



# Improved quality of care for patients infected or colonised with ESBL-producing Enterobacteriaceae in a French teaching hospital: impact of an interventional prospective study and development of specific tools

Véronique Mondain<sup>1</sup> · Florence Lieutier<sup>2</sup> · Céline Pulcini<sup>1</sup> · Nicolas Degand<sup>3</sup> · Luce Landraud<sup>3</sup> · Raymond Ruimy<sup>3</sup> · Thierry Fosse<sup>4</sup> · Pierre Marie Roger<sup>1</sup>

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## Abstract

The increasing incidence of ESBL-producing *Enterobacteriaceae* (ESBL-E) in France prompted the publication of national recommendations in 2010. Based on these, we developed a toolkit and a warning system to optimise management of ESBL-E infected or colonised patients in both community and hospital settings. The impact of this initiative on quality of care was assessed in a teaching hospital. The ESBL toolkit was developed in 2011 during multidisciplinary meetings involving a regional network of hospital, private clinic and laboratory staff in Southeastern France. It includes antibiotic treatment protocols, a check list, mail templates and a patient information sheet focusing on infection control. Upon identification of ESBL-E, the warning system involves alerting the attending physician and the infectious disease (ID) advisor, with immediate, advice-based implementation of the toolkit. The procedure and toolkit were tested in our teaching hospital. Patient management was compared before and after implementation of the toolkit over two 3-month periods (July–October 2010 and 2012). Implementation of the ESBL-E warning system and ESBL-E toolkit was tested for 87 patients in 2010 and 92 patients in 2012, resulting in improved patient management: expert advice sought and followed (16 vs 97%), information provided to the patient's general practitioner (18 vs 63%) and coding of the condition in the patient's medical file (17 vs 59%), respectively. Our multidisciplinary strategy improved quality of care for in-patients infected or colonised with ESBL-E, increasing compliance with national recommendations.

## Introduction

Extended spectrum beta-lactamase-producing Enterobacteriaceae (ESBL-E) are being isolated with increasing frequency worldwide, both as colonisers and as pathogens, and treatment options are limited. Their presence in the hospital setting increases the care burden and costs related to patient isolation and treatment. Optimal patient management strategies require

multidisciplinary involvement [1]. In view of the recent and alarming increase in rates of ESBL-E isolates in France [2], recommendations for the management of colonisation and infection due to ESBL-E were published in 2010 (<http://www.hcsp.fr/explore.cgi/avisrapportsdomaine?clefr=162>), stressing the importance of seeking advice from infectious disease and infection control specialists to manage patients appropriately, as well as informing the patient and his/her attending general practitioner (GP).

Applying these recommendations is difficult, because (1) these infections or colonisations are scattered among the patient population as they may occur in the community and, when in the hospital setting, usually concern a population which up to now has seldom been affected by antimicrobial resistance, namely in urologic, geriatric or gynaecological practice [3]; (2) these Enterobacteriaceae are easily transmitted as they are harboured within the gut reservoir, persisting for extended periods [3, 4]; and, finally, (3) physicians are not

✉ Véronique Mondain  
mondain.v@chu-nice.fr

<sup>1</sup> Infectiologie, Centre Hospitalo-Universitaire de Nice, Nice, France  
<sup>2</sup> Pharmacie, Centre Hospitalo-Universitaire de Nice, Nice, France  
<sup>3</sup> Bactériologie, Centre Hospitalo-Universitaire de Nice, Nice, France  
<sup>4</sup> Hygiène, Centre Hospitalo-Universitaire de Nice, Nice, France

sufficiently trained to deliver appropriate information to their patients.

Management of these patients requires numerous resources and is costly for the national health insurance, so that accurate coding, i.e. specific statement of infection due to multi-drug resistant (MDR) bacteria, to justify expenses, is mandatory. In Nice University Hospital, there were 0.45 and 0.8 clinical cases of ESBL-E per 100 admissions in 2010 and 2012, with an incidence rate of 0.54 and 1.04 per 1000 hospital days, respectively, calculated over a 3-month period each time.

We describe a resource intended to improve overall management of patients harbouring these organisms.

Our aim was to develop pragmatic tools and a warning system for the Antimicrobial Stewardship (AMS) team and to evaluate the impact of this organisation in our hospital in terms of requests for, and compliance with, expert advice, provision of information to the GP and adequate coding of the condition, in view of further dissemination across healthcare providers in our region.

## Methods

Before 2011, upon identification of an ESBL-E on a clinical isolate, the microbiology lab entered the result in the patient's computerised medical file with a suggestion for the attending physician to request ID specialist advice. This was thus requested at the discretion of the attending physician.

