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Original

Healthcare resource utilization and costs associated with inadequate initial antibiotic treatment of bacteraemia produced by carbapenem-resistant Gram-negative bacilli (CRGNB): a descriptive, observational study in Spanish hospitals

Utilización de recursos sanitarios y costes asociados al tratamiento antibiótico inicial inadecuado de la bacteriemia producida por bacilos gramnegativos resistentes a carbapenémicos: un estudio observacional descriptivo en hospitales españoles

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Abstract

Introduction: Carbapenem-resistant gram-negative bacilli (CRGNB) are one of the main causes of nosocomial infections, posing a major public health challenge. Blood stream infections (BSI) require special attention because of the higher morbidity and mortality associated.

Objective: To assess the impact of initial adequate or inadequate antibiotic treatment on the length of stay (LOS) and healthcare resource utilisation of patients with bloodstream infections (BSI) caused by a Carbapenem-resistant gram-negative bacilli (CRGNB) in the Spanish clinical practice.

Methods: A descriptive, observational, retrospective chart review study of patients diagnosed with CRGNB bacteriemia in 6 Spanish public hospitals.

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Results: The overall median LOS of the total population (n=64) was 26.5 days (Q1: 16 days; Q3: 40 days). The median LOS for the initially adequately treated group was 27 days (Q1: 17; Q3: 50), and 24 days (Q1: 15; Q3: 38) for the initially inadequately treated (t-test p= 0.5031). In the Hospital Ward group (n=44), initially adequately treated patients spent hospitalised a median of 6 days less than the initially inadequately treated patients (18 days [Q1: 12; Q3: 27] vs 24 days [Q1: 15; Q3: 38] respectively, p=0.0269). In the total population analysis, initially adequately treated patients had a lower use of resources (20,895.02 € [Q1: 11,543.67 €; Q3: 61,773.17 €]) compared to initially inadequately treated patients (24,444.02 € [Q1: 11,571.63 €; Q3: 40,790.64 €).

Conclusion: Results suggest that inadequate empirical treatment for BSI caused by CRGNB in the hospital ward could be associated with an increase in the LOS and resource utilization of these patients.

Keywords: Carbapenem-resistant gram-negative bacilli. Blood stream infections. Length of stay. Antibiotic treatment adequacy. Healthcare resource utilization.

Resumen

Introducción: Los bacilos gramnegativos resistentes a carbapenémicos (BGNRC) son una de las principales causas de infecciones nosocomiales, lo que supone un importante reto para la salud pública. Las infecciones del torrente sanguíneo (BSI) requieren especial atención por la mayor morbimortalidad asociada.

Objetivo: Evaluar el impacto del tratamiento antibiótico inicial adecuado o inadecuado sobre la duración de la estancia hospitalaria (LOS) y la utilización de recursos sanitarios de los pacientes con infecciones del torrente sanguíneo (BSI) causada por bacilos gramnegativos resistentes a carbapenémicos (BGNRC) en la práctica clínica española.

Material y métodos: Estudio descriptivo, observacional, retrospectivo de revisión de historias clínicas de pacientes diagnosticados de BSI por BGNRC en 6 hospitales públicos españoles**.**

Resultados: La mediana global de la LOS de la población total (n=64) fue de 26,5 días (Q1: 16 días; Q3: 40 días). La mediana de LOS para el grupo tratado inicialmente de forma adecuada fue de 27 días (Q1: 17; Q3: 50), y de 24 días (Q1: 15; Q3: 38) para el grupo tratado inicialmente de forma inadecuada (t-test p= 0,5031). En el grupo de Planta (n=44), los pacientes tratados inicialmente de forma adecuada pasaron hospitalizados una mediana de 6 días menos que los pacientes tratados inicialmente de forma inadecuada (18 días [Q1: 12; Q3: 27] frente a 24 días [Q1: 15; Q3: 38] respectivamente, p=0,0269). En el análisis de la población total, los pacientes tratados inicialmente de forma adecuada tuvieron un menor uso de recursos (20.895,02 € [Q1: 11.543,67 €; Q3: 61.773,17 €]) en comparación con los pacientes tratados inicialmente de forma inadecuada (24.444,02 € [Q1: 11.571,63 €; Q3: 40.790,64 €).

Conclusiones: Los resultados sugieren que el tratamiento empírico inadecuado de las BSI causadas por CRGNB en la planta de hospitalización podría estar asociado a un aumento de la estancia hospitalaria y de la utilización de recursos de estos pacientes.

Palabras clave: Bacilos gramnegativos resistentes a carbapémicos. Infecciones del torrente sanguíneo. Duración de la estancia. Adecuación del tratamiento antibiótico. Utilización de recursos sanitarios.

Introduction

Antibiotics changed the therapeutic paradigm with their discovery in the early 20th century. But with their widespread use, also came their misuse. Antibiotic resistance has been increasing in the last years and is currently considered one of the most important public health threats by international health organizations and governments [1,2]. Resistance is caused by the development or acquisition of different mechanisms, amongst which the production of inactivating enzymes is one of the most important.

Carbapenems are the most widely used antibiotics to treat severe infections in the intensive care unit (ICU) [3], and their overuse has influenced the emergence of resistant bacteria [4]. Gram-negative bacilli develop carbapenem resistance by different mechanisms: enzymatic inactivation of the antibiotic (carbapenemases), impaired permeability, or enhanced efflux [5]. Carbapenem-resistant Gram-negative bacilli (CRGNB) have become a major challenge to public health because the high case-fatality rates in part due to the limited treatment options available [6].

