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ORIGINAL ARTICLE

A toolkit for the management of infection or colonization by extended-spectrum beta-lactamase producing Enterobacteriaceae in Italy: implementation and outcome of a European project

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Abstract

Among European countries, prevalence rates of extended-spectrum beta-lactamase-producing Enterobacteriaceae (ESBL-E) are particularly high in those bordering the Mediterranean. This is the case for Italy, with 26% of *Escherichia coli* displaying resistance to the 3rd generation cephalosporins in 2013. An ESBL-E toolkit designed to assist clinicians in managing patients harboring ESBL-E was favorably implemented in Southern France. In a context of lack of specific Italian recommendations, its extension to an adjacent region of Italy was made possible through a cross-border EU cooperation program. Italian infectious disease (ID) specialists, microbiologists, and community-based general practitioners from three districts in Liguria were offered a toolkit consisting in a warning system and detailed procedures for the management of patients harboring ESBL-E, including seeking advice from an ID specialist, and were trained during 52 video conferences by an experienced French team. Indications and trends in antimicrobial prescription were studied following implementation of the toolkit. Between November 2013 and November 2014, 476 patients were identified as harboring ESBL-E and expert advice was sought for 364 of these; all patients and/or their caregivers were advised on appropriate hygiene measures and 209/341 with documented management received antimicrobial treatment, while asymptomatic carriers (39%) were not prescribed antibiotics. The ESBL-E toolkit was well received by the healthcare staff. A specific, simple tool consisting in a care-bundle approach to manage ESBL-E carriers can restrict antimicrobial prescription to symptomatic patients while raising awareness among caregivers of the importance of seeking expert advice and implementing appropriate hygiene measures.

Introduction

Enterobacteriaceae producing extended-spectrum beta-lactamase (ESBL-E) are isolated with increasing frequency in Europe, particularly in the Mediterranean area. Extended-spectrum beta-lactamases are enzymes produced by some bacteria with a spectrum of hydrolysis that provide resistance to the 3rd generation cephalosporins (3GC). The resistance mechanisms involved frequently confer non-susceptibility to multiple antimicrobial agents, resulting in shrinking treatment options for infections due to these organisms. Originally limited to the hospital setting, these bacteria are now found within the community, both in clinical situations and among symptom-free carriers [1–4]. Several risk factors for acquisition of ESBL-E have been identified: recent antibiotic treatment (3GC and fluoroquinolones), previous hospitalization, age above 60 years, diabetes, and travel to endemic countries [5]. In Italy, the prevalence rate for *Escherichia coli* resistant to 3GC, most of which are known to produce ESBL, was estimated at 26.2% in 2013 (http://ecdc.europa.eu/en/healthtopics/antimicrobial_resistance/database/Pages/table_reports.asp), i.e., about 4-fold higher than that observed in France. Few primary care physicians are trained to manage patients with ESBL-E as no specific Italian guidelines have been published and access to expert advice is seldom

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available. Among European countries, Italy has one of the highest rates of antibiotic consumption, with an increasing trend and an estimated 19% of non-prescribed antibiotic use [6]. Furthermore, in this country, few microbiology laboratories are available to identify ESBL-E outside the hospital setting. Since the cost of urine culture is not endorsed by the Italian national health insurance, many patients with suspected infection receive empirical treatment.

As an initiative led by a network of infectious diseases specialists in Southeastern France (Réso-Infectio-PACA-Est) (http://www.reso-infectio.fr/) including all local public hospitals and several private clinics in the Eastern part of the Provence Alpes Côte d'Azur region, a warning system combined with a toolkit for managing ESBL-E colonization or infection was developed in collaboration with microbiologists from private laboratories and community-based general practitioners. This toolkit was intended to provide advice and procedures to assist the latter in the event of isolation of ESBL-E in a patient. It was initially tested among general practitioners (GPs) in the Nice area in Southeastern France and met with participants' satisfaction, while resulting in improved patient management. In view of these results, implementation of this toolkit promoting French recommendations was offered to a neighboring region of Italy. As part of an EU-sponsored cross-border cooperation (http://www.interreg-alcotra.org/2007-2013/index.php?pg=progetto&id=231), the proposition consisted in offering a framework in order to establish a warning system, based on the availability of infectious diseases (ID) expert advice, and providing the ESBL-E toolkit, once customized for antimicrobial agents available in Italy, to healthcare professionals in an administrative district within Liguria. This area includes a population of 214,000, 3 hospitals, 4 elderly nursing homes, 31 long-term care facilities, and 180 GPs.

