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**Title:** Spontaneous decolonization during hospitalization in intensive care unit patients colonized by extended-spectrum beta-lactamase-producing *Enterobacterales*

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## **Abstract**

We aimed to analyze how frequently spontaneous decolonization occurred in intensive care unit patients colonized by extended-spectrum beta-lactamase-producing *Enterobacteriales* (ESBL-E), to assess the added value of continuing weekly ESBL-E rectal carriage screening. We included 49,468 weekly rectal screening samples taken from 20,846 patients over 12 years. Among the 4,280 ESBL-E carriers, only 109 patients (2.5%) could be considered decolonized at the end of their hospitalization with at least three consecutive negative samples. Overall, 7,957 samples (16.1%) were requested for patients already identified as ESBL-E carriers. Avoiding unnecessary weekly screening following positive ESBL-E colonization results could decrease nursing and laboratory workloads.

Words = 100

## Introduction

Extended-spectrum beta-lactamase-producing *Enterobacterales* (ESBL-E) have disseminated worldwide, both in the hospital setting and in the community. In intensive care units (ICU), ESBL-E carriage is linked to a constant influx of strains from the community and cross-transmission between critically ill patients. ESBL-E infections are associated with an increase in mortality, length of ICU of stay, and carbapenem use. In critically ill patients, prior identification of colonization by ESBL-E may assist in guiding empirical antimicrobial therapy<sup>1</sup>. Since the gut microbiota is the main reservoir for ESBL-E, guidelines propose systematic screening for ESBL-E rectal carriage in ICU<sup>2</sup>.

Once an ICU patient is identified as an ESBL-E carrier, the added value provided by the continuation of weekly ESBL-E screening is unclear. The median duration of ESBL-E colonization was estimated at one month for international travelers<sup>3</sup> and more than six months for hospitalized patients<sup>4</sup>. There is no clear definition of the threshold number of consecutive negative samples needed to assess eradication of colonization<sup>5</sup>, even if a criterion of at least three negative samples was suggested in European guidelines<sup>2</sup>. We hypothesize that spontaneous ESBL-E decolonization of patients during their hospital stay may be a rare event.

We aimed to analyze how frequently spontaneous decolonization occurred in intensive care unit patients colonized by ESBL-E, to assess the added value of continued weekly ESBL-E rectal carriage screening in these patients.

## Methods

We performed a retrospective study including all ESBL-E rectal carriage screening samples obtained from patients admitted to the surgical and mixed ICUs of Lille university hospital between January 2008 and December 2019. These patients were further followed until March 2020. Patients could be included multiple times if they were discharged from the hospital then readmitted over the 12 years.

Rectal swabs were routinely sampled upon ICU admission, followed by weekly sampling, using eSwabs® (Copan Diagnostics, Murrieta, CA) or Transwabs® (Medical Wire Ltd, Corsham, UK). Patients continued to be tested weekly, regardless of previous rectal swabbing results. Duplicate samples in a given week were excluded (not counting the sample taken at admission). Weekly sampling stopped after the patients left the ICU. Swabs were cultured on CHROMID® ESBL selective chromogenic media (BioMérieux, Marcy l'Etoile, France). Bacterial strains were identified using VITEK-2 colorimetric cards (BioMérieux, Marcy l'Etoile, France) from 2008 to 2009, then using MALDI-TOF mass spectrometry (Bruker Daltonics, Wissembourg, France) from 2009 to 2020. *Klebsiella aerogenes* was considered as included in the genus *Enterobacter*. ESBL production was confirmed using either the MAST D68C test (Mast Group, Amiens, France) or inhibition with clavulanic acid<sup>6</sup>.

If ESBL-E carriage was identified, additional infection control precautions (contact precautions) were used: individual room with a specific signboard on the door, protective clothing (plastic aprons or gowns), and dedicated medical equipment. Gloves

were mandatory only in case of contact with blood or body fluids, according to French recommendations.