Bloodstream infections (BSI) require special attention because of their high morbidity and mortality [6–8]. The choice of empirical antibiotic treatment in severe cases can be a challenge for physicians, due to the lack of microbiological data when a clinical decision is required. Adequate initial antibiotic therapy has been demonstrated as the key independent factor of patient outcomes in patients with sepsis and/or BSI [9,10]. More specifically, adequate empirical

antimicrobial therapy is crucial in terms of survival in patients with BSI caused by CRGNB [11–13].

However, the impact of initial adequate treatment for CRGNB BSI on the use of healthcare resources by these patients has not been so extensively assessed. In this context, the aim of this study was to determine, based on real clinical practice data, the impact of the adequacy of the empirical therapy on the length of stay (LOS) and healthcare resource utilization in patients with CRGNB BSI hospitalised in Spanish Hospitals.

Methodology

Study design. A descriptive, observational, retrospective chart review study was performed, using existing medical records of patients diagnosed with CRGNB BSI in 6 Spanish hospitals. The population of study included patients aged ≥18 years at the time of hospital admission, and who had been diagnosed of CRGNB BSI between the 1st of January 2019 and the 28th of February 2022.

Exclusion criteria were:

1) Patients under 18 years at time of hospital admission.
2) Patients with incomplete medical records for the following core variables:
    a. First prescribed antibiotic treatment regimen variables (type of antibiotic, posology, duration, route of administration) and antibiogram sensitivity.
    b. LOS in hospital due to the bacteraemia: date of bacteraemia diagnosis and end of treatment.
3) Bacteraemia caused by bacteria that are not carbapenem-resistant (CR), or concomitant with viral or fungal infections.
4) Documentation in the patient's notes objecting to any inclusion in research projects.
5) Patients participating in randomised clinical trials during the period considered in this study.
6) Patients that received cefiderocol as part of the Early Access Program in Spain.
7) Patients that have died during the period of bacteriemia.
8) Patients with BSI with suspected origin of osteomyelitis or endocarditis.

This study was designed, and conducted, according to the requirements of the European Network of Centers for Pharmacoepidemiology and Pharmacovigilance (ENCePP) [14], the International Society for Pharmacoepidemiology (ISPE) guidance [15] and ICH GCP [16] as appropriate.

Ethics. This study was reviewed and approved by the Ethics Committee of Hospital Universitario Marques de Valdecilla/CEIM de Cantabria, under approval number 2020-266-3.

Participants. Investigators from 6 public hospitals from different Spanish regions participated in the study: Hospital Universitario Marqués de Valdecilla (Santander, Cantabria), Complejo Hospitalario Universitario de La Coruña (La Coruña, Galicia), Hospital del Mar (Barcelona, Catalonia), Hospital Universitario y Politécnico La Fe (Valencia, Comunidad Valenciana), Hospital Universitario 12 de Octubre (Madrid) and Hospital Universitario Virgen de la Macarena (Sevilla, Andalucía).

Data collection. Each centre collected data for patients with BSI due to CRGNB meeting the inclusion/exclusion criteria. Data collected by the physicians included:

- Demographic data and patient medical history.
- Baseline qSOFA [17].
- CRGNB identification and source of BSI.
- Antibiotic treatment regimen.
- Length of hospital stay, use of other resources and associated costs.
- Outcomes of CRGNB BSI.

Study objectives and definitions. The study objective was to describe the length of stay (LOS) in hospital for the BSI of patients with bacteraemia due to CRGNB, stratified by 1) initial adequate or inadequate antibiotic treatment and 2) hospital setting: hospital ward and ICU.

The secondary objective was to model the utilization of healthcare resources and their associated costs according to the initial treatment adequateness and to hospital setting. Study definitions are included in the panel below (**Figure 1**).

Use of resources and costs. For the use of resources and the corresponding cost analysis, the following cost inputs were considered:

- Hospital-setting costs: Including costs associated with hospitalization (ICU and hospital ward) for each patient during the study period.
- Treatment costs: Including the cost of the antibiotic treatment during the study period, adjusted according to the number of doses taken.

Adequate initial **antibiotic therapy** is defined as 1) at least one effective drug for which the isolate is found susceptible to the antibiotic treatment is included in the antibiotic treatment within the first 24 hours of bacteriemia, and 2) the dose and pattern of administration are in accordance with current standards for the treatment of bacteraemia following the Antimicrobial therapeutic Mensa Guide [29].

Carbapenem-resistance: in vitro resistance of the isolate to all tested antibiotics from the category of carbapenems.

Empirical prescription: antibiotic therapy prescribed before the availability of any culture data, guided by clinical symptoms.

Length of stay (LOS): Days of hospital stay since CRGN bacteria BSI diagnosis (Blood culture extraction) until clinical cure determined by physician or antibiotic cessation.

Clinical cure: complete resolution of presenting symptoms and signs by the end of treatment (fever, leucocytosis, hypotension, chills).

Figure 1. Study definitions.

- Test costs: Including costs of all the microbiologic and laboratory tests performed during the study period.

The costs sources included the national database of the General Council of Pharmacists (CGCOF) of Spain through the Botplus portal for pharmacological costs, costs of tests and hospitalisation were obtained through cost database eSalud. Costs were calculated for each patient included in the analysis (i.e., calculating the treatment cost adjusted per posology, antibiotic, and treatment duration instead of an average of treatment cost). A descriptive analysis of costs was performed according to patient stratification.