This paper reports the outcome of an intervention aiming to promote antimicrobial stewardship through organized management of ESBL-E infection or colonization, relying on ID expert advice and use of a dedicated toolkit in a region of Italy where no national recommendations were available at the time.

Methods

The toolkit includes four items: an information sheet to raise physicians' awareness of ESBL-related issues with a telephone number to access expert advice from a dedicated infectious diseases specialist, a check list for physicians to ensure the necessary measures have been implemented, detailed antimicrobial treatment protocols adapted to the antimicrobial agents available in Italy, and a list of hygiene measures. These hygiene measures, along with a definition of multi-resistant organisms, are described on a flyer intended for the patient's family and caregivers. According to French recommendations, all microbiologists are expected to systematically warn physicians who prescribe microbiological investigations each time ESBL-producing *Enterobacteriaceae* are identified, with details of antibiotic susceptibility testing specifically mentioning isolation of an ESBL-producing bacterium.

An infectious diseases specialist in San Remo was initially recruited to act as the referral adviser. Two initial plenary information sessions were held to present the procedures and toolkit to the local general practitioners, followed by a meeting in each of the three hospitals (San Remo, Imperia, Bordighera). Each practitioner was supplied with a memory stick containing the ESBL-E toolkit which was also dispatched via email.

To set up the project, 52 video conferences were held between physicians from Nice University Hospital and their Italian counterparts. Patient data were collected by the Genoa hospital information technology department from November 2013 to November 2014.

Weekly contacts between the referral adviser and the attending physician of colonized or infected patients and nursing home supervisors were organized.

Characteristics and susceptibility of isolated organisms were obtained from the microbiologist, while patient demographic details, source of infection (hospital-acquired, community-acquired, from residential nursing, or resting homes), co-morbidities, type and duration of prior antimicrobial therapy, sample type, site and date of sampling, diagnosis (infection or colonization), treatment protocol, and adequate information supplied to the patient and entourage were provided through telephone contact with the patient's attending physician.

Upon isolation of a multi-resistant organism by the microbiology laboratory, the microbiologist was expected to immediately alert the ID specialist who then contacted the patient's attending physician to advise him/her on treatment and management, particularly for bed-ridden patients and those in nursing or resting homes. Clinical and microbiological data were collected, and clinical outcome was monitored.

Statistical analysis

Frequencies for variables of interest were calculated. Pre- and post-intervention distributions of antibiotic prescriptions were compared by means of a chi-square test with 5% level of significance, using Epi-Info 7 software.

Results

Data were recorded from November 2013 to November 2014. Among 476 patients identified as harboring ESBL-E, 46 were untraceable, while the attending physician could not be reached for 66 of them. The analysis thus focused on 364 patients for whom expert advice was provided, and among whom 25 were hospitalized. A flowchart illustrating the

patients in the study is shown in Fig. 1. Median age was 80 years (range 1–101; IQR 72–85), 62% were female. Among the 350 patients with a documented history, 209 (60%) had received antimicrobial therapy within the previous 3 months, with 38 patients receiving more than one agent, totaling 251 antibiotic courses. The distribution of previously administered antimicrobial agents included 34% fluoroquinolones, 19% 3GC, 14% amoxicillin-clavulanate, 10% fosfomycin, 4% nitrofurantoin, 4% piperacillin-tazobactam, 4% cotrimoxazole, and 11% other. Indication for treatment was not documented.

