotype (Supplemental Tables S1-S2). A single dose administered with in vitro susceptibility was also considered appropriate during this period. Antibiotic selection and dosage were selected by treating physicians based on clinical judgment and patient characteristics. ARB of interest included carbapenem-resistant *A. baumannii* (CRAB), carbapenem-resistant Enterobacterales (CRE), carbapenem-resistant *P. aeruginosa* (CRPA), methicillin-resistant *S. aureus* (MRSA) and vancomycin-resistant enterococci (VRE), following the WHO's priority pathogen list.[23]

In-hospital mortality

Mortality status was determined from hospital death records. We focus on two primary endpoints: overall in-hospital mortality and in-hospital mortality at 30 days following the index blood culture. We did not account for deaths outside hospitals due to loss of follow-up.

Patient's sociodemographic and clinical characteristics

Demographic and patient characteristics preceding the index culture were obtained from clinical records. These characteristics included age, sex at birth, previous hospital admissions within the last year (yes/no), length of hospital stay (LOS) from admission until the index blood culture, history of antibiotic usage in the past three months (yes/no), surgical procedures, and mechanical ventilation (all within the past three months and recorded as a dichotomous variable). At admission, pre-existing health conditions were evaluated using the Charlson Comorbidity Index (CCI).[24] For the BSI episode, we analysed whether the infection was community-acquired or hospital-acquired (defined as occurrence <48 hours or >48 hours following admission, respectively), source of BSI as defined by

the primary health team (e.g., primary, catheter-related, respiratory, gastrointestinal), presence of indwelling catheters, and antibiotic consumption quantified in defined daily doses (DDD) per antibiotic class, following WHO ATC/DDD index standards.[25] Time-varying characteristics reported after the index culture included mechanical ventilation, admission to the ICU, and the need for any surgery (yes/no). Variables were selected based on their availability in hospital records, clinical experience, and alignment with existing literature.[10]

Statistical analysis

We followed methodological recommendations from a systematic review by McGregor *et al*.[26] to enhance the generalisability of our results. First, we examined patient characteristics univariately, comparing those with appropriate empirical antibiotic therapy to those with IEAT during BSI episodes. Depending on the variable distribution, we used unpaired t-tests or chi-squared (χ^2) tests for variable assessment.

We used inverse probability weighting (IPW)[27,28] using propensity scores at baseline to estimate the likelihood of receiving IEAT before BSI diagnostic or initiation of IEAT. To account for potential confounding, we used a logistic regression model to generate the propensity scores, adjusting for multiple factors related to disease severity before BSI diagnostic, such as age, mechanical ventilation, CCI, hospitalization, antibiotic treatment, sex, surgery, and fixed effects for pathogen, year, and hospital. Based on these propensity scores, we quantified predicted probabilities for receiving IEAT and then assigned IPW weights for (1) individuals who received IEAT (IPW weight= 1/propensity score) and (2) individuals who did not (IPW weight= 1/(1-propensity score)). IPW balanced baseline characteristics between groups receiving appropriate and inappropriate treatments by adjusting for confounders with propensity scores.

Our analysis involved three stages. First, we estimated the average treatment effect of IEAT on in-hospital mortality (30 days and overall) using an IPW model with logistic regressions (univariate and multivariate). Second, we applied a survival model using the Fine & Gray method[29] to estimate individual probabilities of mortality over time, accounting for competing risks, such as discharge and

presented cumulative incidence of mortality curves. Third, we used IPW-weighted logistic and competing-risk models to evaluate the impact of IEAT on mortality, using univariate and multivariate analyses with time-invariant and time-varying variables. We examined the interaction between IEAT and ARB on mortality outcomes. We used patient-clustered standard errors and addressed missing data (<3%) with predictive mean matching across ten imputed datasets to preserve data integrity and avoid imputation misspecification.[30] Finally, we estimated the economic costs of premature mortality (in 2023 USD) using the human capital approach and a societal perspective and assessed disease burden using disability-adjusted life years (DALYs) based on disease severity (Supplemental Material).

All statistical analyses were performed using R version 3.4.4. and Stata v17.

The study was approved by the Pontificia Universidad Católica Chile Human Research Ethics Committee (Protocol ID: 200706001).

RESULTS

Inappropriate empirical antibiotic therapy

During the study period, 432 (33%) out of 1,323 BSI episodes were linked to IEAT. Supplemental Figure S2 shows the proportion of appropriate and IEAT by hospital. IEAT was more frequent in BSI involving *Enterococcus* spp. and *P. aeruginosa*, regardless of their antibiotic susceptibility profile, constituting 50% and 35% of the total, respectively. Overall, BSI episodes due to ARB presented significantly greater proportions of IEAT as compared to their antimicrobial-susceptible counterparts (39% and 26%, respectively, χ^2 test $p<0.001$). For ARB, the proportions of IEAT were 67% for VRE, 44% for MRSA, 38% for CRPA, 33% for CRE, and 32% for CRAB (Table 1). Pearson correlation between ARB and IEAT was $\rho=0.14$.