Data analysis. Data was analysed using descriptive statistics, including frequencies (n, %) for categorical variables and means (standard deviation) or medians

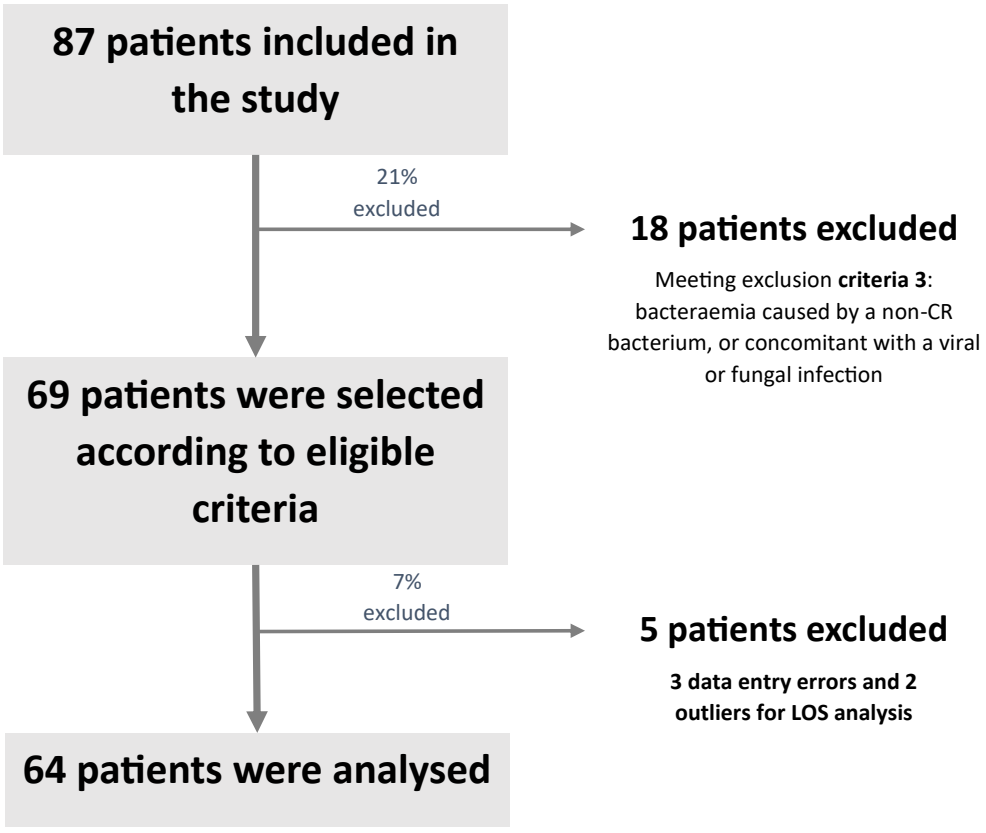

Figure 2. Study population.

(interquartile range) for continuous variables, whether the distribution was normal or not (Shapiro-Wilk test), respectively. For the statistical analysis, t-test or ANOVA were used. For not-normally distributed data, log-transformation was performed previous to the statistical analysis. Significance threshold was set at $p < 0.05$. Study definitions are included in **Figure 1**.

Results

A total of 87 patients were included in the study database, the patient flow is shown in **Figure 2**. Of the included patients, 69 met all inclusion and no exclusion criteria. The other 18 patients were excluded due to exclusion criterion 3 (Bacteraemia caused by a non-CR bacterium, or concomitant with a viral or fungal infection). Out of the 69 patients that met the study criteria, 3 patients were excluded from the analysis due to data entry errors that prevented from calculating the initial adequateness of treatment and LOS. Additionally, 2 other patients were excluded from the analysis, as they were considered outliers from a statistical point of view for the LOS variable. Finally, 64 patients were included in the study analysis; their demographic characteristics are presented in **Table 1**.

Most of the population in the study were male (70%) and the median age was 60 years (Q1: 50; Q3: 72).

Table 1. Study population characteristics.

	Hospital ward	ICU	Hospital Ward plus ICU	Total
Sex, n	44	16	4	64
Male	31 (70%)	12 (75%)	2 (50%)	45 (70%)
Age, median [Q1; Q3]	64 [52; 76.3]	60.5 [46; 67]	52 [45.3;58.5]	60 [50;72]
Treatment adequateness, n (%)	44	16	4	64
Adequate initial treatment	19 (43%)	9 (56%)	1 (25%)	29 (45%)
CRGN Pathogen, %				
Klebsiella pneumoniae	14 (32%)	8 (50%)	4 (100%)	26 (40%)
Pseudomonas aeruginosa	16 (36%)	7 (44%)	0 (0%)	23 (36%)
Stenotrophomonas maltophilia	4 (9%)	1 (6%)	0 (0%)	5 (7%)
Escherichia coli	2 (5%)	0 (0%)	0 (0%)	2 (3%)
Acinetobacter baumannii	1 (2%)	0 (0%)	0 (0%)	1 (2%)
Other	7 (16%)	0 (0%)	0 (0%)	7 (10%)
qSOFA				
qSOFA 0	20 (45%)	7 (44%)	0 (0%)	27 (42%)
qSOFA 1	20 (45%)	5 (31%)	4 (100%)	29 (45%)
qSOFA 2	4 (9%)	2 (12%)	0 (0%)	6 (9%)
qSOFA 3	0 (0%)	2 (12%)	0 (0%)	2 (3%)
Suspected origin of the bacteriemia				
Catheter	11 (25%)	6 (37%)	1 (25%)	18 (28%)
Pneumonia	3 (7%)	7 (44%)	3 (75%)	13 (20%)
Urinary tract	13 (30%)	0 (0%)	0 (0%)	13 (20%)
Biliar	8 (18%)	0 (0%)	0 (0%)	8 (13%)
Skin or soft tissue	4 (9%)	0 (0%)	0 (0%)	4 (6%)
Intraabdominal	2 (4%)	1 (6%)	0 (0%)	3 (5%)
Other	3 (7%)	2 (13%)	0 (0%)	5 (8%)

Table 2. Study population characteristics by initial adequate/inadequate treatment.