ESBL-E infection was confirmed in 224 (61%) patients according to clinical criteria reported by the physician; the other patients were considered colonized. Among confirmed cases of infection, conditions accounting for microbial investigation included uncomplicated lower urinary tract infection (LUTI) (6%), complicated LUTI (73%), pyelonephritis (9%), acute prostatitis (2%), chronic prostatitis, sepsis (3%), and other (7%). Organisms were identified as community-acquired in 42% of cases, nosocomial in 24% of cases, while 34% were acquired in a nursing or resting home. Most ESBL-E isolates were *E. coli* (319, i.e., 88%), followed by Proteus spp. (25, i.e., 7%) and *K. pneumoniae* (20, i.e., 5%). Antimicrobial susceptibility profiles of these organisms are shown in Fig. 2.

Of the 364 patients identified as harboring ESBL-E, details of management were unavailable for 13 patients. Among the 351 remaining patients, 209 (59%) were treated. Distribution of antimicrobial agents according to infection site is shown in Table 1. Information and advice regarding hygiene measures, in order to avoid spread was provided to 331 (90%) patients or their caregivers.

Following implementation of a warning system, access to antimicrobial susceptibility data and to an infectious diseases specialist, and availability of a management toolkit, 39% of patients with asymptomatic ESBL-E colonization received no treatment but only advice on hygiene control measures to be implemented, and for cases of clinically confirmed, i.e., symptomatic infection, prescription of aminoglycosides and nitrofurantoin was introduced, while carbapenem use was reduced to a minimum. Trends in prescription of main antimicrobial agents pre- and post-intervention are shown in Fig. 3. In particular, among documented antimicrobial prescriptions, i.e., 251 antimicrobial agents during the 3-month pre-intervention and 207 post-intervention, the proportion of FQ decreased from 34.3 to 12.1% ($p < 10^{-5}$) and of