Table 1. Bloodstream infection episodes by empirical antibiotic appropriateness and pathogen, including antibiotic-resistant bacteria (n=1,323)

Pathogen	Resistance profile	Empirical antibiotic therapy		Total
		Appropriate	Inappropriate	
		(N=891)	(N=432)	**(N=1,323)**
Gram-positives (n= 567)				
Enterococcus spp.	Vancomycin-susceptible (VSE)	60 (53%)	53 (47%)	113
(n= 173)	Vancomycin-resistant (VRE)	26 (43%)	34 (67%)	60
	Subtotal	86 (50%)	87 (50%)	173
Staphylococcus aureus	Methicillin-susceptible (MSSA)	227 (86%)	38 (14%)	265
(n= 394)	Methicillin-resistant (MRSA)	72 (56%)	57 (44%)	129
	Subtotal	299 (76%)	95 (24%)	394
Gram-negatives (n=756)				
Acinetobacter baumannii	Carbapenem-susceptible (CSAB)	4 (80%)	1 (20%)	5
(n= 61)	Carbapenem-resistant (CRAB)	38 (68%)	18 (32%)	56
	Subtotal	41 (67%)	20 (33%)	61
Enterobacterales	Carbapenem-susceptible (CSE)	170 (73%)	62 (27%)	232
(n= 459)	Carbapenem-resistant (CRE)	140 (62%)	87 (38%)	227
	Subtotal	310 (68%)	149 (32%)	459
Pseudomonas aeruginosa	Carbapenem-susceptible (CSPA)	51 (62%)	31 (38%)	82
(n= 236)	Carbapenem-resistant (CRPA)	103 (67%)	51 (33%)	154
	Subtotal	154 (65%)	82 (35%)	236

Notes: ARB, Antibiotic-resistant bacteria. BSI, Bloodstream infections.

Supplemental Table S3 shows significant univariate differences (p<0.05) between cohorts with appropriate and IEAT in their characteristics before and after the index blood culture. Differences include previous hospitalization history, history of an indwelling catheter, mechanical ventilation, transfer from another hospital, and length of hospital stay. Regarding clinical attributes post-BSI diagnosis, surgical interventions, mechanical ventilation, and ICU admission were more frequently observed in the IEAT group as compared to subjects receiving appropriate empirical antibiotic therapy (50.7 vs. 36.7, χ^2 p<0.001; 15.7 vs. 8.1, χ^2 p<0.001, and 62.7 vs. 54.7, χ^2 p<0.001, respectively). Antibiotic consumption was 2.2-fold greater in instances of IEAT (10.2 versus 4.7 DDDs, respectively), with the length of therapies equivalent to 12 more days among the IEAT group.

Antibiotic consumption was greater under IEAT, with additional five, six, and seven DDD units for *S. aureus*, Enterobacterales, and *P. aeruginosa*, respectively, compared to appropriate empirical antibiotic therapy (Figure 1, panel B).

[Insert Figure 1 about here]

Figure 1. Crude in-hospital mortality and antibiotic consumption, by pathogen and empirical antibiotic therapy appropriateness **(A)** Crude in-hospital mortality by pathogen and antibiotic therapy appropriateness (**B)** Crude antibiotic consumption by antibiotic therapy appropriateness and pathogen. ATB= Antibiotic. DDD= Daily defined dose. CI= Confidence interval. Spp= species. BC= Blood culture. DDD= Daily defined doses. Antibiotic classified as "Others" included lincosamides, polymyxins, monobactams, antimycobacterial and other antibacterial.

Risk factors before index blood culture

Supplemental Table S4 shows that a history of an indwelling catheter and prior surgical procedures before the index blood culture were independently associated with an increased likelihood of receiving IEAT (OR: 2.65, 95% CI: 1.90-3.68, $p<0.001$; OR: 1.96, 95% CI: 1.28-2.99, $p<0.002$, respectively). Conversely, a longer LOS before index blood culture was significantly correlated with a lower probability of IEAT administration (LOS OR: 0.99, 95% CI: 0.98-1.00, $p=0.003$). Supplemental Figure S3 presents the kernel density distributions of the predicted IEAT values, illustrating an overlap in scores and weights between appropriate empirical antibiotic therapy and IEAT ($R^2=40\%$). Similar results in risk factors were found after exploring differences by bacterial Gram type (Supplemental Tables S5-S6, and Figures S4-S5).