### 1. Development of a regional ESBL-E toolkit

In 2011, a network of infectious disease physicians in Southeastern France (Réso-InfectiO-PACA-Est), including Nice University Hospital and regional hospitals, developed a toolkit that contained all the necessary items for optimal management of patients colonised or infected with ESBL-E. These items are the following:

- an information sheet informing physicians of the current epidemiological context, of the issues relating to ESBL-E and the goal of the procedure,
- treatment protocols advising carbapenem discontinuation or re-evaluation of their indication after the first 2 days, due to the lack of available national protocols at the time,
- a special sheet describing infection control measures to be given and explained to the patient, specifically created by the infection control committee for this situation. Indeed, previous available tools in hospital settings applied to nosocomial resistant bacteria, which was no longer the case.
- a letter template to be sent to the patient's GP.
- a check list included in each file to ensure that all the procedures were followed, and files duly recorded

2. Development of a notification procedure for any critical result on a clinical sample (as opposed to systematic screening results which are directly reported to the infection control team), requiring the microbiologist to send an email to all involved healthcare staff including the ID physician as soon as an ESBL-E was identified in a patient by the microbiology lab.

In our teaching hospital, advice on antibiotic therapy is coordinated by a team consisting of microbiologists, infectious disease (ID) specialists, pharmacists, and specialists in infection control, and all members of the team, as well as the patient's attending physician, were then informed. The objective of this procedure was to systematically provide real-time advice for patient management.

As soon as the ID specialist was alerted, he/she would contact the attending physician and recommend management, recording it in the patient's electronic chart, and send a number of tools from the ESBL toolkit whenever appropriate. The ward nurses were informed by the infection control team and reminded of the appropriate measures.

During the development of the tool KIT and the setting up of the warning procedure, 20 staff training sessions on ESBL-E were organised by the AMS team in the different hospital departments.

### 3. Auditing procedure

An uncontrolled interventional prospective study was conducted, in order to compare standards of care over two 3-month periods (16th July to 16th October) in 2010 and 2012: all consecutive cases of ESBL-E infection with clinical signs (thus excluding systematic screening results), as recorded in the hospital medical systems information programme over the two study periods, were investigated.

In 2012, patients were followed prospectively, all of them benefited from the ID specialist's advice and the clinical characteristics of the infection or eventually urinary colonisation were entered in a database.

The following data was collected from the computerised medical record, hospitalisation summaries and IDC coding:

- ID specialist's recommendations,
- information provided to the patient's general practitioner,
- coding of multi-drug resistant bacteria (MRB) and of patient isolation.

## Statistical analysis

Data were collected and entered in Excel format and analysed with Epi-Info 7 software. Frequencies of variables of interest

during each study period were compared using the chi-square test for qualitative data and means for continuous data were compared using Student's *t* test.

## Results

Management of patients identified as harbouring ESBL-E in Nice University Archet Hospital was compared over a 3-month period in 2010 and 2012, between July 16th and October 16<sup>th</sup>. Patient numbers were comparable over both periods (87 and 92, respectively).

Compliance with the main standards of care recommended nationally for ESBL-E infection/colonisation significantly improved after the intervention.

In 2010, only 18% of patients benefited from expert ID advice, in spite of a suggestion for the attending physician to request it that accompanied the microbiology result. When advice was indeed requested, the average delay between availability of the microbiological result and the request was of 5.1 days. In 2012, almost all patients (97%,  $p < 10^{-3}$ ) benefited from specialised advice, with total compliance with the advice given, which was provided on average within 4 h of receiving the result of bacterial identification ( $p < 10^{-3}$ ).

There was major improvement in the provision of information to the GP regarding microbial resistance and infection control hygiene measures to be continued after discharge (18 vs 67%;  $p < 10^{-3}$ ).

Coding improved following the intervention with adequate coding increasing from 17 to 59% of cases ( $p < 10^{-3}$ ).

Patients were located in 52 different hospital units. There were more cases of asymptomatic bacteriuria than of infection ( $n = 44$  patients). Fewer than 50% of the infected patients ( $n = 20$ ) were initially treated with carbapenem, with quick de-escalation. Certain patients with positive samples, initially considered as infected, proved to be colonised following a discussion with the attending physician, and thus did not receive antimicrobial treatment. However, recommendations for infection control measures and patient information were provided.

None of the colonised patients received antibiotics. Details of infection sites and treatment are shown in Table 1.