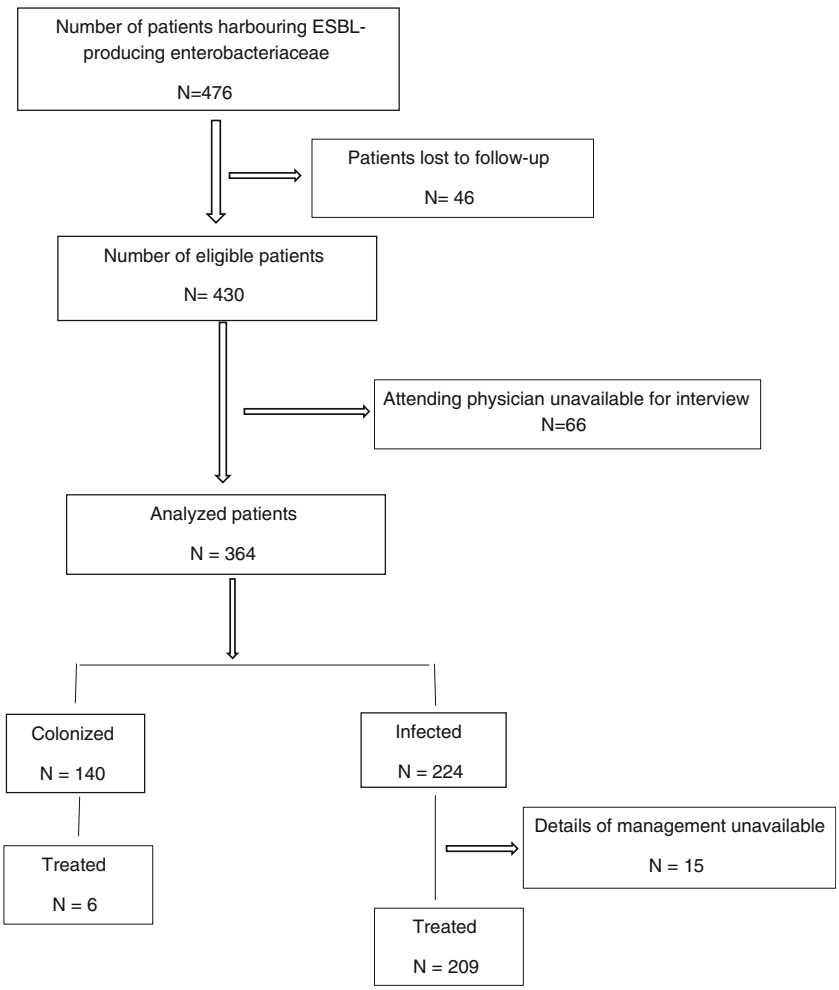

Fig. 1 Flow chart illustrating the patients included in the study

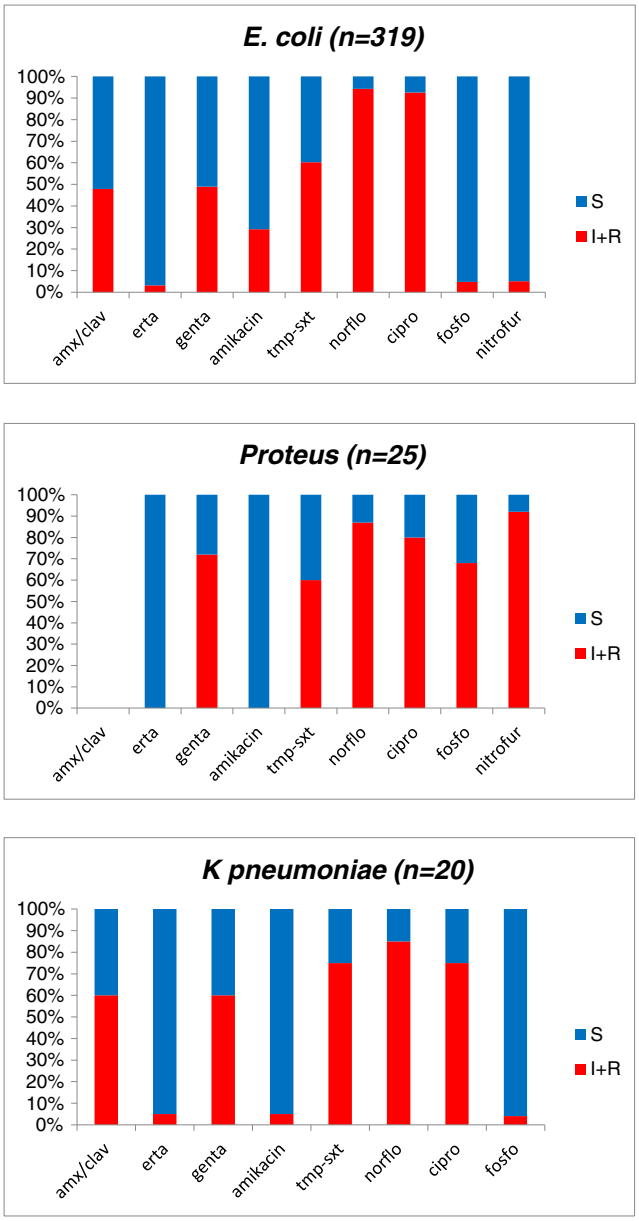

Fig. 2 ESBL-producing *E. coli*, *Proteus*, and *K. pneumoniae* antimicrobial susceptibility profile: amx/clav, amoxicillin-clavulanate; erta, ertapenem; genta, gentamycin; tmp-sxt, cotrimoxazole; norflo, norfloxacin; cipro, ciprofloxacin; fosfo, fosfomycin; nitrofur, nitrofurantoin

3GC from 18.2 to 8.2% ($p = 0.002$) while that of fosfomycin rose from 9.6% to 25.1% ($p < 10^{-4}$) and that of nitrofurantoin from 3.2 to 20.8% ($p < 10^{-5}$).

Discussion

The intervention, consisting in the implementation of a warning procedure by the microbiologist to alert the ID specialist and the patient's attending physician, who was offered a dedicated toolkit, resulted in avoiding antibiotic prescription in 39% of patients, a substantial improvement considering that, in this Italian region, all ESBL-E carriers, whether colonized or infected, previously received systematic antimicrobial prescriptions. Following the intervention, symptomatic ESBL-E patients were more likely to receive nitrofurantoin or fosfomycin for cystitis and fewer patients were prescribed 3GC or fluoroquinolones. Moreover, acceptability of the intervention was high among nursing staff and their supervisors who expressed their satisfaction in having suitable tools at their disposal.

