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Beta-lactam allergy labeling in intensive care units

An observational, retrospective study

Marc Leone, MD, PhD[a,b,*], Claire Zunino, MD[a] [ID], Vanessa Pauly, MSc[c], Calypso Mathieu, MD[a],
François Antonini, MD[a], Veronica Orlean, MSc[c], Nadim Cassir, MD[b], Vincent Pradel, MD[c],
Jérémy Bourenne, MD[d], Salah Boussen, MD, PhD[e,f], Sami Hraiech, MD, PhD[g], David Lagier, MD, PhD[h],
Joana Vitte, MD, PhD[b], Sandrine Wiramus, MD[i], Laurent Zieleskiewicz, MD[a], Laurent Papazian, MD, PhD[g],
Laurent Boyer, MD, PhD[c], for the GRAM+[*] GRAM+: Groupe de Recherche en Réanimation et Anesthésie de
Marseille Pluridisciplinaire

Abstract

This retrospective study aimed to describe the association between the "β-lactam allergy" labeling (BLAL) and the outcomes of a cohort of intensive care unit (ICU) patients.

Retrospective cohort study.

Seven ICU of the Aix Marseille University Hospitals from Marseille in France.

We collected the uses of the label "β-lactam allergy" in the electronic medical files of patients aged 18 years or more who required more than 48 hours in the ICU with mechanical ventilation and/or vasopressors admitted to 7 ICUs of a single institution.

We retrospectively compared the patients with this labeling (BLAL group) with those without this labeling (control group).

The primary outcome was the duration of ICU stay. Among the 7146 patients included in the analysis, 440 and 6706 patients were classified in the BLAL group and the control group, respectively. The prevalence of BLAL was 6.2%. In univariate and multivariate analyses, BLAL was weakly or not associated with the duration of ICU and hospital stays (respectively, 6 [3–14] vs 6 [3–14] days, standardized beta −0.09, $P=.046$; and 18 [10–29] vs 15 [8–28] days, standardized beta −0.09, $P=.344$). In multivariate analysis, the ICU and 28-day mortality rates were both lower in the BLAL group than in the control group (aOR 0.79 95% CI [0.64–0.98] $P=.032$ and 0.79 [0.63–0.99] $P=.042$). Antibiotic use differed between the 2 groups, but the outcomes were similar in the subgroups of septic patients in the BLAL group and the control group.

In our cohort, the labeling of a β-lactam allergy was not associated with prolonged ICU and hospital stays. An association was found between the labeling of a β-lactam allergy and lower ICU and 28-day mortality rates.

Trial registration: Retrospectively registered.

Abbreviations: BLAL = beta-lactam allergy labeling, CI = confidence intervals, ICU = intensive care unit, MDR = multidrug resistant, OR = odds ratio.

Keywords: allergy, antibiotic, intensive care unit, labeling

1. Introduction

Beta-lactams are the most common classes of antibiotics administered in the intensive care unit (ICU).[1] In parallel, a β-lactam allergy is reported by at least 10% of patients, whereas 90% of those labeled with this allergy in their medical file are able to tolerate these antibiotics.[2,3] This incorrect labeling can result in antimicrobial treatments that do not adhere to standard recommendations, thereby reducing the treatment success and possibly increasing the risk of multidrug-resistant (MDR) pathogens due to the increased use of drugs like fluoroquinolones.[4] This situation poses a specific risk in the ICU, in which inappropriate antimicrobial treatments are associated with increased mortality.[5]

Several observational studies have suggested that the label of "β-lactam allergy" in medical files was associated with impaired outcomes, including prolonged hospitalization duration. In a large Dutch study, the prevalence of β-lactam allergy labeling (BLAL) among hospitalized patients was 5.6%, and this label affected antibiotic prescribing and was associated with a higher risk of readmission within 12 weeks.[6] In a retrospective, matched cohort study performed in Southern California, Macy et al matched 51,582 unique hospitalized subjects with penicillin "allergy" to 2 controls each. The patients with penicillin allergy had a longer duration of hospitalization and received significantly more fluoroquinolones, clindamycin, and vancomycin than the controls. In addition, they developed more infectious complications.[7]

To the best of our knowledge, there are no specific data for patients with a β-lactam allergy label hospitalized in ICUs.

