

Effects of Discontinuing Contact Precaution on Control of Extended-Spectrum β -lactamase-producing Enterobacteriaceae Nosocomial Acquisition: An Interrupted Time Series Analysis

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Abstract

Background:

Interest of contact precautions (CP) to prevent cross-transmission in addition to standard precautions (SP) is actually debated in the literature for some microorganisms, like extended-spectrum β -lactamase-producing *Enterobacteriaceae* (ESBLE). We took advantage of the decision to stop CP for ESBLE in our hospital to study in real life if this discontinuing has an impact on the ESBLE acquisition rate.

Methods:

An interrupted time series (ITS) was performed in 3 wards and the week was used as the temporal unit. The ESBLE acquisition and importation incidence density (ID) and potential risks factors (colonization and selective pressure, Alcohol-Based hand rub solution consumption rates, demographic patients data) were collected between two periods: the pre-intervention (July 2018 to June 2019) when patients infected or colonized by ESBLE were cared with PC and SP and the post-intervention (September 2019 to March 2020) when patients were cared with SP only.

Results:

ESBLE acquisition ID were of 1.32 ± 1.36 and 1.17 ± 1.25 cases per 1000 patient-days for the pre- and post-intervention period respectively with no significant change in slope ($p = 0.15$). The only confounding variable significant ($p = 0.04$) in ITS was the antibiotics consumption, with a positive increasing trend.

Conclusion:

This study showed that the SP alone in order to control the ESBLE nosocomial did not lead to increasing the ESBLE nosocomial cross-transmission.

Introduction

Extended-spectrum beta-lactamase-producing *Enterobacteriaceae* (ESBLE) infections have been steadily rising since the 2000s. These infections represent a real issue in the healthcare settings, since they increase healthcare costs, length of stay (LOS) and are a cause of mortality worldwide (1). In 2017, the incidence density (ID) of ESBLE in French hospitals reached 0.62 per 1 000 patient days, while the ID of methicillin-resistant *Staphylococcus aureus* (MRSA) continued to decreased to 0.23 per 1 000 patients days (2).

International and national guidelines to prevent the spread of multidrug-resistant organisms (MDRO) within hospitals include two ways : limiting the emergence of resistance through the antimicrobial

stewardship (3) and preventing the transmission of a resistant species between patients through the respect of barrier measures. These consist of standard precautions (SP) and transmission-based precautions like contact precautions (CP) in order to reduce microorganisms' cross-transmission. CP bundles usually involve the use of a single-bed room, patient-dedicated equipment, carriage signalization and to wear an apron for healthcare workers (HCWs) during direct contact with colonized or infected patients. (4) CP has been used for years and still allow today the control of microorganisms' cross-transmission such as *Clostridium difficile* or extremely drug resistant bacteria (5).

ESBLE are spreading not only in the hospital but also in the community. In France, the incidence density of *Escherichia Coli* BLSE samples from all sites increased from 0.2 per 1000 patient days in 2001 to 3.9 per 1000 patient days in 2017 (6). The CP contribution compared to SP and their global impact are debated. Indeed, many studies suggest that CP are related to an increased rate of anxiety and depression patient symptoms, decreasing patient satisfaction with care (7) and an increased rate of adverse events associated with CP (8), notably due to a lack of patient HCWs contact. In addition to the substantial burdens on hospital resources, when CP are required for HCWS teams (9).

Lastly, *Enterobacteriaceae* are present in the intestinal human tract and are part of the commensal gut flora. The two mains preventing measures against this type of microorganism cross transmission are management of excreta and hand hygiene (HH), both part of SP (10). In other words, compliance and strict application of SP may be the strategy to prevent ESBLE transmission.

In June 2019, the decision to discontinue CP for EBLSE infected or colonized patients (except for the respiratory site where additional "droplet" precautions are still maintained) was taken by our infection prevention and control team. We took advantage of the practices change and the opportunity to place ourselves in real conditions to set up our study.

The aim of this study was to determine if the SP alone by discontinuing CP does not increase the acquired ESBLE density incidence, our main outcome.