## Discussion

This intervention, involving an ID specialist each time a patient was identified as harbouring ESBL-E, resulted in prompt advice on management, which was duly followed, provision of detailed information to GPs, and improved diagnosis coding. Patients who were colonised but not infected, i.e. with no clinical signs, namely in urinary samples, did not receive antibiotics. The intervention was not extended to patients with no clinical suspicion of infection, i.e. those for whom systematic screening

resulted in identification of ESBL-E. Indeed, in Nice University Hospital, systematic screening for MDR organisms by rectal swab is performed in medical and surgical intensive care and in haematology units, and for patients with a history of hospitalisation abroad during the previous year. This screening procedure is conducted by the infection control department and has not been included in our protocol.

The study design did not aim to assess trends in ESBL-E incidence nor antibiotic prescription rates between the two study periods. However, the fact that ID specialist advice was systematically requested could only result in improved antimicrobial prescription and infection control, and the procedure was shown to have a positive impact on patient management.

Several countries have put forward recommendations to optimise ESBL-E diagnosis or curb their dissemination. However, data are scarce regarding compliance with these recommendations in a real-life setting. Ghana [5] and China [6] have thus identified colonisation rates exceeding 30% among hospitalised patients and report major within-hospital transmission. Differences in cross-transmission characteristics between *Escherichia coli* and *Klebsiella pneumoniae* have been described showing more limited amplification of *E. coli* compared to *K. pneumoniae*, thus pointing to potential tailoring of prevention measures according to the type of bacterial agent [7]. A recent review by Canadian authors identified only two studies comparing systematic screening and isolation with a targeted approach or with abstaining from any infection control measure [8]. The cost of isolation procedures, but also the negative psychological impact on isolated patients who may suffer from depression as a result, may explain such diverging attitudes. Indeed, misinterpretation of isolation measures often results in patient confinement, as frequently observed in our hospital setting, although no studies have been published on the subject. Such a drastic and demanding approach dictated by certain recommendations is not compatible with available health resources ([9]; [https://www.cadth.ca/sites/default/files/pdf/hntis/sept-2012/RE0028\\_VREReport\\_e.pdf](https://www.cadth.ca/sites/default/files/pdf/hntis/sept-2012/RE0028_VREReport_e.pdf)) and may even not be desirable. Arnaud et al. have recently published a review describing the key elements that influence the success of infection control measures [10]. These should be urgently standardised, simplified and, most of all, fully understood by the various caregivers in order to focus on the most effective measures which are essentially the simplest ones, such as hand-washing [11]. Birgand insists on the importance of relationships between caregivers, on behaviour change techniques and on coordination among the multidisciplinary units involved under the leadership of international societies [1]. Kac et al. had already shown the impact of electronic alerts, providing these were directed at all the staff and, namely, directly to the nurses [12].

In France, recommendations for controlling the spread of ESBL-Enterobacteriaceae were published in 2010 by the

**Table 1** Distribution of infection sites and antimicrobial agents among patients harbouring ESBL-E

Infection sites	Number of patients	Number of antimicrobial agents	Penems	3GC	FQ	NF	TMP-SXT	Fosfo iv
Pyelonephritis	12	13	6	3	2		2	
Prostatitis	9	11	5	2			1	3
Lower UTI	9	7				7		
Respiratory tract infection	4	5	4		1			
Bacteremia	5	5	2	1	1			1
Digestive tract	3	3	2	1				
Other	2	4	1				1	
Total	44	48	20	7	4	7	4	4

UTI urinary tract infection; *Penems* ertapenem, imipenem, meropenem; 3GC ceftoxitin; FQ fluoroquinolones; NF nitrofurantoin; TMP-SXT cotrimoxazole; Fosfo iv IV fosfomycin

Public health council (Haut conseil de santé publique) and appear to be among the few that offer comprehensive management including both hospital and community settings ([http://www.hcsp.fr/Explore.cgi/Telecharger?NomFichier=hcspr20100202\\_enterobactBLSE\\_en.pdf](http://www.hcsp.fr/Explore.cgi/Telecharger?NomFichier=hcspr20100202_enterobactBLSE_en.pdf)). They include training of caregivers, improved laboratory diagnostic procedures, development of a national surveillance network, reduced prescription of critical antibiotics known to exert selective pressure, and ambitious management propositions upon identification of an ESBL-E. Indeed, according to the HCSP, all ESBL-E infections require specialised advice, treatment must be appropriate and use of carbapenems should be avoided, infection control measures must be implemented, and both the patient and his/her GP must be informed ([http://www.hcsp.fr/Explore.cgi/Telecharger?NomFichier=hcspr20100202\\_enterobactBLSE\\_en.pdf](http://www.hcsp.fr/Explore.cgi/Telecharger?NomFichier=hcspr20100202_enterobactBLSE_en.pdf)).