Here, we hypothesized that BLAL is associated with a prolonged duration of ICU stay, especially in the subgroup of patients requiring antimicrobial treatment. Our first end-point was the duration of ICU stay. The secondary end-points were the ICU and 28-day mortality rates; the ICU readmission rate at day-28; the duration of mechanical ventilation, hospital stay, and vasopressor infusion; the need for renal replacement therapy; the number of infections caused by *Clostridium difficile*; the rate of MDR organisms; and the antibiotic classes.

2. Materials and methods

2.1. Study population

Patients from the Aix Marseille University Hospitals (Hôpital Nord, Hôpital de la Timone, Hôpital de la Conception), Marseille, France, aged 18 years or more and hospitalized in 1 of the 7 ICUs of our institution from April 1, 2014 to September 30, 2018 were retrospectively screened (Fig. 1). The patients who required more than 48 hours in the ICU with mechanical ventilation and/or vasopressors were included in the study. For each patient admitted to the ICU during the study period, the label of β-lactam allergy was electronically searched for in the electronic medical files using a keyword process. For patients requiring re-admission, only the first ICU stay was considered in the analysis. The ICU patients were managed according to international guidelines as described elsewhere.[8]
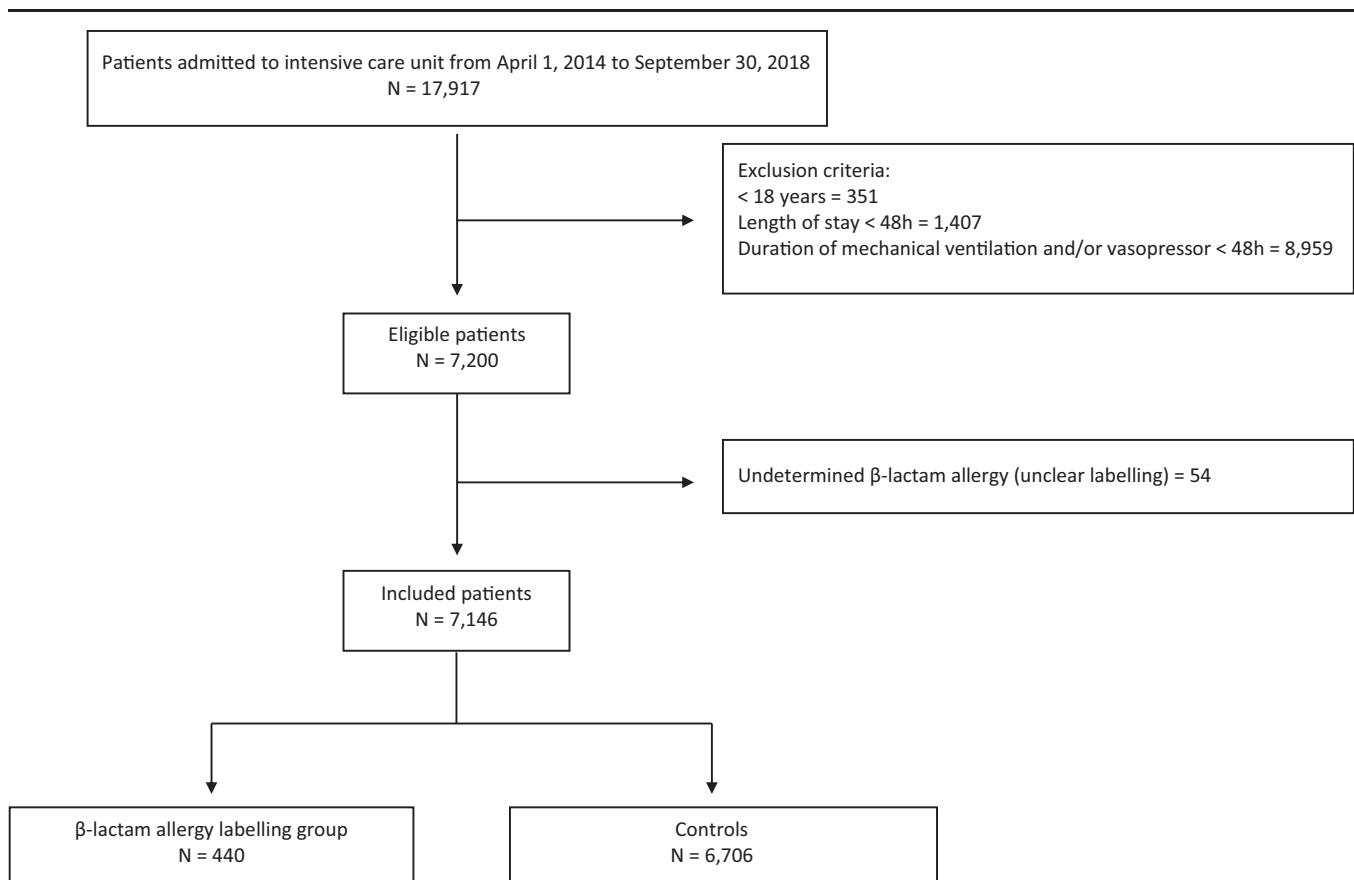