In-hospital mortality

Overall and 30-day in-hospital mortality was higher in the IEAT group as compared to those receiving appropriate empirical antibiotic therapy (overall in-hospital mortality: 36.3% vs. 31.9.1%, χ^2 $p=0.091$; 30-day mortality: 33.6% vs. 27.1%, χ^2 $p=0.015$) (Supplemental Table S7). In examining specific pathogens and mortality, Figure 1 illustrates elevated in-hospital mortality rates following the index blood culture for patients receiving IEAT across all bacterial species except for *A. baumannii* (panel A).

Table 2 shows robust associations between IEAT and mortality using various model specifications (full regression and competing-risks model results are shown in Supplemental Tables S8-S20 and Figure S6). Specifically, the impact of IPW-weighted IEAT was 1.31-, and 1.24-fold larger for 30-day and overall in-hospital mortality (95% CI: 0.99-1.49, p=0.057; 95% CI: 1.11-1.55, p=0.001, and 95% CI: 1.06-1.46, p=0.008, respectively) (Table 2, Logistic models). Similar effect sizes and statistical significance were found after adjusting for fixed effects and time-varying variables post-BSI diagnosis, showing that models did not hinge on the specifications used (Table 2). ICU admission impacted 30-day and overall in-hospital mortality by 1.46 (p=0.004), 1.68 (p<0.001), and 1.85 (p<0.001) greater odds in our models, respectively (Supplemental Table S12). Post BSI diagnostic IPW-weighted logistic models restricted to Gram-negative bacteria displayed lower impacts of IEAT in overall in-hospital mortality compared to Gram-positive bacteria (OR= 1.26, 95% CI=1.01-1.58, p=0.042; OR= 1.40, 95% CI= 1.09-1.81, p<0.001, respectively) (Supplemental Tables S16-S17).

Table 2. Adjusted regression analyses for the impact of inappropriate empirical antibiotic therapy on in-hospital mortality (n=1,323)

Outcome variable	Main variable	OR/HR	95% CI	*p*
In-hospital mortality 30-days: Logistic model	IEAT	1.31	1.11, 1.55	0.001
	IEAT + FE	1.31	1.10, 1.55	0.002
	IEAT + FE + TV	1.33	1.12, 1.58	0.001
Overall in-hospital mortality: Logistic model	IEAT	1.24	1.06, 1.46	0.008
	IEAT + FE	1.24	1.06, 1.47	0.009
	IEAT + FE + TV	1.28	1.08, 1.51	0.004
In-hospital mortality: Competing-risks survival model	IEAT	1.19	1.04, 1.34	0.009
	IEAT + FE	1.19	1.04, 1.35	0.010
	IEAT + FE + TV	1.20	1.05, 1.36	0.007

Notes: Results from IPW multivariable regressions. IEAT, Inappropriate empirical antibiotic therapy. Individual-clustered standard errors were estimated, and all models incorporated a constant term except for the competing risks model. IPW= Inverse probability weighting. CI Confidence interval. OR= Odds ratio, HR= Hazard ratio. FE, Fixed effect "time unvarying" variables including hospital and year. TV= Time-varying variables, including intensive care unit admission after BC, surgery after BC, and mechanical ventilation after BC. All models included a constant term. Supplemental Tables S8-S20 contain full results of the regression and competing-risk models.

The competing-risks survival model also showed a robust association between IEAT and in-hospital mortality while accounting for hospital discharge. Indeed, the IPW-weighted model accounting for time fixed-effects and post-BSI diagnosis independent variables suggested greater in-hospital mortality among IEAT (HR= 1.20, 95% CI= 1.05-1.36, p=0.007) compared to appropriate empirical antibiotic therapy (Table 2, lower panel, Figure 2, panel A, and Supplemental Table S21). ICU admission after BSI diagnosis was the most significant contributing factor to mortality (HR=1.60, 95% CI= 1.36, 1.88, p<0.001) (Supplemental Table S20). Administration of IEAT to individuals with Gram-positive bacteria was associated with the highest in-hospital mortality burden (HR=1.36, 95% CI = 1.12-1.66, p<0.002) (Supplemental Table S20).

[Insert Figure 2 about here]

Figure 2. IPW-weighted cumulative incidence of hospital mortality using the competing-risks model controlling for time-unvarying and time-varying independent variables. (A) Cumulative incidence of hospital mortality by empirical antibiotic therapy appropriateness. (B) Cumulative incidence of hospital mortality by empirical antibiotic therapy appropriateness and antibiotic resistance. Notes: ARB, Antibiotic-resistant bacteria; ATB, Antimicrobial; BSI, Bloodstream infections. Estimates were IPW-weighted. IEAR= Inappropriate empirical antibiotic therapy. AEAT= Appropriate empirical antibiotic therapy. ASB= Antibiotic susceptible bacteria. Supplemental Table S21 shows the number of individuals at risk at 10, 20, 30, 40, 50 and 60 days.

