Beta-lactam allergy labeling in intensive care units
An observational, retrospective study

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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 endpoint 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 BLAL group” (control group).

2.4. Data collection

For each patient, we collected sociodemographic characteristics: 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 pathogens, 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 χ² 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 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 (≤.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. 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 undetermined 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 (±16.3) years and 60.3 (±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).
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).
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 Clostridium 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 endpoints (Table 2).

4. Discussion

In our institution, the prevalence of BLAL for ICU patients was around 6%. However, our study showed that labeling regarding beta-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 3

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

| Outcome                  | Population | BLAL group | Control group | Univariate analysis | Multivariate analysis |
|--------------------------|------------|------------|---------------|---------------------|-----------------------|
|                          |            | Beta ± se  | \( P \) value | Beta ± se           | \( P \) value          |
| Length of hospital stay  | Discharged |            |               |                     |                       |
|                          | Median, IQR| 18 [12;30] | 17 [11;31]    | 0.027 ± 0.0442      | 0.541                 |
|                          |            |            |               | −0.0627 ± 0.0391    | 0.109                 |
|                          | Died in the hospital |         |               |                     |                       |
|                          | Median, IQR| 13 [4;27]  | 7 [3;18]      | 0.322 ± 0.0867      | 0.0073                |
|                          |            |            |               | −0.0086 ± 0.104     | 0.934                 |
|                          | Overall events |       |               |                     |                       |
|                          | Median, IQR| 18 [10;29] | 15 [6;28]     | 0.1061 ± 0.046      | 0.021                 |
|                          |            |            |               | −0.0395 ± 0.0418    | 0.344                 |

### Table 4

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

| Whole population | BLAL group | Control group | Univariate analysis | Multivariate analysis |
|------------------|------------|---------------|---------------------|-----------------------|
|                  | n (%)      | n (%)         | \( P \) value        | aOR                   |
| Whole population | n = 440    | n = 6706      |                     |                       |
| ICU mortality    | 86 19.6    | 1797 26.8     | 0.0007              | 0.79 (0.64; 0.98)     |
| 28-day hospital mortality | 76 17.3 | 1665 24.8 | 0.0003 | 0.79 (0.63; 0.99) |
| ICU readmission within 28 days following first ICU discharge | 51 11.6 | 616 9.2 | 0.093 | 0.99 (0.72; 1.38) |

| Population with sepsis | BLAL group | Control group | Univariate analysis | Multivariate analysis |
|------------------------|------------|---------------|---------------------|-----------------------|
|                        | n (%)      | n (%)         | \( P \) value        | aOR                   |
| Population with sepsis | n = 133    | n = 1496      |                     |                       |
| ICU mortality          | 44 33.1    | 520 34.8      | 0.683               | 0.95 (0.60; 1.31)     |
| 28-day mortality       | 34 25.6    | 432 28.9      | 0.632               | 1.04 (0.76; 1.43)     |
| ICU readmission        | 28 21.1    | 264 17.6      | 0.326               | 1.19 (0.74; 1.92)     |

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 clinical outcomes.

| Outcome                  | Population | BLAL group | Control group | Univariate analysis | Multivariate analysis |
|--------------------------|------------|------------|---------------|---------------------|-----------------------|
|                          |            | n (%)      | n (%)         | \( P \) value        | aOR                   |
|                          |            |            |               |                     |                       |
| Whole population         | n = 440    | n = 6706   |                     |                       |
| ICU mortality            | 86 19.6    | 1797 26.8 | 0.0007 | 0.79 (0.64; 0.98) |
| 28-day hospital mortality| 76 17.3    | 1665 24.8 | 0.0003 | 0.79 (0.63; 0.99) |
| ICU readmission within 28 days following first ICU discharge | 51 11.6 | 616 9.2 | 0.093 | 0.99 (0.72; 1.38) |

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[13] 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.[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

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