Figure 1. Flow chart.

2.2. Ethics statement

This retrospective, non-interventional study was based on the review of clinical and laboratory medical records. Under the French law,[9] ethics committee approval and patient consent were not required for this type of non-interventional study, provided the patients had received information about the potential use of anonymized medical data for research purposes and retained the right to oppose it (SFAR CERAR committee: IRB 00010254K 2018K 136; CNIL authorization number: 2018-81).

2.3. Type of BLAL

According to the wording found in the electronic medical file, the patients were classified as follows:

(1) No mention of β-lactam allergy.
(2) No β-lactam allergy (written in the electronic medical file).
(3) Undetermined β-lactam allergy (unclear labeling).
(4) Suspected β-lactam allergy.
(5) Reported β-lactam allergy.
(6) Confirmed β-lactam allergy (skin tests or description).
(7) Anaphylaxis and angioedema.

The patients classified with undetermined β-lactam allergy were excluded from our analysis. The patients classified in groups 4 to 7 were included in the "BLAL group" (BLAL group). The patients classified in groups 1 and 2 were included in the "no BLALgroup" (control group).

2.4. Data collection

For each patient, we collected sociodemographic character-istics: age, sex, and an area-level deprivation index (FDep99 index) based on the patient's address and validated by French data that were used as a proxy for the social environment;[10] clinical characteristics: Simplified Acute Physiology Score II (SAPS II) score, diagnosis of sepsis, infection cases caused by *Clostridium difficile*, infection cases caused by MDR patho-gens, multiple trauma, acute respiratory failure, stroke, type of admission to the ICU (from surgery, medical unit, or direct admission to the ICU), and 17 comorbidities from the Charlson comorbidity index based on the algorithm developed by Quan et al[11]; antimicrobial treatment; and ICU and hospital management characteristics: duration of ICU and hospital stay, invasive mechanical ventilation and number of days free from mechanical ventilation, vasopressor use and a number of days free from vasopressor use, and renal replacement therapy.

2.5. Statistical analysis

Category variables are presented as frequencies. Continuous quantitative variables are each presented as the median, range, and interquartile range (IQR). The association between category variables was evaluated with the χ^2 test and Fisher exact test as applicable. Continuous variables were compared with Student t test and multiple t tests for comparison of groups.

Multivariate logistic analysis and a generalized linear model for gamma distribution were performed to identify variables potentially associated with ICU mortality, 28-day mortality, ICU

Table 1

Type, number, and percentage of labeling.