	Initial adequate				Initial inadequate			
	Hospital ward	ICU	Hospital Ward plus ICU	Total	Hospital ward	ICU	Hospital Ward plus ICU	Total
Sex, n	19	9	1	29	25	7	3	35
Male	13 (68%)	7 (78%)	0 (0%)	20 (96%)	18 (72%)	5 (71%)	2 (67%)	25 (71%)
Age, median [Q1; Q3]	64.8 [48; 82.5]	66.1 [65; 71]	66 [66; 66]	65.2 [56;77]	58.8 [49; 72]	56.9 [51; 60.5]	55.7 [52; 60]	58.1 [49;68.5]
CRGN Pathogen, %								
Klebsiella pneumoniae	10 (53%)	6 (67%)	1 (100%)	17 (59%)	4 (16%)	2 (29%)	3 (100%)	9 (26%)
Pseudomonas aeruginosa	3 (16%)	2 (22%)	0 (0%)	5 (17%)	13 (52%)	5 (71%)	0 (0%)	18 (51%)
Stenotrophomonas maltophilia	1 (5%)	1 (11%)	0 (0%)	2 (7%)	3 (12%)	0 (0%)	0 (0%)	3(9%)
Escherichia coli	1 (5%)	0 (0%)	0 (0%)	1 (3%)	1 (4%)	0 (0%)	0 (0%)	1 (3%)
Acinetobacter baumannii	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (4%)	0 (0%)	0 (0%)	1 (3%)
Other	4 (21%)	0 (0%)	0 (0%)	4 (14%)	3 (12%)	0 (0%)	0 (0%)	3 (9%)
qSOFA								
qSOFA 0	7 (37%)	4 (44%)	0 (0%)	11 (38%)	13 (52%)	3 (43%)	0 (0%)	16 (46%)
qSOFA 1	10 (53%)	4 (44%)	1 (100%)	15 (52%)	10 (40%)	1 (14%)	3 (100%)	14 (40%)
qSOFA 2	2 (11%)	0 (0%)	0 (0%)	2 (7%)	2 (8%)	2 (29%)	0 (0%)	4 (11%)
qSOFA 3	0 (0%)	1 (11%)	0 (0%)	1 (3%)	0 (0%)	1 (14%)	0 (0%)	1 (3%)
Suspected origin of the bacteriemia								
Catheter	3 (16%)	3 (33%)	0 (0%)	6 (21%)	8 (32%)	3 (43%)	1 (33%)	12 (34%)
Pneumonia	1 (5%)	6 (67%)	1 (100%)	8 (28%)	2 (8%)	1 (14%)	2 (67%)	5 (14%)
Urinary tract	6 (32%)	0 (0%)	0 (0%)	6 (21%)	7 (28%)	0 (0%)	0 (0%)	7 (20%)
Biliar	5 (26%)	0 (0%)	0 (0%)	5 (17%)	3 (12%)	0 (0%)	0 (0%)	3 (9%)
Skin or soft tissue	2 (11%)	0 (0%)	0 (0%)	2 (7%)	2 (8%)	0 (0%)	0 (0%)	2 (6%)
Intraabdominal	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (8%)	1 (14%)	0 (0%)	3 (9%)
Other	2 (11%)	0 (0%)	0 (0%)	2 (7%)	1 (4%)	2 (29%)	0 (0%)	3 (9%)

Table 3. LOS by initial treatment adequateness.

	Initial adequate treatment				Initial inadequate treatment			
Hospital setting	**ICU**	**Hospital ward**	**Hospital Ward plus ICU**	**Total**	**ICU**	**Hospital ward**	**Hospital Ward plus ICU**	**Total**
Patients, n	9	19	1	29	7	25	3	35
LOS (median days)*	41	18	24	27	35	24	34	24
[IQR (Q1;Q3)]	(38;50)	(12;27)	(N/A)	(17;50)	(23;50)	(13;50)	(20;60)	(15;38)

Table 4. Use of resources by cost source for adequate and inadequate treatment.

	Initial adequate treatment					Initial inadequate treatment				
Cost source	**ICU**	**Hospital ward**	**Treatment**	**Tests**	**Total**	**ICU**	**Hospital ward**	**Treatment**	**Tests**	**Total**
Median, € (%)	**63,142.40 (83%)**	**9,460.90 (13%)**	**2,269.81 (3%)**	**783.75 (1%)**	**20,895.02**	**38,674.72 (69%)**	**14,634.73 (26%)**	**1,906.50 (3%)**	**927.81 (2%)**	**24,444.02**
Q1	59,985.28	7,253.03	248.05	419.66	11,543.67	24,467.68	8,075.86	507.83	604.88	11,571.63
Q3	71,035.20	16,690.58	6,166.70	1,976.58	61,773.17	65,904.88	25,981.83	4,580.96	1,792.01	40,790.64

Table 5. Use of resources by treatment adequateness stratifying by hospital setting.