Material And Method

Study design

The present study was conducted from July 2018 to March 2020 at a 1667-bed teaching hospital in France. The period study was divided into three phases: the pre-intervention period defined as July 2018 through June 2019 (52 weeks), the intervention period extended from July to September 2019 (8 weeks) and the post-intervention period defined as September 2019 through March 2020 (27 weeks). The week was defined as the temporal unit.

During the pre-intervention phase, the patients colonized or infected with EBLSE were assigned to receive care under CP in addition of SP. The intervention phase consisted to inform HCWs about the ESBLEs, the new recommendations about discontinuing PC for the ESBLE colonized or infected patients and the SP's

awareness. This information was performed by the Infection prevention and control team (IPCT) either by an intern or a nurse. During the post-intervention phase, strict application of SP was applied for all patients expected for patients who CP was indicated according to the hospital's infection control and isolation policies.

Population

Systematic fecal screening for ESBLE colonization is performed at the stage of admission and weekly for patients hospitalized in the adult Intensive Care Units (ICU) and hematology ward. The main interest is to guide the empiric treatment of acquired infections because of the suspected link between colonization and infection (11, 12).

All patients admitted for more than 48 hours in the ICU and hematology ward during the study period were included. A patient was included for each of his hospital stay.

Data collection

Patient, microbiological, antibiotic consumption and hand hygiene compliance data were collected:

- Patient demographic and risk factors information from the computerized records system. Clinical data were collected retrospectively: gender, age, admission Acute Physiology and Chronic Health Evaluation (APACHE), the LOS.
- Microbiological data:
- History of ESBLE carriage,
- Results of ESBLE research at an early stage of admission and on a weekly basis. In case of positive culture, we were studying the type of organism, site of infection or colonization, documented history of ESBL-positive organisms,
- Completeness of swabs: number of rectal swabs performed divided by the number of expected swabs,
- The incidence density (ID) rate, was calculated, where the incidence represents the number of patients infected by an ESBLE (infection or colonization) divided by the cumulative duration of stay of all potentially exposed patients.

A positive rectal swab within the 48 hours following admission the ESBLE case was considered as an imported carriage; whereas a positive surveillance swab for patients with a negative admission sample was considered as a nosocomial or acquired acquisition.

Then, the acquisition ID, our main outcome variable, was reported to the number of acquisitions per 1,000 patient days a week. We did the same for the importation ID.

- "Colonization pressure" i.e., the number of patients colonized or infected during the week divided by the number of patients treated during the week. Colonization pressure is indeed a risk factor for cross-transmission acquisition of ESBLE if it is higher than or equal to 10%. (15, 16)

- Hand hygiene compliance: as a surrogate, we used the French index of Alcohol-Based Hand Rub (ABHR) solution consumption, requested by the French Ministry of Health (13) and defined by the French National Authority for Health. This indicator is the ratio between the ward consumption (in liters) provided by the pharmacy database divided by hypothetical consumption, defined by opportunities of hand disinfection during an patient day depending on the ward specialty (For example 43 minimum opportunities for hand rubbing per patient per day in ICUs) (14). We reported the index per month.
- Antibiotic consumption: we calculated monthly the antibiotic exposure in Defined Daily Dose (DDD) from the pharmacy database and the denominator: exposed population. The DDD are expressed per 1,000 patient days.

Data Analysis

The univariate analysis consisted of a descriptive analysis: continuous quantitative variables were presented by means and standard deviations and qualitative variables were exposed by absolute and relative frequencies in order to study the distributions of our data. The quantitative variables were compared with Student tests and the qualitative variables were compared with Chi2 tests.

Weekly trends in ESBLE infection/colonization's incidence density were plotted to highlight and characterize patterns of change.

We used a single interrupted time series (ITS) analysis (SITSA), to assess the changes in ESBLE incidence density before and after the CP's discontinuing. The ITS allows a quasi-experimental approach for evaluating longitudinal intervention's effects and the segmented regression is particularly useful for assessing the impact of policy or some other healthcare initiative. Residuals were tested for autocorrelation by Durbin-Watson test. The SITSA model follows the regression:

$$y = \beta_0 + \beta_1 T + \beta_2 X + \beta_3 T_x$$

Where y = outcome variable, β_0 the baseline at $T = 0$, β_1 represents the underlying pre-intervention trend, β_2 the level change following the intervention, β_3 indicates the slope change following the intervention. $\beta_1 + \beta_3$ represents the post-intervention trend.