Labeling	N	Percentage
No mention of β-lactam allergy	6347	88.8
No β-lactam allergy	359	5.0
Suspected β-lactam allergy	20	.3
Reported β-lactam allergy	136	1.9
Confirmed β-lactam allergy	221	3.1
Severe β-lactam allergy	63	.9
Total (all)	7146	100.00

readmission within 28 days following first ICU discharge, and ICU and hospital length of stays after adjusting for confounding factors. Variables relevant to the models were selected based on a threshold P value ($\leq$.2) in the univariate analysis: age, gender, SAPS II, sepsis, multiple trauma, type of admission to the ICU, Charlsoncomorbidity score, acute renal failure, invasive mechan-ical ventilation, and vasopressor use. Odds ratios (OR) or standardized beta with confidence intervals (CI) were calculated. Statistical significance was defined as $P < .05$. The statistical analyses were performed with Statistical Analysis Software (SAS), Version 9.4 (SAS Institute).

3. Results

3.1. Features of patients

During the study period, 7146 patients were included in the analysis, including 440 patients in the BLAL group and 6706 patients in the control group (Fig. 1). The prevalence of BLAL was 6.2% in our cohort. The distribution of patients according to the type of labeling is shown in Table 1. Fifty-four (0.75%) patients were excluded from the analysis because of undeter-mined labeling. Of note, no labeling for β-lactam allergy was found in 94% of electronic medical files.

The characteristics of patients are described in Table 2. The average ages of the patients were 60.6 ($\pm$16.3) years and 60.3 ($\pm$16.5) years in the BLAL group and control group, respectively ($P=.738$). Females represented 49.8% of the BLAL group and 32.4% of the control group ($P < .001$). The level of deprivation index was similar in the BLAL group and the control group ($P=.522$).

At admission, the SAPS II score was lower in the BLAL group than in the control group (43 ± 17 vs 46 ± 19, $P=.002$), while the rate of sepsis during the ICU stay was higher in the BLAL group than in the control group (30.2% vs 22.3%, $P < .001$). The Charlson comorbidity score was not statistically different between the BLAL group and the control group ($P=.083$). Invasive mechanical ventilation was used in 88.9% of patients in the BLAL group and 91.8% of patients in the control group ($P=.032$). The types of antibiotics differed between the 2 groups: penicillin use was similar between the BLAL group and control group (41.4% vs 43.9%, $P=.299$), while macrolides and tetracyclines (15.5% vs 10.2% and 8.7% vs 5.9%, all $P < .001$) were preferentially used in the BLAL group.

3.2. Outcomes

Univariate analysis revealed that the duration of ICU stay was similar in the 2 groups (6 [3–14] vs 6 [3–14] days, $P=.195$).

Table 2

Characteristics of the 440 patients with recorded β-lactam allergy and 6706 controls.