	Initial adequate treatment				Initial inadequate treatment			
Hospital setting	**ICU**	**Hospital ward**	**Hospital Ward plus ICU**	**Total**	**ICU**	**Hospital ward**	**Hospital Ward plus ICU**	**Total**
Patients, n	9	19	1	29	7	25	3	35
Median (€)	**73,266.93**	**11,768.13**	**35,861.95**	**20,895.02**	**57,343.80**	**19,378.63**	**43,105.82**	**24,444.02**
Q1	61,798.78	10,319.77	35,861.95	N/A	45,435.55	10,919.53	33,380.41	N/A
Q3	82,416.32	20,548.04	35,861.95	N/A	79,661.47	26,777.33	33,380.41	N/A

The majority of the population was hospitalised in Hospital Ward (69%); followed by ICU (25%), and finally both Hospital Ward plus ICU (6%). Regarding initial treatment adequateness, 45% of patients were adequately treated, while 55% of patients were classified as inadequately treated as per protocol. The main pathogens causing the CRGN bacteriemia were *Klebsiella pneumoniae* (40%) and *Pseudomonas aeruginosa* (36%). Most patients presented a low qSOFA score, of 0 or 1 at start of BSI, respectively 40% and 45% of study population. Main suspected origins of the bacteriemia were catheter (28%), pneumonia (20%) and urinary tract (20%). ICU Patient characteristics are described in (**Supplementary Table 1**). The clinical characteristics of patients with inadequate empirical antimicrobial therapy and those who received adequate empirical antimicrobial therapy is shown in **Table 2**.

Length of stay (LOS). The overall median LOS of the total population was 26.5 days (Q1: 16 days; Q3: 40 days). The minimum LOS observed was of 3 days and the maximum of 97 days (**Table 3**). When stratifying patients by initial adequate or inadequate antibiotic treatment, the median LOS for the initially adequately treated group was 27 days (Q1: 17; Q3: 50), and 24 days (Q1: 15; Q3: 38) for the initially inadequately treated. The difference observed was statistically non-significant (t-test p= 0.5031).

A subanalysis was performed to assess the differences observed by hospitalisation site (**Table 2**).

In the Hospital Ward group (n=44), initially adequately treated patients spent hospitalised a median of 6 days less than initially inadequately treated patients (18 days [Q1: 12; Q3: 27] vs 24 days [Q1: 15; Q3: 38] respectively, p=0.0269). In the ICU population, initially adequately treated patients (n=9) had a longer LOS (41 days [Q1: 38; Q3: 50]) than initially inadequately treated patients (n=7) (35 days [Q1: 23; Q3: 50], p=0.2683) although this difference was not statistically significant. As for the group of Hospital Ward plus ICU, initially adequately treated patients (n=1) had a shorter LOS (24 days [IQR: N/A]) than initially inadequately treated patients (n=3) (34 days [Q1: 20; Q3: 60], p= N/A).

Use of resources. The analysis of the use of resources and associated costs for the objective 1: "use of resources by cost source for initial adequate and inadequate treatment", is shown in **Table 4**. In the total population analysis, initially adequately treated patients have a lower cost associated with the use of resources (20,895.02 € [Q1: 11,543.67 €; Q3: 61,773.17 €]) than initially inadequately treated patients (24,444.02 € [Q1: 11,571.63 €; Q3: 40,790.64 €]). The analysis of the source of these costs shows that ICU costs represent the main driver of resource utilisation, both in the initially adequate and the initially inadequate treatment groups. For adequate treatment, ICU costs represented 83% of total expense (63,142.40 € [Q1: 59,985.28 €; Q3: 71,035.20 €]), while for initial inadequate treatment they represented 69% (38,674.72 € [Q1: 24,467.68 €; Q3: 65,904.88 €]). Hospital ward costs represented 13% (9,460.90 € [Q1: 7,253.03 €; Q3: 16,690.58 €]) and 26% (14,634.73 € [Q1: 8,075.86 €; Q3: 25,981.83 €]) of total costs for initial adequate and inadequate treatment, respectively. Treatment costs represented 3% (2,269.81 € [Q1: 248.05 €; Q3: 6,166.70 €]) of total costs for initial adequate treatment and 3% (1,906.50 € [Q1: 507.83 €; Q3: 4,580.96 €]) for initial inadequate treatment. Finally, tests represented 1% (783.75 € [Q1: 419.66 €; Q3: 1,976.58 €]) and 2% (927.81 € [Q1: 604.88 €; Q3: 1,792.01 €]) of total costs, for the initial adequate and inadequate groups respectively.

When looking at the cost associated to the use of resources by hospital setting subgroups (**Table 5**), for the ICU group, initially adequately treated patients showed higher costs than initially inadequately treated patients (73,266.93 € [Q1: 61,798.78 €; Q3: 82,416.32 €]). For the Hospital Ward subgroup, initial adequately treated patients have lower costs (11,768.13 € [Q1: 10,319.77 €; Q3: 20,548.04 €]) than initial inadequately treated patients (19,378.63 € [Q1: 10,919.53 €; Q3: 26,777.33 €]). In the Hospital Ward and ICU subgroup, initially adequately treated patients showed lower cost associated with the use of resources (35,861.95 € [IQR: N/A]) than initially inadequately treated patients (43,105.82 € [IQR: N/A]).