All analyses were performed using R Studio® (RStudio Inc., Boston, MA, USA) version 1.1.456 and SAS software (version 9.2, SAS Institute Inc., NC, USA). The statistical significance was fixed at $p < 0.05$.

Results

Patients, Hand Hygiene and Exposure to Antibiotics

The patients' characteristics are described in Table 1 for the two periods. 2051 patients had a LOS of more than 2 days (1412 patients for the pre-intervention phase and 640 for the post-intervention phase)

and were included. Mean age was significantly higher in post-intervention (+ 1.8years, p = 0.02).

Table 1
Baseline characteristics in the pre- and post- intervention period

Patient characteristics	Pre intervention	Post intervention	p value
	Contact precaution (n = 1412)	Standard precaution (n = 640)	
Age (years) (mean (± SD*))	57.6 (16.8)	59.4 (15.7)	0.02
Gender, Women (number (%))	583 (41.2%)	249 (38.9%)	0.42
APACHE II, only for ICU patients	55.6 (20.0)	58.8 (20.6)	0.07
Length of stay (days) (mean (± SD*))	12.1 (12.5)	12.5 (12.4)	0.55
Antibiotic consumption** (systematic ATC J01) (mean (± SD))	1479 (136)	1474 (269)	0.87
Index of ABHR solution consumption (%)	111.1	111.8	0.94
*SD: Standard Deviation, NA: not available; **DDD per 1000 patient days			

The monthly ICSHA was constantly higher than 80%. The ICSHA and total antibiotic consumption showed no significant change between intervention periods (p = 0.87 and p = 0.94 respectively).

Microbiological Data

The microbiological data are presented in Table 2. From July 2018 to March 2020, a total of 229 ESBLE positive cultures were documented in the three wards. Rectal swabs were the most positive samples collected (87.8%). Our main outcome, the mean of ESBLE acquisition ID was 1.32 cases per 1000 patient days (± 1.36) during the pre-intervention period versus 1.17 (± 1.25) during the post-intervention period. Concerning the ESBLE importation, the mean of ESBLE importation ID was 1.40 (± 1.37) in pre-intervention and 1.77 (± 1.45) in post-intervention. We observed a significant increase of first screening (from 37.6–49.3%, p < 0.001) and completeness of swabs (from 49.2–56.5%, p < 0.001). The colonization pressure was higher (13.9% versus 6.3%) during the post-intervention phase. *Escherichia coli* was the most common ESBL-producing pathogen detected in patients' samples (39.7%), with no significant change between the two periods. Followed by *Enterobacter cloacae* (26.2%) significantly less found (p = 0.01) in the post intervention period and *Klebsiella pneumoniae* (20.1%). No statistically significant change was observed regarding to the clinical site between the two phases.

Table 2
Microbiological data samples in the pre- and post-intervention periods

	Pre intervention	Post intervention	p value
	Contact precaution	Standard precaution	
Microbiological data			
Number of screening	4942	3901	NA
Positive culture	125	104	NA
History of ESBL carriage, number	94	62	NA
First screening (ESBL search < 48 hours after admission), %	37.6 (1026/2727)	49.3 (664/1346)	< 0.001
Completeness of swabs, %	49.2 (4942/10035)	56.5 (3901/6900)	< 0.001
Colonization pressure, %	6.3	13.9	< 0.001
ESBL by species (%)			0.03
<i>Escherichia Coli</i>	36.0 (n = 45)	44.2 (n = 46)	0.25
<i>Enterobacter cloacae</i>	33.6 (n = 42)	17.3 (n = 18)	0.01
<i>Klebsiella pneumoniae</i>	16.0 (n = 20)	25 (n = 26)	0.13
Other ESBL producers	14.4 (n = 18)	13.4 (n = 14)	0.99
Clinical site (%)			0.13
Stool	83.2 (n = 104)	93.2 (n = 97)	NA
Urine	8.0 (n = 10)	3.8 (n = 4)	NA
Blood culture	1.6 (n = 2)	1.0 (n = 1)	NA
Others	7.2 (n = 9)	1.9 (n = 2)	NA
NA: not available			