Variables	BLAL group (n = 440)		Control group (n = 6706)		
	n	(%)	N	(%)	P
Demographic characteristics					
Age, mean (SD), years	60.6	(16.3)	60.3	(16.5)	.738
Gender (female)	219	(49.8)	2171	(32.4)	<.001
Low deprivation index	235	(53.4)	3472	(51.8)	.522
Clinical characteristics					
SAPS II score at ICU admission, mean (SD)	43.2	(17.1)	45.7	(18.9)	.002
Sepsis	133	30.2	1496	22.3	<.001
Multidrug-resistant bacteria	15	3.4	127	1.9	.027
Clostridium difficile infection	6	1.4	41	0.6	.059
Multiple trauma	18	4.1	486	7.2	.012
Type of admission in ICU					.065
From Surgery unit	265	60.2	3770	56.2	
From Medical unit	51	11.6	687	10.2	
Direct admission in ICU	124	28.2	2249	33.5	
Acute respiratory failure	8	1.8	205	3.1	.139
Stroke	28	6.4	367	5.5	.428
Comorbidities					
Charlson comorbidity score					.083
0	120	(27.3)	2140	31.9	
1–2	183	(41.6)	2729	40.7	
≥3	137	(31.1)	1837	27.4	
Renal disease	51	(11.6)	452	(6.7)	<.001
Rheumatologic disease	7	(1.6)	40	(0.6)	.012
Peripheral vascular disease	65	(14.8)	739	(11.0)	.016
Peptic ulcer disease	11	(2.5)	140	(2.1)	.560
Hemiplegia or paraplegia	39	(8.9)	708	(10.9)	.261
Moderate or severe liver disease	6	(1.4)	223	(3.3)	.024
Mild liver disease	20	(4.5)	397	(5.9)	.233
AIDS/HIV	5	(1.1)	46	(0.7)	.277
Diabetes with complications	21	(4.8)	241	(3.6)	.202
Diabetes without complications	71	(16.1)	846	(12.6)	.032
Cerebrovascular disease	61	(13.9)	1194	(17.8)	.035
Chronic pulmonary disease	41	(9.3)	442	(6.6)	.003
Congestive heart failure	101	(23.0)	1137	(17.0)	.001
Myocardial infarction	47	(10.7)	678	(10.1)	.701
Dementia	5	(1.1)	57	(0.8)	.530
Malignancy	74	(16.8)	916	(13.7)	.063
Metastasis	13	(3.0)	228	(3.4)	.616
Antibiotic treatment	331	(75.2)	4557	(68.0)	<.001
Penicillin	182	(41.4)	2944	(43.9)	.299
Other beta-lactams	219	(49.8)	2984	(44.5)	.031
Tetracyclines	45	(10.2)	396	(5.9)	<.001
Sulfamides	31	(7.0)	393	(5.9)	.308
Macrolides	68	(15.5)	581	(8.7)	<.001
Aminosides	131	(29.8)	1627	(24.3)	.009
Quinolone	98	(22.3)	583	(8.7)	<.001
Others	144	(32.7)	1519	(22.7)	<.001
Main ICU supportive therapies					
Invasive mechanical ventilation	391	(88.9)	6155	(91.8)	.032
Duration of invasive mechanical ventilation, median (IQR), days	3	(1–7)	3	(2–8)	.249
Vasopressor	373	(84.8)	5209	(77.7)	<.001
Renal replacement therapy	68	(15.5)	900	(13.4)	.227

% = percentage, AIDS = acquired immunodeficiency syndrome, BLAL = beta-lactam allergy labelin, HIV: human immunodeficiency virus, ICU = intensive care unit, IQR = interquartile range, N = effective, SAPS II score: Simplified Acute Physiology Score II, SD = standard deviation.

Multivariate analysis revealed that BLAL was associated with a shorter duration of ICU stay, but this effect size was weak (Beta −0.094, SE = 0.047, P = .046) (Table 3). The duration of hospital stay did not differ between the 2 groups (Beta −0.04, SE = 0.04, P = .344) (Table 3). The ICU and 28-day mortality rates were both lower in the BLAL group than in the control group according to univariate and multivariate analyses (aOR 0.79, 95% CI, [0.64–0.98] P = .032 and 0.79 [0.63–0.99] P = .042). The rate of ICU re-admission was similar in the 2 groups (aOR 0.99, 95% CI [0.72–1.38] P = .992) (Table 4).

Table 3

Association between BLAL and length of stays: univariate and multivariate analyses.

Association between BLAL (reference: the absence of labeling) and length of hospital stay

					Univariate analysis		Multivariate analysis[*]	
Outcome	Population		BLAL group	Control group	Beta[†] ± se	P value	Beta[†] ± se	P value
Length of hospital stay	Discharged	N	343	4765				
		Median, IQR	18 [12;30]	17 [11;31]	0.027 ± 0.0442	.5419	−0.0627±0.0391	.109
	Died in the hospital	N	97	1941				
		Median, IQR	13 [4;27]	7 [3;18]	0.3223 ± 0.0867	.0073	−0.0086±0.104	.934
	Overall events	N	440	6706				
		median, IQR	18 [10;29]	15 [8;28]	0.1061 ± 0.046	.021	−0.0395±0.0418	.344

Association between BLAL (reference: the absence of labeling) and length of ICU stay

					Univariate analysis		Multivariate analysis[*]	
Outcome	Population		BLAL group	Control group	Beta[†] ± se	P value	Beta[†] ± se	P value
Length of ICU stay	Discharged from ICU	N	354	4909				
		Median, IQR	6 [3;13]	6 [3;14]	0.0305 ± 0.0564	.5886	−0.086±0.0445	.054
	Died in ICU	N	86	1797				
		Median, IQR	8 [3;22]	6 [2;14]	0.222 ± 0.124	.074	−0.101±0.1052	.337
	Overall events	N	440	6706				
		Median, IQR	6 [3;14]	6 [3;14]	0.0672±,0.0518	.1951	−0.0941±0.0472	.046

BLAL = beta-lactam allergy labeling, ICU = intensive care unit, IQR = interquartile range.