Analysing the source of the costs of the Hospital Ward group, hospitalisation represents the 83% of costs in initial adequate treated patients (9,716.60 € median [Q1: 7,454.64 €; Q3: 16,718.03 €]), followed by cost of treatment representing the 7% (792.77 € [Q1: 194.52 €; Q3: 3,945.36 €]) and cost of tests representing the 4% (507.76 € [Q1: 383.14 €; Q3: 963.75 €]). In the initially inadequately treated patients, hospitalisation represents the 76% of costs (14,689.64 € [Q1: 8,075.86 €; Q3: 25,570.00€]), followed by cost of treatment representing the 10% (1,848.06 € [Q1: 673.09 €; Q3: 4,004.94 €]) and cost of tests representing the 4% (799.96 € [Q1: 498.34 €; Q3: 1,114.06 €]).

Discussion

Our study suggests that in patients hospitalised in the general ward with CRGNB BSI, the administration of inadequate empirical antimicrobial therapy increases the length of hospitalization, with the subsequent increment of costs. This association has not been observed in the critically ill (ICU population) population.

Numerous studies have demonstrated that inadequate empirical therapy in patients with severe infections, sepsis and septic shock is an independent predictor of mortality [17–20]. In addition, in septic patients, inadequate antimicrobial therapy increases the LOS with the associated increment of total costs [21]. More specifically, inadequate empirical antimicrobial therapy is also an independent predictor of mortality in patients with BSI caused by CRGNB [12,13].

Several well-designed studies have also demonstrated that CRGNB BSI are associated with high mortality rates especially when critically ill patients are affected. Thus, a meta-analysis that included 17 studies found that the risk of in-hospital death due to carbapenemase-producing Enterobacterales (CPE) BSI was considerably greater than in case of a carbapenem-susceptible BSI [22].

The clinical and economic burden imposed by CRGNB BSI is particularly high. The mortality rate of BSI due to CRGN bacteria in a cohort of critically ill patients doubled that of the control group that was bacteraemia-free (49.3% vs 25.6%), being an independent risk factor for mortality after adjusting for several confounding variables. Moreover, CRGNB BSI was associated with an extended length of stay (median of 30 days vs 12 days) with the corresponding associated higher hospital costs [23]. In a case-control study, the mean total length of stay for cases (patients carbapenem-resistant Enterobacterales BSI) was 1.90 times that of patients with antibiotic-susceptible bacteraemia. The economic burden caused by CRE bacteraemia was approximately five times higher than that of controls without infection [24].

Nevertheless, information about the impact of inadequate empirical treatment of these BSIs on the LOS and associated costs is sparse. Reckoning the socio-economic burdens of this infection is essential to provide a relevant rationale for decisions regarding infection treatment. In a retrospective, multicentre study that included 29,570 BSI, the adjusted analysis using multivariable regression modelling, the

post-BSI LOS for the group treated inadequately was significantly longer than the LOS in the cohort that received adequate empirical therapy [14.6 days (95% CI, 13.9, 15.2) vs 13.9 days (95% CI, 13.4, 14.6), respectively, P < 0.0001] [25]. In patients hospitalised with infections caused by Enterobacterales or *P. aeruginosa*, delayed start to newer active antibacterial therapy (ceftazidime-avibactam, ceftolozane-tazobactam, cefiderocol, meropenem-vaborbactam, eravacycline, or imipenem-cilcastatin-relebactam) that were active against the isolated pathogen was associated with significantly greater hospital mortality and significantly longer post-culture LOS [26].

In our series, in patients hospitalised in the general ward, those who received adequate empirical therapy spent hospitalised a median of 6 days less than those patients initially treated inadequately. In consequence, the total cost of hospitalization was lower in those treated adequately since the bacteraemia onset, as the main driver of the total costs is the length of stay either in hospital wards or ICU [27]. Moreover, in the total population analysis, the use of economic resources was lower in the group that received adequate empirical therapy (20,895.02 € [Q1: 11,543.67 €; Q3: 61,773.17 €]) than in patients with inadequate empirical therapy (24,444.02 € [Q1: 11,571.63 €; Q3: 40,790.64 €).

Conclusions cannot be drawn for ICU and Hospital Ward plus ICU as the number of patients included in these groups were very small (n= 16 and 4 respectively), reflecting probably only interindividual variability. Additionally, the ICU population, as consequence of the exclusion criteria (death during the period of BSI) does not adequately represent a typical ICU population, comprising instead less severe cases with low mortality risk; 75 % of the ICU patients had a qSOFA score 0 or 1. Also, the patients in the ICU with initial adequate treatment showed a more severe profile than ICU initial inadequately treated patients, with a higher number of patients presenting shock (88% 7/8 vs 57% 4/7), mechanical ventilation (100% 8/8 vs 86% 6/7) and renal replacement therapy due to acute renal failure (38% 3/8 vs 29% 2/7).

An observational study conducted in three Spanish ICU revealed that the mean total cost of patients with CRGNB infections hospitalised in ICU was 96,878€ per patient, being the length of stay either in hospital wards or ICU the main driver of the total costs. The lowest part of the resource consumption (13%) was represented by diagnostic tests and treatments, including the costs of the prescribed antibiotics [28]. The differences between these figures and the expenses found in this study can be explained by the fact that in the present study the majority of the patients were hospitalised in the general ward and only 25 % in the ICU, whereas in the study by Ferrer et al [28] all the patients were hospitalised in the ICU.

There are some limitations to this study that need to be discussed. First, the number of patients included in the study is low, limiting the subgroup analysis. Thus, only 16 and 4 patients were in the ICU and ICU plus Hospital ward groups with not a typical representative ICU population, what precludes to draw definitive conclusions about the impact on costs of inadequate empirical in the critically ill patient. As mentioned above, one of the reasons behind the few patients in the ICU setting is that per study protocol, patients that died during the period of bacteriemia could not be included in the study therefore impacting in more critically ill population. Second, the time elapsed since blood culture collection and initiation of adequate target therapy in patients treated inadequately in the empirical regimen was not available for the analysis, as initially inadequately treated patients could potentially receive an adequate therapy after the first 24h of the bacteriemia. We could speculate that the shorter this interval is the lower is the impact of inadequate therapy on mortality and LOS. Third, the infection focus control was not included in the database. Fourth, the small sample size impeded us to perform a matched case control study what may have generated more precise information.