Data analysis was performed with R software version 3.6.3. (R Foundation for Statistical Computing, Vienna, Austria). Qualitative variables were presented as percentages and continuous variables as medians with interquartile ranges, or as means with standard deviations. In patients previously colonized by ESBL-E, decolonization was assessed for each subsequent sample, using the criteria of at least either one negative sample, two consecutive negative samples, or three consecutive negative samples. Patients could be counted as decolonized according to each criterion. Patients assessed as decolonized at a particular sampling rank were not removed from the analysis if they had further samples.

## Results

We included 49,468 samples over 12 years obtained from 20,846 patients, of which 18,901 patients were unique and 1,945 corresponded to multiple hospitalizations. Of the total patients, 3,787 (18.2%) were admitted to a surgical ICU and 17,059 (81.8%) to a mixed ICU. Overall, 12,836 patients (61.6%) were male, the median age was 60 years (IQR 46 – 70), and the median length of stay in hospital was 16 days (IQR 7 – 32). The median number of samples per patient was 2 (IQR 1 – 3), with a mean at 2.4 samples (SD 2.6). The ratio of the number of samples per patient divided by the length of hospitalization (in weeks) had a median of 0.9 (IQR 0.5 – 1.4) and a mean of 1.3 (SD 1.5).

Overall, ESBL-E carriage was identified for 4,280 patients (20.5%). Pre-existing ESBL-E colonization on admission was found in 2,130 patients (49.8%). An additional 2,150 patients (50.2%) were identified as ESBL-E carriers during their hospitalization after the initial negative screening. The repartition of the ESBL-E genera is reported in Table 1. Colonization with multiple ESBL-E genera was identified for 655 patients (15.3%).

For the 4,280 patients colonized by ESBL-E during their hospitalization, spontaneous decolonization during hospitalization was assessed after the first positive sample (Figure 1). Using a criterion of at least one negative sample to define decolonization, between 22.9% and 27.0% of the patients could be considered decolonized at their second to tenth samples. If two consecutive negative samples were required to define decolonization, between 12.5% and 16.6% patients could be

considered decolonized at their third to tenth sample. Using a criterion of three consecutive negative samples, between 9.8% and 11.8% of the patients were considered decolonized at their fourth to tenth sample.

Details of decolonization at the end of the ICU hospitalization, depending on the ESBL-E genus and the minimal number of consecutive negative samples, are presented in Table 1. Among the 4,280 ESBL-E carriers, only 109 patients (2.5%) could be considered decolonized using a criterion of at least three consecutive negative samples at the end of their hospitalization. Of note, 167 ESBL-E carriers (3.9%) reached the threshold of three consecutive negative samples at least once during their hospitalization, but 58 were later recolonized by ESBL-E. Using a criterion of three consecutive negative rectal swabs, the median time to decolonization after the first positive sample was 28 days (IQR 21 – 42), with a mean of 36 days (SD 25).

This low percentage of spontaneous decolonization (defined as three consecutive negative samples) could be explained by two factors: (i) only 936 patients out of the 4,280 ESBL-E carriers (21.9%) had at least three samples taken after their first positive sample (most were discharged from the ICU before), (ii) for the patients who had at least three samples taken after their first positive sample, only 11.6% of them were defined as decolonized at the end of their hospitalization.

During the 12 years, 7,957 samples (16.1% of the total number of samples) were requested for patients already identified as ESBL-E carriers.

## Discussion

In this study, decolonization during hospitalization was a rare event. Only 2.5% of the ICU patients identified as ESBL-E carriers could be considered decolonized with at least three consecutive negative samples before discharge from the hospital. Thus, the added value provided by continuing to screen patients identified as ESBL-E carriers was low.