[*] Variables included in the multivariate models were selected based on a threshold P value (≤.2) in the univariate analysis: age, gender, SAPS II, sepsis, multiple trauma, type of admission to the ICU, Charlson comorbidity score, acute renal failure, invasive mechanical ventilation, and vasopressor use.

[†] The Beta examines the association between the BLAL (reference: the absence of labeling) and length of stay according to each population (discharged, died in the hospital, and overall events).

3.3. Subgroup analysis

A specific analysis of the 1629 patients with sepsis, including 133 (8.2%) in the BLAL group and 1496 (91.8%) in the control group, was performed. Sepsis due to MDR pathogens and *C difficile* occurred more frequently in the BLAL group than in the control group (3.4% vs 1.9% and 1.4% vs 0.6%, all $P < .001$). In the multivariate analysis, no differences were found between the primary end-point and the secondary end-points (Table 2).

4. Discussion

In our institution, the prevalence of BLAL for ICU patients was around 6%. However, our study showed that labeling regarding β-lactam allergy was largely under-reported in the electronic medical files because it was not found in 94% of them. Our findings for a large ICU cohort from a single institution indicated that the BLAL group was not associated with a prolonged duration of ICU stay and was associated with a lower 28-day mortality rate after adjusting for possible confounding factors.

Table 4

Association between clinical outcomes and BLAL: univariate and multivariate analyses.

Whole population

	Univariate analysis					Multivariate analysis[*]		
	BLAL group		Control group			[†]		
Outcomes	n	(%)	n	(%)	P	aOR	95% CI	Adjusted P
Whole population	n=440		n=6706					
ICU mortality	86	19.6	1797	26.8	.0007	0.79	(0.64;0.98)	.032
28-day hospital mortality	76	17.3	1665	24.8	.0003	0.79	(0.63;0.99)	.042
ICU readmission within 28 days following first ICU discharge	51	11.6	616	9.2	.093	0.99	(0.72;1.38)	.992

Population with sepsis

	Univariate analysis					Multivariate analysis[*]		
	BLAL group		Control group			[†]		
Outcomes	n	(%)	n	(%)	P	aOR	95% CI	Adjusted P
Population with sepsis	n=133		n=1496					
ICU mortality	44	33.1	520	34.8	.683	0.95	[0.69; 1.31]	.764
28-day mortality	34	25.6	432	28.9	.632	1.04	(0.76;1.43)	.799
ICU readmission	28	21.1	264	17.6	.326	1.19	(0.74; 1.92)	.482

95% CI = 95% confidence interval, % = percentage, aOR = adjusted odds ratio, BLAL = beta-lactam allergy labeling, IQR: interquartile range, ICU: intensive care unit, N: effective.

[*] Variables included in the multivariate analyses were selected based on a threshold P value (≤.2) in the univariate analysis: age, gender, SAPS II, sepsis, multiple trauma, type of admission to the ICU, Charlson comorbidity score, acute renal failure, invasive mechanical ventilation, and vasopressor use.

[†] The aOR examines the association between the BLAL (reference: the absence of labeling) and each outcome.

After analyzing a specific subgroup of septic patients, we found that the β-lactam allergy label was associated with significant differences in the distribution of antibiotics used but was not associated with outcome changes.

Our prevalence is lower than those reported in previous studies. Large variations have been reported, including rates reaching 15.6% observed in a US study highlighting large variabilities between healthcare providers.[12] However, our results are in line with those reported in a European study[6] in which the prevalence was 5.6%. The variations can result from differences in the genetic background, with differences between European and US populations.[13] Of note, the increased rate of females in the BLAL group, confirming a sexual dimorphism in antibiotic allergy, also suggests the effect of the genetic background.[14,15] A BLAL was found in only 11% of electronic medical files. This under-reporting could have participated to the low prevalence rate that we found. It is likely that the systematic registration of this label would increase the number of at-risk patients. However, the BLAL is most of the time identified during a detailed medical history, which is often limited at ICU admission due to coma or sedation. This could explain differences in the prevalence found in conventional wards.