In summary, CRGNB BSI has emerged as a serious global health concern not only for their high mortality rates but also for the substantial associated costs. This economic burden is increased with the administration of inadequate therapy in the empiric antimicrobial regimen as shown in this study in hospital ward patients. Therefore, renewed efforts should be implemented to minimize the prescription of incorrect antimicrobials in patients with CRGNB BSI. This may be considered not only as a lifesaving but also as a cost-effective strategy. A rapid diagnostic test that may allow the identification of these cases in the first hours is clearly needed. Additional studies including a larger population with a representative ICU population are necessary to confirm the outcomes observed in this study.

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Conflict of interest

Dr. Garnacho-Montero has nothing to disclose. Dr. Aguado has nothing to disclose. Dr. Alemparte reports personal fees from Pfizer, personal fees from Shionogi, outside the submitted work; Dr. Horcajada reports personal fees from Pfizer, personal fees from

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Author contributions

Conceptualization, JG-M, AGP, MB and BS; methodology, AGP and MB; validation and formal analysis, AGP and MB; data curation and interpretation: JG-M, JMA, EA, JPH,FL-M,PR, AG-P, MB, BS; writing—original draft preparation, AGP and MB; writing—review and editing all authors; All authors have read and agreed to the published version of the manuscript.

Supplementary data

Supplementary Table 1 is available as supplementary data on REQ online.

References

1. Salam MA, Al-Amin MY, Salam MT, Pawar JS, Akhter N, Rabaan AA, et al. Antimicrobial Resistance: A Growing Serious Threat for Global Public Health. Healthcare (Basel) 2023;11. https://doi.org/10.3390/healthcare11131946.
2. Aljeldah MM. Antimicrobial Resistance and Its Spread Is a Global Threat. Antibiotics (Basel) 2022;11. https://doi.org/10.3390/antibiotics11081082.
3. Díaz-Martín A, Luisa Martínez-González M, Ferrer R, Ortiz-Leyba C, Piacentini E, Jesus Lopez-Pueyo M, et al. Antibiotic prescription patterns in the empiric therapy of severe sepsis: combination of antimicrobials with different mechanisms of action reduces mortality. Crit Care 2012;16:R223. https://doi.org/10.1186/cc11869.
4. Teshome BF, Vouri SM, Hampton N, Kollef MH, Micek ST. Duration of Exposure to Antipseudomonal β-Lactam Antibiotics in the Critically Ill and Development of New Resistance. Pharmacotherapy. 2019 Mar;39(3):261-270. https://doi.org/10.1002/phar.2201
5. Garnacho-Montero J, Amaya-Villar R. The problem of multi-resistance in gram-negative bacilli in intensive care units: Treatment and prevention strategies. Med Intensiva (Engl Ed). 2022 Jun;46(6):326-335. https://doi.org/10.1016/j.medine.2022.04.006.
6. Foglia F, Della Rocca MT, Melardo C, Nastri BM, Manfredini M, Montella F, et al. Bloodstream infections and antibiotic resistance patterns: a six-year surveillance study from southern Italy. Pathog Glob Health 2023;117:381–91. https://doi.org/10.1080/20477724.2022.2129161.
7. Verway M, Brown KA, Marchand-Austin A, Diong C, Lee S, Langford B, et al. Prevalence and Mortality Associated with Bloodstream Organisms: a Population-Wide Retrospective Cohort Study. J Clin Microbiol 2022;60. https://doi.org/10.1128/JCM.02429-21.
8. Santoro A, Franceschini E, Meschiari M, Menozzi M, Zona S, Venturelli C, et al. Epidemiology and Risk Factors Associated With Mortality in Consecutive Patients With Bacterial Bloodstream Infection: Impact of MDR and XDR Bacteria. Open Forum Infect Dis 2020;7. https://doi.org/10.1093/OFID/OFAA461.
9. Lodise TP, Patel N, Kwa A, Graves J, Furuno JP, Graffunder E, et al. Predictors of 30-Day Mortality among Patients with Pseudomonas aeruginosa Bloodstream Infections: Impact of Delayed Appropriate Antibiotic Selection. Antimicrob Agents Chemother 2007;51:3510–5. https://doi.org/10.1128/AAC.00338-07.
10. Sligl WI, Dragan T, Smith SW. Nosocomial Gram-negative bacteremia in intensive care: epidemiology, antimicrobial susceptibilities, and outcomes. Int J Infect Dis. 2015; 37:129–34. https://doi.org/10.1016/j.ijid.2015.06.024.
11. Calo F, Retamar P, Perez-Crespo PMM, Lanz-Garcia J, Sousa A, Goikoetxea J, et al. Catheter-related bloodstream infections: predictive factors for Gram-negative bacteria aetiology and 30 day mortality in a multicentre prospective cohort. J Antimicrob Chemother 2020;75:3056–61. https://doi.org/10.1093/JAC/DKAA262.
12. Giacobbe DR, Del Bono V, Bruzzi P, Corcione S, Giannella M, Marchese A, et al. Previous bloodstream infections due to other pathogens as predictors of carbapenem-resistant Klebsiella pneumoniae bacteraemia in colonized patients: results from a retrospective multicentre study. Eur J Clin Microbiol Infect Dis. 2017;36:663–9. https://doi.org/10.1007/s10096-016-2843-1.
13. Falcone M, Giordano C, Leonildi A, Galfo V, Lepore A, Suardi LR, et al. Clinical Features and Outcomes of Infections Caused by Metallo-β-Lactamase–Producing Enterobacterales: A 3-Year Prospective Study From an Endemic Area. Clin Infect Dis. 2024;78:1111–9. https://doi.org/10.1093/CID/CIAD725.
14. The European Network of Centres for Pharmacoepidemiology & Pharmacovigilance (ENCePP). https://encepp.europa.eu/index_en?prefLang=es (accessed July 30, 2024).
15. International Society for Pharmacoepidemiology (ISPE). https://www.pharmacoepi.org/ (accessed July 30, 2024).
16. ICH E6 (R2) Good clinical practice - Scientific guideline | European Medicines Agency (EMA). https://www.ema.europa.eu/en/ich-e6-r2-good-clinical-practice-scientific-guideline (accessed July 30, 2024).
17. Singer M, Deutschman CS, Seymour C, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016;315:801–10. https://doi.org/10.1001/JAMA.2016.0287.
18. Garnacho-Montero J, Garcia-Garmendia JL, Barrero-Almodovar A, Jimenez-Jimenez FJ, Perez-Paredes C, Ortiz-Leyba C. Impact of adequate empirical antibiotic therapy on the outcome of patients admitted to the intensive care unit with sepsis. Crit Care Med 2003;31:2742–51. https://doi.org/10.1097/01.CCM.0000098031.24329.10.
19. Kang C-I, Kim S-H, Park WB, Lee K-D, Kim H-B, Kim E-C, et al. Bloodstream Infections Caused by Antibiotic-Resistant Gram-Negative Bacilli: Risk Factors for Mortality and Impact of Inappropriate Initial Antimicrobial Therapy on Outcome. Antimicrob Agents Chemother 2005;49:760–6. https://doi.org/10.1128/AAC.49.2.760-766.2005.
20. Vazquez-Guillamet C, Scolari M, Zilberberg MD, Shorr AF, Micek ST, Kollef M. Using the number needed to treat to