Final Model

Series characteristics and trends are presented in Table 3 and represented in Fig. 1. The Durbin-Watson statistic confirmed no autocorrelation (Durbin Watson $1.98 < D < 2.4$) for the models. The SITSA showed no significant change in slope or trend for our main variable, ESBL acquisition ID ($p = .15$). We integrated

the independent variables, which might explain the variations of the acquisition ID, into a SITSA. According to the estimated coefficient reported the post-intervention colonization pressure, acquisition and importation density incidence, and the HH compliance rates (ICSHA) increased, but no association with significant changes. The only confounding variable with a significant change was the antibiotic consumption, for which slope and trend increased during the post-intervention period ($p = 0.04$).

Table 3
Segmented interrupted regression analysis parameters

	Regression Intercept (p-value)	Pre-intervention trend (p-value)	Post-intervention trend (p-value)	Level change after the intervention (p-value)	Change in slope after the intervention (p-value)
ESBLE acquisition incidence density *	1.854 (< 0.001)	- 0.019 (0.15)	0.023(0.41)	- 0.018 (0.97)	0.043 (0.15)
ESBLE importation incidence density *	1.440 (< 0.001)	- 0.002 (0.91)	0.033 (0.25)	- 0.012 (0.86)	0.035 (0.25)
Colonization pressure	0.077 (< 0.001)	- 0.001 (0.17)	0.023 (0.19)	0.057 (0.12)	0.003 (0.12)
ICSHA**	114.54 (< 0.001)	-0.519 (0.23)	2.545 (0.11)	- 9.267 (0.22)	3.064 (0.07)
Total antibiotics use	1386.58 (< 0.001)	15.46 (0.34)	17.40 (0.04)	-450.97 (0.04)	64.16 (0.04)

Discussion

We observed no significant increase or decrease of acquired ESBL-producing bacteria after the intervention, neither did Thompson & al (17) when similar interventions were performed. Numerous studies have been reported that nowadays the transmission are predominant in the community (18, 19). Acquisition of ESBLE seems to be much more common in the community than in healthcare setting. This statement was verified in our study where the incidence of imported ESBL-producing bacteria is superior to acquired one.

The potential population confounders: the APACHE II, gender and LOS were comparable between the two periods. The patients were significantly older in the post-intervention period, but studies who aimed to investigate the risk factors associated with acquisition of ESBL-producing bacteria did not report the age as one. (21, 22) The fact that our study was conducted not only in ICUs (ICUs LOS are 8 days on average) can explained that the LOS observed (12 days throughout both periods) is slightly higher than in others (22). Taking account that the LOS could increase the risk to acquired MDRO (23), our acquisition ID was still comparable to previous findings (24). The ABHR consumption rates were unchanged between the two periods, always above 80% and consequently showed the adherence in hand hygiene. Finally, the application of SP was also observed through routine audits carried out in wards.

During the post-intervention phase, the colonization pressure defined by Torres-Gonzales & al. (16) as a risk factor for MDRO acquisition, was higher, which involve that the cross-infection's risk for a no colonized patient was majored. Alves et al. observed that the LOS and the colonization pressure were positively correlated, which seems to apply in our study.(23) To our knowledge, the present study is one of the first to consider this variable in order to assess its impact in the ESBLE acquisition. The completeness and first screening were significantly better for the CP period, which allowed saying on one hand that the HCWs screenings observance was better and provided a more accurate view of EBLSE colonized patients. On the other hand, we cannot exclude that during the pre-intervention period, HCWs chose to screen only the patients they considered more prone to ESBLE's infections.

Lastly, the antibiotics consumption trend increased significantly during the SP period according to the SITSA. Several findings identified this factor as a risk for ESBLE acquisition and selection, like Graffunder & al. (20) who documented that in addition of the third-generation cephalosporins, others antibiotics (fluoroquinolones for example) provide selective pressures in maintaining ESBL organisms because of the multiple resistance genes. Moreover, our antibiotic consumption was high comparable with the consumption reported in the Meyer study in ICU (25) and the Tan study in two hematology wards before their intervention on the antibiotics' consumption. (26) This increase could have influenced our ESBLE acquisition ID and could explain the higher trend (not significant) in post-intervention period. This increase might be explained too by the increase of ESBLE ID trend (not significant). Analysis by antibiotics' class could be carried out to confirm our hypothesis.