The duration of ICU and hospital stays were little affected by the BLAL. This finding was confirmed in the patients with sepsis, whereas significant differences were noted for the antimicrobial treatments between the BLAL group and the control group. In other studies, the duration of hospital stay was prolonged for patients with this label in their medical file. Charneski et al reported that the presence of an allergy label in the medical file was associated with a longer length of hospital stay and worse clinical outcomes compared with no allergy label in hospitalized patients treated with antimicrobials.[16] However, we conducted the first study focusing specifically on ICU patients, which could explain this divergent result. A low prevalence of patients with BLAL probably contributed to this difference.

Surprisingly, we found lower ICU and 28-day mortality rates in the BLAL group than in the control group after adjusting for covariates. This finding is probably due to the patients without sepsis because this difference was not found in the subgroup of patients with sepsis. As suggested by Leibovici,[17] observational studies that find differences in treated (those with BLAL) and non-treated patients (those without BLAL) may only reflect that treated patients were "better managed" than non-treated patients and received a higher level of care before hospital admission. This difference before admission may affect the outcomes of patients during their hospitalization. The fact that our study was conducted only on ICU patients can also explain the divergent findings from other studies.[7,18] In addition, although the analysis was adjusted, the severity scores of patients with BLAL were lower than those of their controls. This can be explained by the fact that most severely ill patients are comatose or required sedation, precluding the collection of medical history. Regarding antimicrobial treatment, the differences in the distribution of antibiotics may have been associated with differences in outcome. Our data do not make it possible to explore the effects of different antibiotic treatments with accuracy.

However, the difference in patient outcomes was not confirmed in the patients with sepsis. Most patients received β-lactam antibiotics, independent of the labeling, meaning that intensivists did not consider the labeling as a hurdle to administer β-lactams. One can suppose that cephalosporins were preferentially used in the patients with BLAL. Cross sensitivity is below 1% in recent reports.[19,20] In our institution, no graded challenge and specific protocol were performed when a β-lactam was administered for the first time.

In the BLAL group, the prevalence of infections caused by MDR pathogens was significantly higher, suggesting a possible role of antibiotic choice on the selection of pathogens or these patients experiencing an increased exposure. This higher rate, albeit relatively low in absolute number, may have resulted in inadequate empirical antimicrobial therapy and thus worse outcomes. Indeed, antimicrobial stewardship is especially challenging in the presence of MDR pathogens.[21] This is 1 hypothesis to explain why the difference in terms of mortality was not confirmed in the subgroup of patients with sepsis.

Our study was a retrospective analysis of electronic medical files, involving inherent limitations because of this retrospective design. We did not collect information on the variability at the physician level. Although a large number of patients was included, our study was performed in a single institution and should be considered as a single center investigation. Thus, these findings need to be confirmed in a multicenter study. In addition, we do not have details on the type of antibiotics used, making it difficult to determine the number of patients receiving cephalosporins or carbapenems. Our database does not include the patients with allergic reactions, which deserves a future investigation.

5. Conclusions

In conclusion, our retrospective study included a large number of ICU patients and showed that the prevalence of BLAL was around 6%; thus, this information was lacking in most electronic medical files. In the entire cohort, this labeling was not associated with increased ICU duration, but it was protective in terms of ICU and 28-day mortality rates. These findings suggest that a better detection system for β-lactam allergy may lead to improved outcomes.

Author contributions

Conceptualization: Marc Leone, Vanessa Pauly.
Formal analysis: François Antonini, Veronica Orlean, Laurent Boyer.
Methodology: Calypso Mathieu, François Antonini.
Resources: Nadim Cassir.
Validation: Vincent Pradel, Jérémy Bourenne, Salah Boussen, Sami Hraiech, David Lagier, Joana Vitte, Sandrine Wiramus, Laurent Zieleskiewicz, Laurent Papazian, Laurent Boyer.
Writing – original draft: Claire Zunino.