Such wide-ranging management requirements can only be implemented through establishing warning procedures, by systematically informing the institution's antibiotic consultant upon isolation of an ESBL-E. Indeed, since patients harbouring these organisms can be found in any hospital department due to the frequently community-acquired origin of their infection or colonisation, attending physicians cannot be expected to be familiar with the issue, comply with recommendations and prescribe appropriate antibiotic treatment. The ESBL toolkit aims to assist them. Furthermore, while treatment protocols remain an essential tool for standardised management of these patients, French recommendations were developed without offering such protocols ([http://www.hcsp.fr/Explore.cgi/Telecharger?NomFichier=hcspr20100202\\_enterobactBLSE\\_en.pdf](http://www.hcsp.fr/Explore.cgi/Telecharger?NomFichier=hcspr20100202_enterobactBLSE_en.pdf)).

At Nice University hospital, we wished to implement national recommendations while being aware of the need for customised management of patients harbouring ESBL-E, with the support provided by the AMS team. Many issues around these patients cannot be taken into account within procedures and protocols. How should bedridden patients be isolated? Can an aminoglycoside be prescribed as the single agent for

ESBL-E-related pyelonephritis? What treatment strategy in case of chronic prostatitis in an elderly patient who can only receive parenteral treatment? Such issues require specialised advice, with answers provided in real time. This was done according to the specific clinical context by the antibiotic consultant whose advice was systematically followed.

The mention in the patient's discharge letter of multi-drug-resistant bacteria can raise difficulties for GPs managing such a situation: the difference in infection control recommendations between the hospital and the community, where this notion is quite new, leads to much questioning. Grandparents have been forbidden to visit their grandchildren, couples express concerns regarding their sexual relationships, and GPs lack the necessary tools or links to advise their patients. We developed a standard letter to inform GPs of infection control measures. On the ESBL-E kit website, an email address is available which GPs can use to request any further information regarding surveillance of carriage, infection control measures or assistance for treatment.

To our knowledge, little is known at present of the cost of patient management. A recent report mentions inadequate treatment in 50% of ESBL-E related infection and an overhead cost mainly due to a 30% extension of hospital stay [13]. In France, disease coding is the only means for hospitals to be paid for the duration of hospital stay. In our study, diagnosis codes that generate substantial compensation were better documented, thanks to a check list that included them.

Lastly, a major issue to be considered in MDR management, which we were not able to assess, is patient information, in the form of an explanatory leaflet developed by the infection control committee and that all healthcare institutions should theoretically give and explain to any patient harbouring a MDR organism. In a survey conducted by Wiklund et al., all the patients interviewed declared they had not been adequately informed, that caregivers did not have the appropriate knowledge to answer their questions and that they felt stigmatised [14]. Patients should be able to get help by having at least the possibility of contacting a member of a



specialised team. This was our aim when developing our website, which is accessible to all, patients and professionals, and which provides email addresses of members of the AMS team. We thus receive messages from patients and this simple link reassures them.

The automatic warning procedure via email implemented in our teaching hospital is simple and effective and allows multidisciplinary involvement in the management of these MDR bacteria. Setting up such a procedure requires the intervention of the Information Technology Department and helps to create a prospective database of ESBL epidemiology including the following data: infection or colonisation, type of bacteria, treatment, infection control measures, information delivered to the patient and GP, and outcome.

The availability of the ESBL-E toolkit allows consistent, consensual and coordinated patient management, simplifying the implementation of complex protocols, infection control measures and communication with patients and hospital and general practitioners through simultaneous real-time provision of advice and resources. Systematic and appropriate bacterial coding favours adequate resource allocation for patient isolation, infection control measures and eventual prescription of costly antimicrobial agents.

This is further facilitated by the development of a dedicated website: <http://kit-blse.com> that can be accessed both by hospital-based physicians and community-based practitioners. It contains all the necessary tools for comprehensive patient management (infection control, treatment, information, contact with a member of the AMS team) and thus provides a pragmatic approach to the complex situation related to ESBL-E.

We expect this care-bundle approach on the management of ESBL-E infection or colonisation in hospitalised patients to ensure optimal coordination among health workers and to have a favourable impact on patient outcome and on controlling the spread of ESBL-E. This initiative complies with current recommendations allowing non-ID specialists to deal with a complex situation requiring multiple tasks ([http://www.hcsp.fr/Explore.cgi/Telecharger?NomFichier=hcsp20100202\\_enterobactBLSE\\_en.pdf](http://www.hcsp.fr/Explore.cgi/Telecharger?NomFichier=hcsp20100202_enterobactBLSE_en.pdf)).

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