Table 3 shows the IPW-weighted regression results for the combined impacts of IEAT and ARB on in-hospital mortality. The logistic models showed statistically significant (p<0.001) combined impacts between IEAT and ARB in the order of 1.78- and 1.82-times greater 30-day and overall in-hospital mortality, respectively. A similar association was observed after adjusting for competing risks (HR=1.61, 95% CI=1.35-1.93, p<0.001) (Figure 2, panel B, and Supplemental Table S21).

Table 3. Adjusted regression analyses for the combined impact of inappropriate empirical antibiotic therapy and antibiotic-resistant bacteria on in-hospital mortality (n=1,323)

Outcome variable	Main variable	OR/HR	95% CI	*p*
In-hospital mortality 30-days: Logistic model	AEAT + ASB	Reference		
	AEAT + ARB	1.38	1.08, 1.76	0.010
	IEAT + ASB	1.17	0.91, 1.51	0.221
	IEAT + ARB	1.78	1.43, 2.22	<0.001
Overall in-hospital mortality: Logistic model	AEAT + ASB	Reference		
	AEAT + ARB	1.38	1.10, 1.75	0.006
	IEAT + ASB	0.99	0.77, 1.26	0.913
	IEAT + ARB	1.82	1.47, 2.25	<0.001
In-hospital mortality: Competing-risks survival model	AEAT + ASB	Reference		
	AEAT + ARB	1.31	1.07, 1.61	0.009
	IEAT + ASB	1.01	0.81, 1.25	0.916
	IEAT + ARB	1.61	1.35, 1.93	<0.001

Notes: Results from IPW multivariable regressions. ASB, Antibiotic-susceptible bacteria. ARB, Antibiotic-resistant bacteria. IEAT, Inappropriate empirical antibiotic therapy. AEAT= Appropriate empirical antibiotic therapy. Individual-clustered standard errors were estimated, and all models incorporated a constant term except for the competing risks model. IPW= Inverse probability weighting. CI Confidence interval. OR= Odds ratio, HR= Hazard ratio. All models included a constant term.

Economic costs associated with premature mortality and disability-adjusted life-years

The excess cost associated with premature mortality resulting from IEAT was estimated at an average of about $9,883 per patient, with excess DALYs gauged at 0.46 per individual. Assuming that our multicentre sample of patients was representative of the BSI adult patients in the country, extrapolating these findings to the national level based on the Global Burden of Disease estimates of national BSI incidence in 2019[4] suggests about ~$4.2 million in excess costs and around ~200 excess DALYs annually.

DISCUSSION

Our study provides estimates of the impact of IEAT among patients presenting with BSIs in three Chilean hospitals between 2018 and 2022. Our findings suggest that IEAT substantially impacted 30-day and overall in-hospital mortality among all BSI episodes. Notably, the impact was substantially higher among ARB BSIs for mortality outcomes, with Gram-positive bacteria exhibiting the highest

burdens. These results provide an estimate of the potential economic and health burden associated with the impact of IEAT and underscore the importance of addressing and improving empirical antibiotic therapy practices to enhance patient outcomes, particularly in the context of ARB in settings with limited resources.

We found that 33% of patients received IEAT. Although IEAT definitions can vary substantially in the scientific literature, a recent systematic review and meta-analyses of 27 studies utilising similar IEAT definition found that IEAT was ~50% among severe infections,[31] and another report estimated ~30% of IEAT among 9,962 patients with BSIs[10]. Notably, only two studies in these analyses were from Latin America[10], specifically from Brazil.[18,19] Guilarde and colleagues found that IEAT was 39% among *S. aureus* BSIs[18] in a 350-bed Brazilian hospital, whereby we found it to be 24% among our sampled patients. Contrastingly, Tuon *et al.* found that IEAT did not impact health outcomes among *Klebsiella pneumoniae* BSI patients, but IEAT was ~47% among 104 patients from a 660-bed tertiary-care hospital in Brazil.[19] Our data showed lower proportions of IEAT among Enterobacterales (32%). Our study had a larger sample size than previous studies representing the most substantive work to date to help understand the disease and economic burden of IEAT in the region.

Previous studies have found that patients with ARB BSIs were more likely to receive IEAT,[10,31,32] consistent with our findings. Despite the introduction of antibiotic stewardship initiatives, refinement of rapid diagnostic methodologies, and formulation of guidelines potentially contributing to improvements,[17,33,34] the challenge of selecting suitable therapy persists, especially in the context of ARB. Our study reveals that the transition to appropriate treatment among patients with IEAT occurred, on average, around 4.6 days after the index blood culture (time zero is culture collection). Current practice typically results in a 48 to 72 hours waiting period from the initial culture to finalised microbiology results.[35] Therefore, we hypothesize that the prolonged duration to initiate adequate therapy aligns with the norms inherent in culture and susceptibility protocols. To address this challenge, integrating advanced strategies and innovative diagnostic tools[36] is crucial to expedite effective therapeutic interventions upon the availability of culture results. Failing to optimise this window could extend the duration of the infection and worsen patient outcomes and prognosis.