In a meta-analysis, Bar-Yoseph *et al.* found that carriage rates of ESBL-E and carbapenemase-producing *Enterobacterales* remained high in the healthcare setting, with 76.7% of carriers still colonized at one month, 75.2% at three months, 55.3% at six months and 35.2% at 12 months of follow-up<sup>5</sup>. However, there was substantial heterogeneity in the included studies because the definition of decolonization was not standardized. Indeed, while most studies used a threshold of one negative culture to define decolonization, some used a threshold of two or three consecutive negative samples not followed by any positive results. Bar-Yoseph *et al.* concluded that more than one negative sample should be obtained to define decolonization<sup>5</sup>. European guidelines suggest using a criterion of at least three negative samples to discontinue contact precautions for ESBL-E carriers<sup>2</sup>.

From both infection control and antimicrobial stewardship standpoints, the usefulness of systematic screening for intestinal carriage of ESBL-E is currently challenged in the literature<sup>7</sup>. One of the potential benefits of identifying ESBL-E carriers is to limit their spread by implementing additional hygiene precautions. However, contact precautions recently showed no benefits compared to standard precautions for controlling the spread of ESBL-E<sup>8</sup>. In critically ill patients, identification of colonization by

ESBL-E at ICU admission may help to guide empirical antimicrobial therapy. Carbapenems should be considered in the case of a known history of colonization by ESBL-E in the last three months<sup>9</sup>. In a recent meta-analysis, the sensitivity and specificity of prior colonization to predict ESBL-E infection during ICU hospitalization were 95.1% and 89.2%, respectively<sup>1</sup>. The absence of digestive tract colonization by ESBL-E had a negative predictive value between 93.4% and 99.2% for ESBL-E presence in respiratory samples, depending on the length of stay<sup>10</sup>. Once a patient is identified as an ESBL-E carrier, however, the impact of the change in ESBL-E carriage status from positive to negative on antimicrobial prescribing remains unclear.

Our study has several limitations. First, we did not report data, inconstantly available in our hospital information system, concerning antimicrobial therapy use and presence of invasive procedures (intravenous central line), which can impact the acquisition and duration of colonization by multi-drug resistant bacteria. Secondly, rectal screening swabs were obtained only when the patient was in the ICU. Samples obtained during hospital stay in other wards were not taken into account because there is no systematic weekly screening policy for medical or surgical wards in our hospital. Moreover, missing samples did occur since this study was retrospective. However, the median number of samples per patient divided by the length of hospitalization was high (0.9 samples per patient per week). Last, this was a monocentric study in a university hospital following French infection control guidelines, affecting the potential generalizability of our results.

Systematic screening procedures represent a high workload for microbiology laboratories. Our study shows that spontaneous decolonization during hospitalization is

a rare event (2.5%), and that 16.1% of the samples were requested for patients already identified as ESBL-E carriers, which may have been unnecessary. Avoiding unnecessary weekly screening of ICU patients following positive ESBL-E rectal screening results could decrease nursing and laboratory workloads.