One of our study's strengths is the approach chosen: the SITSA. This analysis permitted to establish a time dependent relationship and allows forecasting future trends. This method has already been used in others findings (17, 24) but not yet using weeks as temporal unit. For our objective, using a weekly data is a strength since the majority of our samples were rectal; and they were supposed to be done on a weekly basis. However, this weekly collection has been also a weakness with regard to missing data when rectal swabs were not performed.

Our study includes some limitations; screenings at admission were not made in a systematic but partial way (37.6% and 49.3% respectively for pre and post intervention period). The realization of these samplings depends on the day of admission and that could explain this weakness. (For instance: most of the time the samplings are scheduled on Monday, and if a patient is admitted on Tuesday, the rectal screening will not be taken until six days later). However, some studies did not take into account bacterial carriage at admission thus increasing the possibility of mistakenly identifying community-associated colonization as healthcare-associated after several days of hospitalization (17, 23). Moreover, we can point out that since the intervention, the HCWs are more observant with regard to rectal screening: completeness of swabs and screenings at admission have increased significantly. Several potential reasons could explain this increase: just the intervention's consequence but also a new way for stool sample collection at the same time was set up in the hospital and had allowed an easier way to collect samples for the HCWs and to process it for the laboratory. Finally, several studies have questioned the rectal screening's relevance in non-epidemic situations which is in line with our study and the wide

dissemination in the community.(27) The systematic ESBLE screening could not be adequate anymore to guide contact precautions since the HCWs have just to apply the SP.

Some data risk factors of ESBLE acquisition had not been collected such as the presence of invasive medical devices (central venous or urinary catheters, invasive ventilation...) during the hospitalization and their uses' duration to determine whether there were differences in the two periods based on this factor. Boyer & al (28) reported an increasing in the uses of medical devices particularly central venous catheters and urinary catheters over their seven years study period but did not speak about the impact of this increase in ESBLE acquisition.

Our post-intervention period's points represent the half of the pre-intervention period's points; because of feasibility issues, we could not continue the data collection due to the COVID-19 epidemic, which would skew the results. According to Zhang & al. (29) the estimated power for our model with single parameter assuming effect size = 1, a total sample size of 72 points, and an autocorrelation between - 0.2 and 0.2 is between 0.89 and 1. Our model with more than 80% of power was able to detect the effects we were looking for. Furthermore, the time series method is the most robust modelling technique (30) for evaluating longitudinal intervention's effect in situations where randomization is not feasible. At the end of the epidemic episode, data collection will be able to resume.

Finally, molecular typing was not performed, and this method could have confirmed the patient-to-patient transmission by identifying the microorganism's genetic.

Conclusion

Discontinuing contact precaution for patients colonized or infected by ESBLE did not result in a negative outcome; our main variable, the acquisition ID is upwards but not significantly. Our study, confirmed that nowadays the ESBLE are spreading not only in the hospital but also in the community, with an importation ID higher than the acquisition ID. One of the driving factors in order to control the ESBLE nosocomial acquisition could be to improve the use of antibiotics with the intention of decreasing the selective pressure. Monitoring over a longer term is expected.

Abbreviations

ABHR: Alcohol-based hand rub

APACHE: Acute physiology and chronic health evaluation

CP: Contact precaution

DDD: Defined daily dose

ESBLE: Extended-spectrum β -lactamase-producing *Enterobacteriaceae*

HCWs: Healthcare workers

HH: Hand hygiene

ICU: Intensive cares unit

ID: Incidence density

IPCT: Infection prevention and control team

ITS: Interrupted time series

LOS: Length of stay

MDRO: Multidrug-resistant organisms

MRSA: Methicillin-resistant *Staphylococcus aureus*

SITSA: Single interrupted time series analysis

SP: Standard precaution

Declarations

Ethics approval and consent to participate:

not applicable

Consent for publication:

not applicable

Availability of data and materials:

All data generated or analyzed during this study are included in this published.

Competing interests:

The authors declare that they have no competing interests.