Our findings corroborate those found previously regarding IEAT impacts on mortality.[10,15,16,32,37] A recent meta-analysis found that, for empirical antibiotic treatment before culture, results had an adjusted pooled estimate on mortality of OR 2.45 (95% CI= 1.95-3.08, p<0.001), after analysing 30 studies.[10] Yet, most studies from the review were from high-resource countries, focused on single-strain bacteria, and used multivariable analyses without adjusting for baseline confounding factors, such as using IPW techniques. After adjusting for IPW and including five pathogens simultaneously, we found more conservative estimates regarding 30-day mortality and in-hospital mortality (OR 1.33 and HR 1.28, respectively).

The association between IEAT and mortality is complex, and results should be interpreted cautiously. Several conditions might affect this association. First, some studies suggest that specific β-lactam antibiotics, although deemed ineffective, retain some efficacy against pathogens producing BSIs (e.g., MRSA[38]). This could explain why MRSA BSI episodes continued to receive β-lactam antibiotics after blood results (Figure 1). It is possible that outcomes were not fully captured; perhaps these patients manifested clinical amelioration under the purportedly ineffective regimen. Second, while glycopeptides are generally regarded as suitable for addressing MSSA BSI, evidence suggests that vancomycin is not as effective as β-lactam antibiotics for severe MSSA infections,[39] for example. Interestingly, among the group receiving IEAT, patients with BSIs due to ARB exhibited 1.61- and 1.82 times higher mortality compared to patients infected with antimicrobial-susceptible pathogens. A recent review found 2.34-times (95% CI = 1.30-4.21) and 2.40-times (95% CI =1.21-4.74) greater mortality among MRSA and CRE[10] receiving IEAT, respectively. Our lower estimates may be due to the use of IPW. Still, observed differences may also be explained by other factors, such as regional healthcare practices, patterns of antibiotic use, or could reflect microbiological differences in the virulence of the infecting organisms.

We found that IEAT was correlated with substantial morbidities and costs, as evidenced by an increased risk of ICU admissions. This finding aligns with a matched parallel cohort study in Spain[40] that reported a higher rate of ICU admission in patients with BSIs associated with IEAT. In our fully

adjusted models, we found an increase in the rate of ICU admissions on in-hospital mortality among Gram-negative bacteria. This is compounded by the increasing pathogenicity among Enterobacterales in Chile and South America,[4] with the emergence of carbapenemases following the advent of the COVID-19 pandemic.[41] Our results are consistent with the 2021-year predictor of IEAT (Supplemental Table S15) and a recent study from Chile that observed an increased CRE incidence of Enterobacterales (from 12.8% pre-COVID-19, March 2018-2020, to 51.9% post-COVID-19, March 2020-2022), including the emergence of novel genomic lineages.[20] This increase mirrors broader trends of heightened antibiotic usage during the COVID-19 pandemic, notably among broad-spectrum β-lactams (from 78.1 to 142.5 DDD per 1,000 patient days) and carbapenems (from 4.1 to 13.3 DDD per 1,000 hospital-days), potentially reflecting pandemic-related healthcare impacts in our study results.[20]

Consistent with previous studies that assessed the economic implications of IEAT, with additional costs ranging from $750 per patient/day[42] to an aggregate of $10,000 per patient,[43] our study also highlighted a significant economic burden associated with IEAT ($9,883 per patient from a societal perspective). Implementing strategies to improve the use of antimicrobials, such as enforced antimicrobial stewardship programs and hospital guidelines (Supplemental Table S22), could mitigate hospital expenses by approximately 48.4% and improve health outcomes, as a previous study focusing on hospital long-term impacts in Chile has estimated.[33] Failing to optimise this window could extend the duration of the infection and worsen patient outcomes and prognosis.

Our study has some shortcomings. As an observational retrospective cohort study, unobserved confounding may have impacted our estimates. For instance, as with other studies,[37] we did not account for disease severity at the time or after culture results (e.g., Pitt's bacteremia score[44] or septic shock) due data limitations, which could affect our findings. To mitigate bias, we used IPW methods and adjusted for baseline risk factors associated with IEAT utilising the best available data. Additionally, our findings could have been impacted by the COVID-19 pandemic, yet we did not have detailed data on COVID-19 infections. Despite the large sample size, caution should be exercised in interpreting subgroup analyses due to potential limitations in statistical power, particularly for

pathogen-specific data. Furthermore, associations between IEAT-ARB and health outcomes could be due to bacterial virulence or residual confounding associated with patient severity, which we could not further explore due to data constraints. Finally, variations in antibiotic prescribing practices and pathogen profiles across the three hospitals may affect the generalizability of our findings. We partially address this limitation by controlling for hospital-specific characteristics and hospitals from different regions in Chile. These factors may affect the interpretation and generalisability of our study findings.