The present study reveals a high prevalence rate for ESBL-E in the Italian region of Liguria, particularly in nursing homes where over 50% of residents harbor ESBL-producing *E. coli*, a result that has recently been confirmed in Italian long-term care facilities [7, 8]. High prevalence rates for ESBL-E in nursing homes have been reported in various countries, highlighting the need for special control measures in this setting [9–11].

Up to the time of implementation of the warning system and ESBL-E toolkit, all cases of urinary tract colonization or infection with an ESBL-producing organism received antimicrobial treatment, with frequent use of fluoroquinolones and 3GC [12].

In Italy, this situation results from a combination of factors: lack of guidelines for managing urinary tract infections, cost of microbial investigations, lack of awareness of the selective pressure exerted by wide and indiscriminate use of broad-spectrum antimicrobials, and horizontal contamination via caregivers who are not trained to maintain strict hygiene measures to limit the spread of resistant strains. This is particularly the case in long-term care facilities which lack infection control policies with supporting documents to inform the staff.

Furthermore, documented isolation of an ESBL-E, regardless of the clinical context, and lack of awareness of current international guidelines, typically lead to antimicrobial prescription, even in the case of asymptomatic bacteriuria, which further selects for increased resistance. Indeed, in France, strict criteria determined by the French infectious diseases society (SPILF) now limit antibiotic prescription to cases where bacterial isolation is associated with clinical symptoms, except in the case of pregnancy or in the context of surgery of the urinary tract (http://www.infectiologie.com/site/medias/Recos/2014-infections_urinaires-court.pdf). This remains true even if multi-resistant bacteria (MRB) are identified. If definite clinical signs of infection are absent, the patient should be considered colonized and in that case only hygiene measures are required. When antimicrobial treatment is necessary, the choice of antimicrobial agent in case of urinary tract infection should preferably favor compounds least likely to impact the microbiota, i.e., nitrofurantoin rather than or fluoroquinolones (FQ) or 3GC. Indeed, in Italy, FQ resistance in 2013 was estimated to reach 42% of invasive strains (http://ecdc.europa.eu/en/healthtopics/antimicrobial_resistance/database/Pages/table_reports.asp).

Table 1 Distribution of administered antimicrobial agents according to infection site (infection site and/or prescribed antimicrobial agent were unavailable for 20 infected patients)

Infection site	Fosfo (%)	Nitro (%)	FQ (%)	Amox/clav (%)	Penem (%)	TMP-SXT (%)	3GC (%)	Pip-tazo (%)	Other (%)
Uncomplicated LUTI ($n = 12$)	41.7	50.0	83	0.0	0.0	0.0	0.0	0.0	0.0
Complicated LUTI ($n = 144$)	29.2	22.2	15.3	13.2	0.0	9.0	6.3	2.8	2.0
Pyelonephritis ($n = 19$)	0.0	5.3	5.3	5.3	42.0	10.5	21.1	10.5	0.0
Acute prostatitis ($n = 2$)	0.0	50.0	0.0	0.0	50.0	0.0	0.0	0.0	0.0
Chronic prostatitis ($n = 3$)	0.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0	0.0
Sepsis ($n = 13$)	0.0	0.0	7.7	0.0	38.5	7.7	7.7	23.0	15.4
Unknown ($n = 11$)	36.4	27.3	18.1	9.1	0.0	0.0	9.1	0.0	0.0

Fosfo fosfomycin; *nitro* nitrofurantoin; *FQ* fluoroquinolones; *amx/clav* amoxicillin-clavulanate; *penem* mero-, erta-, imi-penem; *TMP-SXT* cotrimoxazole; *3GC* 3rd generation cephalosporins; *pip-tazo* piperacillin-tazobactam

Given the extent and trends of antibiotic use in Italy, major efforts are needed to curb the spread of ESBL-E within the community. Although training GPs on selecting patients eligible for antimicrobial prescription would contribute to these, interventions by public health authorities are essential to educate the public on the dangers of indiscriminate, non-prescribed antibiotic consumption, to fund reimbursement of microbial cultures, and to organize training programs promoting hygiene measures for healthcare givers. Studies conducted in Italy, reviewed by Gualano et al., show that patients' knowledge of antibiotics is poor, with frequent self-management of antimicrobial prescriptions [13].