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Authors' contributions:

Conceptualization, MR, LR AF; Methodology, MR, AF; Formal Analysis, MR; Investigation, MR Data Curation, MR; Writing—Original Draft Preparation, MR; Writing—Review and Editing, JL, LR, AF, BL, CJ; Visualization, MR; Supervision, AF; Project Administration, AF.

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Figures

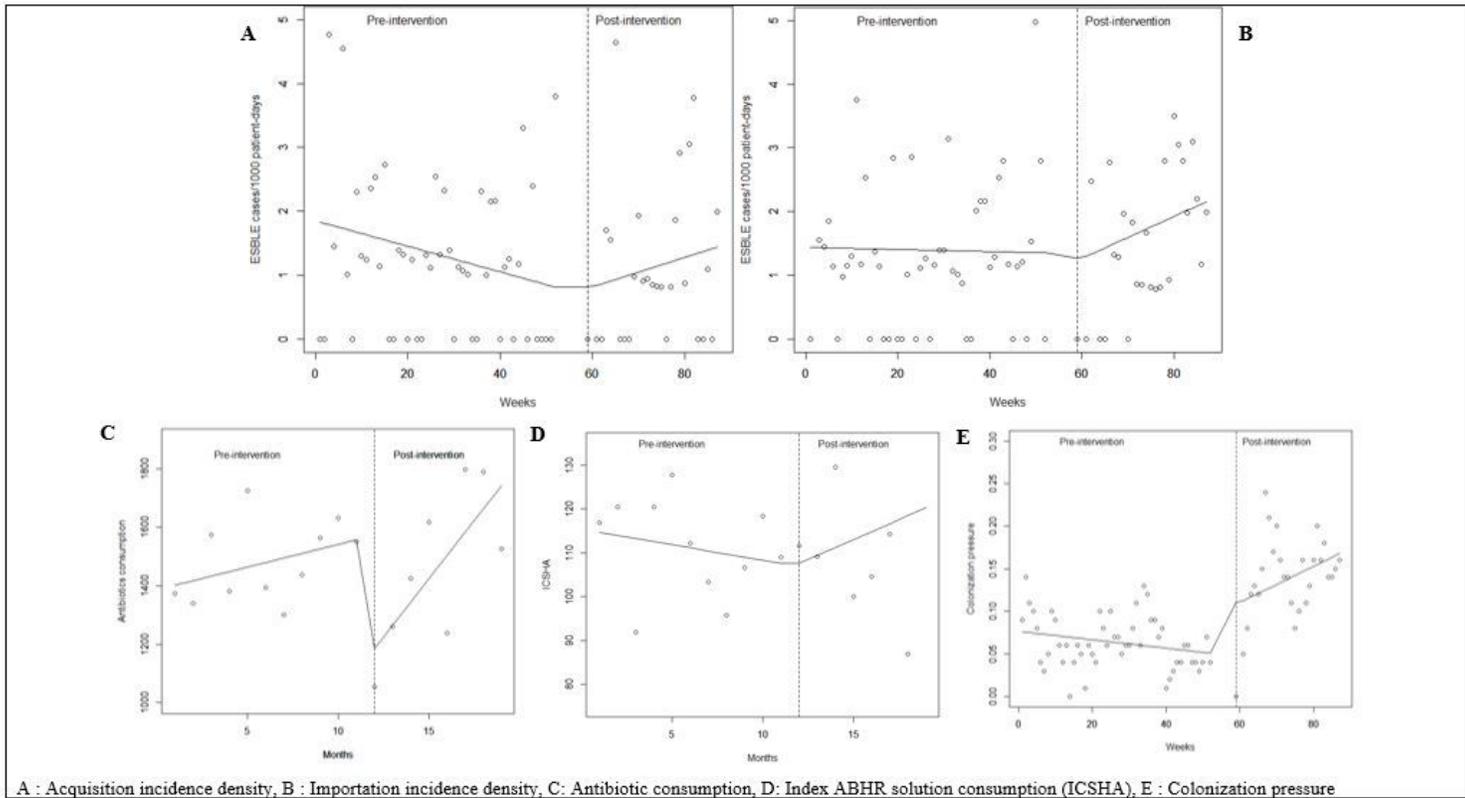


Figure 1

Changes in variables before and after the intervention