We emphasize the crucial role of prompt diagnosis and ensuring that patients receive the adequate treatment at the optimal time. Rigorous implementations of antimicrobial stewardship programs, coupled with improved surveillance incorporating molecular diagnostic testing, may significantly contribute to the accurate and timely dispensing of empirical antimicrobial agents. Identifying potential risk determinants for ARB could enhance appropriate empirical antibiotic therapy selection in patients likely to have ARB BSIs.[45] The integration of these features can potentially improve BSI patient outcomes while concurrently reducing economic costs.

Acknowledgments

We thank our collaborators from participant hospitals for excellent research assistance. We also thank attendants at the 34th European Congress of Clinical Microbiology and Infectious Diseases ECCMID2024, 27-30 April 2024, Barcelona, Spain, at the XVIII Reunión Anual del Grupo Colaborativo de Resistencia Bacteriana 2023, September 8, Santiago, Chile, and at the XXXVIII Congreso Chileno de Infectología SOCHINF 2023, November 14-17, Coquimbo, Chile, for helpful comments and suggestions.

Funding

This research was supported by the Agencia Nacional de Investigación y Desarrollo ANID [Grant/Award Numbers: 1211933, 1242022, 1522A0005, 72210084].
Canadian Institute for Advanced Research [Grant/Award Number: Not Applicable]
Royal Society of Tropical Medicine and Hygiene [Grant/Award Number: Not Applicable]

Competing interests

JM declares to have received research grant support from ANID/FONDECYT, Pfizer, and MSD. EU declares to have received research grant support from ANID/FONDECYT, ANID/FONDAP, CIFAR,

and MSD. KA, AP, LF, MS, EP, and LY declare that the research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

Ethical approval

The study was approved by the Pontificia Universidad Catolica Chile Human Research Ethics Committee (Protocol ID: 200706001).

Author contributions

Conceptualization, KA, LY, JM, EU; methodology, KA, LFK, LY, JM, EU; data collation and extraction, AP, MS, JC, JM, EU; formal analysis, KA; writing—original draft preparation, KA; writing—review and editing, EP, LY, JM, EU; funding, JM, EU; supervision, LY, JM, EU.
KA, AP, MS, JM, and EU have had full access to study data and vouch for the accuracy and completeness of the data. JM and EU are the guarantors of the study. The guarantors accept full responsibility for the finished work and the conduct of the study and controlled the decision to publish. All authors have read and approved the final version of the manuscript, are entirely responsible for study design, data collection, and data analysis, and accept responsibility for publication.

Data Sharing

Our use of data follows Chilean Law 19.628 on personal data protection. Owing to this data privacy law, the individual-level data used in this study cannot be shared. Aggregate, anonymized data are available from the corresponding author upon request.
GATHER and STROBE checklists are shown in Supplemental Tables S23 and S24.

Patient and public involvement

It was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting, or dissemination plans of our research.

REFERENCES

1. Ikuta KS, Swetschinski LR, Aguilar GR, et al. Global mortality associated with 33 bacterial pathogens in 2019: a systematic analysis for the Global Burden of Disease Study 2019. *The Lancet* 2022;400(10369):2221-48.

2. Murray CJL, Ikuta KS, Sharara F, et al. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *The Lancet* 2022;399(10325):629-55. doi: https://doi.org/10.1016/S0140-6736(21)02724-0

3. Mestrovic T, Aguilar GR, Swetschinski LR, et al. The burden of bacterial antimicrobial resistance in the WHO European region in 2019: A cross-country systematic analysis. *The Lancet Public Health* 2022;7(11):e897-e913.

4. Aguilar GR, Swetschinski LR, Weaver ND, et al. The burden of antimicrobial resistance in the Americas in 2019: a cross-country systematic analysis. *Lancet Regional Health - Americas* 2023;25:100561.

5. Ahmad M, Khan AU. Global economic impact of antibiotic resistance: A review. *Journal of global antimicrobial resistance* 2019;19:313-16.

6. Stewardson AJ, Allignol A, Beyersmann J, et al. The health and economic burden of bloodstream infections caused by antimicrobial-susceptible and non-susceptible Enterobacteriaceae and Staphylococcus aureus in European hospitals, 2010 and 2011: a multicentre retrospective cohort study. *Eurosurveillance* 2016;21(33):30319. doi: doi:https://doi.org/10.2807/1560-7917.ES.2016.21.33.30319

7. Cosgrove SE, Carmeli Y. The impact of antimicrobial resistance on health and economic outcomes. *Clinical infectious diseases* 2003;36(11):1433-37.