References

[1] Versporten A, Zarb P, Caniaux I, et al. Antimicrobial consumption and resistance in adult hospital inpatients in 53 countries: results of an internet-based global point prevalence survey. Lancet Glob Health 2018;6:619–29.
[2] Devchand M, Kirkpatrick CMJ, Stevenson W, et al. Evaluation of a pharmacist-led penicillin allergy de-labelling ward round: a novel antimicrobial stewardship intervention. J Antimicrob Chemother 2019;74:1725–30.
[3] Moran R, Devchand M, Smibert O, Trubiano JA. Antibiotic allergy labels in hospitalized and critically ill adults: a review of current impacts of inaccurate labelling. Br J Clin Pharmacol 2019;85:492–500.
[4] Blumenthal KG, Peter JG, Trubiano JA, Phillips EJ. Antibiotic allergy. Lancet 2019;393:183–98.

[5] 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. J Antimicrob Chemother 2008;61:436–41.

[6] Van Dijk SM, Gardarsdottir H, Wassenberg MW, et al. The high impact of penicillin allergy registration in hospitalized patients. J Allergy Clin Immunol Pract 2016;4:926–31.

[7] Macy E, Contreras R. Health care use and serious infection prevalence associated with penicillin "allergy" in hospitalized patients: a cohort study. J Allergy Clin Immunol 2014;133:790–6.

[8] Leone M, Constantin JM, Dahyot-Fizelier C, et al. French intensive care unit organisation. Anaesth Crit Care Pain Med 2018;37:625–7.

[9] Toulouse E, Masseguin C, Lafont B, et al. French legal approach to clinical research. Anaesth Crit Care Pain Med 2018;37:607–14.

[10] Rey G, Jougla E, Fouillet A, Hémon D. Ecological association between a deprivation index and mortality in France over the period 1997–2001: variations with spatial scale, degree of urbanicity, age, gender and cause of death. BMC Public Health 2009;9:33.

[11] Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Med Care 2005;43:1130–9.

[12] Shah NS, Ridgway JP, Pettit N, Fahrenbach J, Robicsek A. Documenting penicillin allergy: the impact of inconsistency. PLoS One 2016;11:e0150514.

[13] Wong A, Seger DL, Lai KH, Goss FR, Blumenthal KG, Zhou L. Drug hypersensitivity reactions documented in electronic health records within a large health system. J Allergy Clin Immunol Pract 2019;7:1253–60.

[14] Moran RL, Devchand M, Churilov L, Warrillow S, Trubiano JA. The burden of antibiotic allergies in adults in an Australian intensive care unit: the BASIS study. Crit Care Resusc 2019;21:265–73.

[15] Mege JL, Bretelle F, Leone M. Sex and bacterial infectious diseases. New Microbes New Infect 2018;26:100–3.

[16] Charneski L, Deshpande G, Smith SW. Impact of an antimicrobial allergy label in the medical record on clinical outcomes in hospitalized patients. Pharmacotherapy 2011;31:742–7.

[17] Leibovici L. Non-antibiotic treatment for bacterial infections: how to validate chance findings. Clin Microbiol Infect 2009;15:298–301.

[18] Huang KG, Cluzet V, Hamilton K, Fadugba O. The impact of reported beta-lactam allergy in hospitalized patients with hematologic malignancies requiring antibiotics. Clin Infect Dis 2018;67:27–33.

[19] Dickson S, Salazar K. Diagnosis and management of immediate hypersensitivity reactions to cephalosporins. Clin Rev Allergy Immunol 2013;45:131–42.

[20] Solensdy R, Khan DA. Drug allergy: an updated practice parameter. Ann Allergy Asthma Immunol 2010;105:273–8.

[21] Leone M, Roberts JA, Bassetti M, et al. Update in antibiotic therapy in intensive care unit: report from the 2019 Nîmes International Symposium. Anaesth Crit Care Pain Med 2019;38:647–56.