**Conflict of interest:** None.

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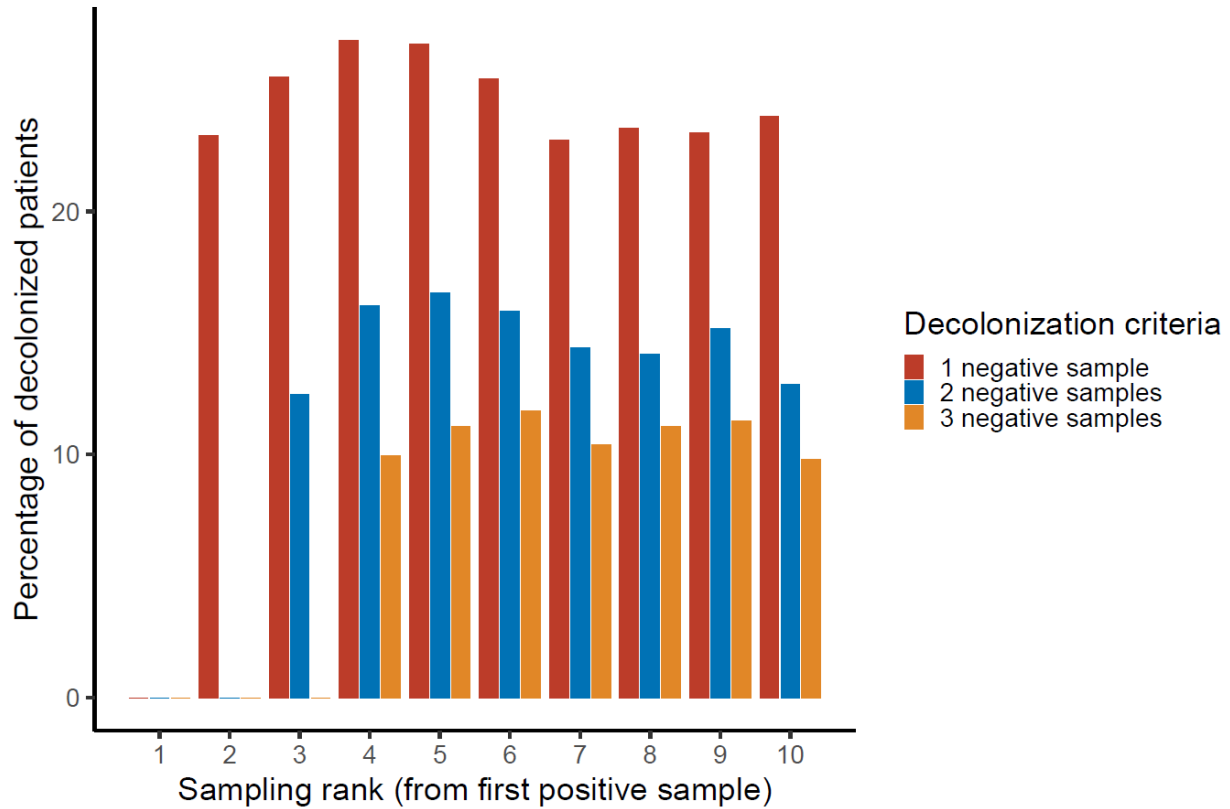
**Words:** 1625

### **Figure Legends**

**Figure 1.** Dynamics of decolonization during hospitalization, depending on the number of consecutive negative samples.

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**Figure 1.** Dynamics of decolonization during hospitalization, depending on the number of consecutive negative samples.

The origin of the horizontal (x) axis is the first positive sample, then the percentage of the sampled patients who were defined as decolonized (based on each criterion) was plotted for each subsequent weekly sample. Not all the patients were sampled ten times after identification of ESBL-E carriage during their hospital stay; n (at each sampling rank) was 4280 (1), 2503 (2), 1450 (3), 936 (4), 655 (5), 491 (6), 375 (7), 269 (8), 211 (9), and 163 patients (10<sup>th</sup> sample).

**Table 1.** ESBL-E decolonization at the end of hospitalization according to different criteria for the minimum number of consecutive negative weekly screening samples.

ESBL-E genus	Colonized patients (n, %)	Decolonization (n, %)		
		Minimum number of consecutive negative samples		
		≥ 1	≥ 2	≥ 3
Any ESBL-E	4280 (100%)	648 (15.1%)	229 (5.4%)	109 (2.5%)
<i>Klebsiella</i>	2364 (55.2%)	305 (12.9%)	104 (4.4%)	48 (2.0%)
<i>Escherichia</i>	1512 (35.3%)	242 (16.0%)	83 (5.5%)	45 (3.0%)
<i>Enterobacter</i>	863 (20.2%)	148 (17.1%)	55 (6.4%)	16 (1.9%)
<i>Citrobacter</i>	201 (4.7%)	33 (16.4%)	13 (6.5%)	8 (4.0%)
Other ESBL-E	58 (1.4%)	7 (12.1%)	2 (3.4%)	1 (1.7%)

Note: *Klebsiella aerogenes* was included in the genus *Enterobacter*