8. Allel K, Stone J, Undurraga EA, et al. The impact of inpatient bloodstream infections caused by antibiotic-resistant bacteria in low- and middle-income countries: A systematic review and meta-analysis. *PLOS Medicine* 2023;20(6):e1004199. doi: 10.1371/journal.pmed.1004199

9. Kang C-I, Kim S-H, Park WB, et al. Bloodstream infections caused by antibiotic-resistant gram-negative bacilli: risk factors for mortality and impact of inappropriate initial antimicrobial therapy on outcome. *Antimicrobial agents and chemotherapy* 2005;49(2):760-66.

10. Hung Y-P, Lee C-C, Ko W-C. Effects of inappropriate administration of empirical antibiotics on mortality in adults with bacteraemia: systematic review and meta-analysis. *Frontiers in medicine* 2022;9:869822.

11. Shorr AF, Micek ST, Welch EC, et al. Inappropriate antibiotic therapy in Gram-negative sepsis increases hospital length of stay. *Critical care medicine* 2011;39(1):46-51.

12. Battle SE, Bookstaver PB, Justo JA, et al. Association between inappropriate empirical antimicrobial therapy and hospital length of stay in Gram-negative bloodstream infections: stratification by prognosis. *Journal of Antimicrobial Chemotherapy* 2016;72(1):299-304.

13. Bassetti M, Rello J, Blasi F, et al. Systematic review of the impact of appropriate versus inappropriate initial antibiotic therapy on outcomes of patients with severe bacterial infections. *International journal of antimicrobial agents* 2020;56(6):106184.

14. Kongnakorn T, Tichy E, Kengkla K, et al. Economic burden of antimicrobial resistance and inappropriate empiric treatment in Thailand. *Antimicrobial Stewardship & Healthcare Epidemiology* 2023;3(1):e109.

15. Davey P, Marwick C. Appropriate vs. inappropriate antimicrobial therapy. *Clinical Microbiology and Infection* 2008;14:15-21.

16. Joo E-J, Kang C-I, Ha Y, et al. Impact of inappropriate empiric antimicrobial therapy on outcome in Pseudomonas aeruginosa bacteraemia: a stratified analysis according to sites of infection. *Infection* 2011;39:309-18.

17. Allel K, Labarca J, Carvajal C, et al. Trends and socioeconomic, demographic, and environmental factors associated with antimicrobial resistance: a longitudinal analysis in 39 hospitals in Chile 2008–2017. *The Lancet Regional Health - Americas* 2023;21:100484.

18. Guilarde A, Turchi M, Martelli C, et al. Staphylococcus aureus bacteraemia: incidence, risk factors and predictors for death in a Brazilian teaching hospital. *Journal of hospital infection* 2006;63(3):330-36.

19. Tuon FF, Kruger M, Terreri M, et al. Klebsiella ESBL bacteremia-mortality and risk factors. *Brazilian Journal of Infectious Diseases* 2011;15:594-98.

20. Allel K, Peters A, Conejeros J, et al. Antibiotic Consumption During the Coronavirus Disease 2019 Pandemic and Emergence of Carbapenemase-Producing Klebsiella pneumoniae Lineages Among Inpatients in a Chilean Hospital: A Time-Series Study and Phylogenomic Analysis. *Clinical Infectious Diseases* 2023;77(Supplement_1):S20-S28. doi: 10.1093/cid/ciad151

21. Wayne P. Clinical and Laboratory Standards Institute: Performance standards for antimicrobial susceptibility testing: 20th informational supplement. *CLSI document M100-S20* 2010

22. Daneman N, Fridman D, Johnstone J, et al. Antimicrobial resistance and mortality following E. coli bacteremia. *EClinicalMedicine* 2023;56

23. Tacconelli E, Carrara E, Savoldi A, et al. Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis. *The Lancet Infectious Diseases* 2018;18(3):318-27.

24. Roffman C, Buchanan J, Allison G. Charlson comorbidities index. *Journal of physiotherapy* 2016;62(3)

25. World health Organization. ATC/DDD Index 2023 2023 [Available from: https://www.whocc.no/atc_ddd_index/?code=J01CR01 accessed 16th of August 2023.

26. McGregor JC, Rich SE, Harris AD, et al. A systematic review of the methods used to assess the association between appropriate antibiotic therapy and mortality in bacteremic patients. *Clinical Infectious Diseases* 2007;45(3):329-37.

27. Austin PC. Variance estimation when using inverse probability of treatment weighting (IPTW) with survival analysis. *Statistics in medicine* 2016;35(30):5642-55.

28. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivariate behavioral research* 2011;46(3):399-424.

29. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *Journal of the American statistical association* 1999;94(446):496-509.

30. Austin PC, White IR, Lee DS, et al. Missing data in clinical research: a tutorial on multiple imputation. *Canadian Journal of Cardiology* 2021;37(9):1322-31.