Implementation of the ESBL-E toolkit succeeded in avoiding antimicrobial prescription in patients identified as ESBL-E carriers who would otherwise have been treated regardless of clinical context. It established a well-defined procedure that physicians were invited to follow, including a request for specialist advice or hospital admission for complex or severe cases.

Several drawbacks were identified that need to be further addressed. In the present case, delays between diagnosis and obtaining expert advice were described as substantial (although accurate documentation for this was not available) due to insufficient direct communication between the microbiologist and the infectious diseases specialist on one hand, and difficulty in contacting the attending physician on the other. Patient details were provided via a telephone conversation with the attending physician and may have been subject to bias.

The reduction in antimicrobial prescription following the intervention could not be quantified but was deducted on the notion that, prior to the intervention, identification of ESBL-E was necessarily followed by antibiotic treatment. Although verbal approval by GPs not to treat colonization was obtained in most cases, adherence to ID specialist's recommendations was not evaluated.

Patient information on the appropriate hygiene measures required may have been omitted or inadequate. Inappropriate antibiotic use persisted, including in the hospital setting, and feedback was scarce concerning response to treatment. Furthermore, urine cultures continued to be prescribed in the absence of clinical symptoms. Lastly, communication between the hospital and the community setting remained difficult. Such shortcomings are also frequently encountered elsewhere [14–17]. Despite these limitations, this experiment in offering general practitioners access to expert advice and providing them with assistance in the management of suspected and/or confirmed urinary tract infection or bacterial colonization shows that progress can be achieved in reducing unnecessary antimicrobial treatment in the community setting. The procedure requires the coordinated commitment of the

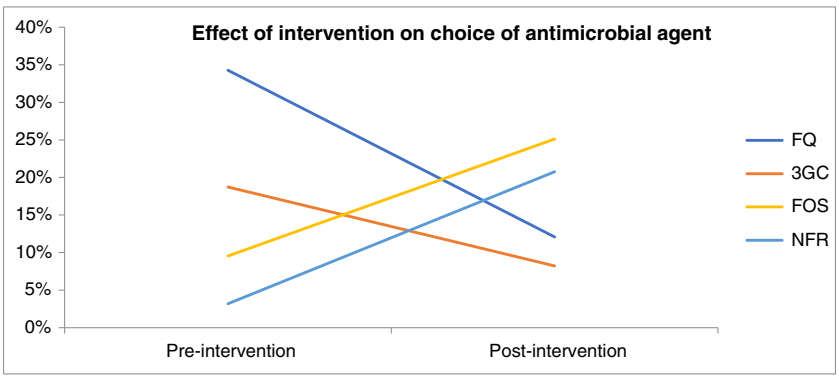

Fig. 3 Trends in prescription of main antimicrobial agents FQ, fluoroquinolones; 3GC, 3rd generation cephalosporins; Fos, fosfomycin; NRF, nitrofurantoin

microbiologist, the attending physician, the infectious diseases specialist and the patient, between whom cooperation is essential.

Conclusion

Given the extent and rate of spread of ESBL-E prevalence in the community setting, efforts to retain ever-diminishing antimicrobial resources are of paramount importance and should be supported through wide ranging interventions by public health authorities, targeting both physicians and the public. Implementation of a well-defined, organized strategy by a motivated team shows that it is possible to avoid unnecessary antimicrobial therapy. Extending such a strategy on a national scale would benefit both the individual patient and the community at large, while reducing the financial burden of antimicrobial resistance.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval For this type of study, ethical approval was not required.

Informed consent Informed consent was not required for this study.

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