assess appropriate antimicrobial therapy as a determinant of outcome in severe sepsis and septic shock. Crit Care Med 2014;42:2342–9. https://doi.org/10.1097/CCM.0000000000000516.

21. Garnacho-Montero J, Ortiz-Leyba C, Herrera-Melero I, Aldabó-Pallás T, Cayuela-Dominguez A, Marquez-Vacaro JA, et al. Mortality and morbidity attributable to inadequate empirical antimicrobial therapy in patients admitted to the ICU with sepsis: a matched cohort study. J Antimicrob Chemother2008;61:436–41.https://doi.org/10.1093/JAC/DKM460.
22. Budhram DR, Mac S, Bielecki JM, Patel SN, Sander B. Health outcomes attributable to carbapenemase-producing Enterobacteriaceae infections: A systematic review and meta-analysis. Infect Control Hosp Epidemiol 2020;41:37–43. https://doi.org/10.1017/ICE.2019.282.
23. Kousouli E, Zarkotou O, Polimeri K, Themeli-Digalaki K, Pournaras S. Impact of bloodstream infections caused by carbapenem-resistant Gram-negative pathogens on ICU costs, mortality and length of stay Infection Prevention in Practice. Infect Prev Pract. 2019; 1(2):100020. https://doi.org/10.1016/j.infpip.2019.100020.
24. Lee CM, Lee S, Kim ES, Kim HB, Park WB, Moon SM, et al. Disease burden of bacteraemia with extended-spectrum beta-lactamase-producing and carbapenem-resistant Enterobacterales in Korea. J Hosp Infect. 2024 Feb;144:85-93. https://doi.org/10.1016/j.jhin.2023.11.013.
25. Cooper L, Yu K, Van Benten K, Patkar A, Ye G, Gregory S, et al. Hospital mortality and length of stay associated with Enterobacterales positive blood cultures: a multicenter analysis. Microbiol Spectr 2024;12. https://doi.org/10.1128/spectrum.00402-24.
26. Riccobene T, Lock J, Yu KC, Ai C, Gregory S, Gupta V. Outcomes of inadequate empiric therapy and timing of newer antibacterial therapy in hospitalized adults with culture-positive Enterobacterales and Pseudomonas aeruginosa: a multicenter analysis. BMC Infect Dis. 2024 Aug 9;24(1):810. https://doi.org/10.1186/s12879-024-09700-7.
27. Cantón R, Huarte R, Morata L, Trillo-Mata JL, Muñoz R, González J, Tort M, Badia X. Determining the burden of infectious diseases caused by carbapenem-resistant gram-negative bacteria in Spain. Enferm Infecc Microbiol Clin (Engl Ed). 2021 Apr;39(4):179-183. English, Spanish. doi: 10.1016/j.eimc.2020.04.009.
28. Ferrer R, Garnacho-Montero J, Rascado P, Contreras S, Cantón-Bulnes L, Barral P, et al. Use of hospital resources in ICU inpatients with infections caused by carbapenem-resistant Gram-negative bacteria: A real clinical practice-based study in Spain. Enferm Infecc Microbiol Clin (English Ed) 2023;41(3):162–8. https://doi.org/10.1016/J.EIMCE.2021.10.009.
29. Mensa J, Soriano A. Guia de terapeutica antimicrobiana. Barcelona: Antares. 2024