31. Marquet K, Liesenborgs A, Bergs J, et al. Incidence and outcome of inappropriate in-hospital empiric antibiotics for severe infection: a systematic review and meta-analysis. *Critical care* 2015;19:1-12.

32. Ohnuma T, Chihara S, Costin B, et al. Association of appropriate empirical antimicrobial therapy with in-hospital mortality in patients with bloodstream infections in the US. *JAMA Network Open* 2023;6(1):e2249353-e53.

33. Fica A, Valenzuela C, Leiva I, et al. Long-term impact of competitive biddings and an antimicrobial stewardship program in a general hospital in Chile. *Rev Med Chil* 2018;146(9):968-77.

34. Ministerio de Salud Chile. Plan Nacional Contra la Resistencia a los Antimicrobianos Chile 2021-2025 Santiago de Chile2021 [Available from: https://bit.ly/3CjRrrE accessed January 10 2022.

35. Lambregts MM, Bernards AT, van der Beek MT, et al. Time to positivity of blood cultures supports early re-evaluation of empiric broad-spectrum antimicrobial therapy. *PLoS One* 2019;14(1):e0208819.

36. Grinberg S, Schubert S, Hochauf-Stange K, et al. Saving time in blood culture diagnostics: A prospective evaluation of the Qvella FAST-PBC Prep application on the Fast System. *Journal of Clinical Microbiology* 2022;60(5):e02533-21.

37. Chen H-C, Lin W-L, Lin C-C, et al. Outcome of inadequate empirical antibiotic therapy in emergency department patients with community-onset bloodstream infections. *Journal of Antimicrobial Chemotherapy* 2013;68(4):947-53.

38. Guignard B, Entenza JM, Moreillon P. β-lactams against methicillin-resistant Staphylococcus aureus. *Current opinion in pharmacology* 2005;5(5):479-89.

39. Lodise Jr TP, McKinnon PS, Levine DP, et al. Impact of empirical-therapy selection on outcomes of intravenous drug users with infective endocarditis caused by methicillin-susceptible Staphylococcus aureus. *Antimicrobial agents and chemotherapy* 2007;51(10):3731-33.

40. Garnacho-Montero J, Ortiz-Leyba C, Herrera-Melero I, et al. Mortality and morbidity attributable to inadequate empirical antimicrobial therapy in patients admitted to the ICU with sepsis: a matched cohort study. *Journal of Antimicrobial Chemotherapy* 2008;61(2):436-41.

41. Thomas GR, Corso A, Pasterán F, et al. Increased detection of carbapenemase-producing enterobacterales bacteria in Latin America and the Caribbean during the COVID-19 pandemic. *Emerging Infectious Diseases* 2022;28(11)

42. Zilberberg MD, Nathanson BH, Sulham K, et al. 30-day readmission, antibiotics costs and costs of delay to adequate treatment of Enterobacteriaceae UTI, pneumonia, and sepsis: a retrospective cohort study. *Antimicrobial Resistance & Infection Control* 2017;6(1):1-7.

43. Zhang D, Micek ST, Kollef MH. Time to appropriate antibiotic therapy is an independent determinant of postinfection ICU and hospital lengths of stay in patients with sepsis. *Critical care medicine* 2015;43(10):2133-40.

44. Al-Hasan MN, Baddour LM. Resilience of the Pitt bacteremia score: 3 decades and counting: Oxford University Press US, 2020:1834-36.

45. Evans L, Rhodes A, Alhazzani W, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. *Intensive care medicine* 2021;47(11):1181-247.

Figure Captions

Figure 1. Crude in-hospital mortality and antibiotic consumption, by pathogen and empirical antibiotic therapy appropriateness **(A)** Crude in-hospital mortality by pathogen and antibiotic therapy appropriateness (**B)** Crude antibiotic consumption by antibiotic therapy appropriateness and pathogen. ATB= Antibiotic. DDD= Daily defined dose. CI= Confidence interval. Spp= species. BC= Blood culture. DDD= Daily defined doses. Antibiotic classified as "Others" included lincosamides, polymyxins, monobactams, antimycobacterial and other antibacterial.

Figure 2. IPW-weighted cumulative incidence of hospital mortality using the competing-risks model controlling for time-unvarying and time-varying independent variables. (A) Cumulative incidence of hospital mortality by empirical antibiotic therapy appropriateness. (B) Cumulative incidence of hospital mortality by empirical antibiotic therapy appropriateness and antibiotic resistance. Notes: ARB, Antibiotic-resistant bacteria; ATB, Antimicrobial; BSI, Bloodstream infections. Estimates were IPW-weighted. IEAR= Inappropriate empirical antibiotic therapy. AEAT= Appropriate empirical antibiotic therapy. ASB= Antibiotic susceptible bacteria. Supplemental Table S21 shows the number of individuals at risk at 10, 20, 30, 40, 50 and 60 days.