Extended-Spectrum Beta Lactamase-producing Enterobacteriaceae among the pediatric population: who is at risk and why? Results from a single-centre prospective study

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SUMMARY

A prospective 18-month case-control study was performed in a tertiary Paediatric Centre in Turin (Italy) to analyse the disease burden and identify risk factors for acquisition of Extended Spectrum Beta Lactamase-producing Enterobacteriaceae (ESBL-pE). Children with ESBL-pE isolation were enrolled as cases, with controls matched according to age, type of pathogen isolated and sample of isolation.
Out of 83 children (37 males, mean age 4.7±5.46 years), 45 were identified as infected (54.2%) and 38 as colonised (45.8%) by ESBL-pE. Twenty-nine (64.4%) infectious disease episodes were categorised as community-acquired, 16 (35.6%) as healthcare-associated. *Escherichia coli* was the most frequently isolated pathogen (52, 62.7%) and the urinary tract the most frequent site involved (26, 57.9%). No deaths occurred, even in bloodstream infection cases. Hospitalisation and exposure to broad-spectrum penicillins and III/IV generation cephalosporins in the 90-day period before bacteria isolation were found to be independent risk factors at multivariate analysis. Immunodepression, prolonged central venous catheter (CVC) and urine catheter stay, and receiving a total parenteral nutrition (TPN) in the previous 30 days were otherwise recognized as potential risk factors at univariated analysis. ESBL-producing Enterobacteriaceae infections are a growing threat even in children. Careful recognition of patients at risk should promote targeted interventions in order to reduce the ESBL burden.

Keywords: ESBL, Enterobacteriaceae, children, hospitalisation, antibiotics.

INTRODUCTION

Multidrug-resistant (MDR) Gram-negative bacteria represent an ever-growing healthcare concern, as causing difficult to treat (and in some cases potentially untreatable) infections with consequent poor prognosis [1].
The production of enzymes called "extended-spectrum β-lactamase" (ESBLs) is one of the resistance mechanisms developed by MDR rods to antibiotics. Under this term different enzyme's families are classically gathered: they all can hydrolyze the β-lactam ring, resulting in bacterial resistance to early generation and extended spectrum cephalosporins (*e.g.*, ceftriaxone and ceftazi-

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dime), monobactams, and penicillins. Additionally, the ESBL-encoding plasmids frequently bear determinants of resistance for other antimicrobial classes, including fluoroquinolones, aminoglycosides and cotrimoxazole. These conditions pose significant therapeutic challenges in treating ESBLs-infections, mainly in children, where fewer antibiotics are approved for clinical use than in adults [1].
Outbreaks sustained by ESBL-producing Enterobacteriaceae (ESBL-pE) in healthcare settings, including neonatal and paediatric Intensive Care Units (ICU), cause significant morbidity and mortality, longer hospitalizations, and increased costs compared with patients infected by susceptible organisms. Moreover, patients infected in the hospital setting may transfer MDR pathogens in the community, and recent data support the increase of community-acquired ESBL-pE infections also in children [1].
This prospective surveillance study was designed in order to analyze the disease burden related to ESBL-pE infection and to identify risk factors for ESBLs acquisition among the population of the referral Paediatric Centre of Piedmont region (North-West Italy).

PATIENTS AND METHODS

Study population
ESBL-pE consecutively isolated from paediatric patients admitted to the Third Level Referral Centre of Regina Margherita Children's Hospital (Turin, Italy) from the 1st May 2012 to the 31th May 2014 were prospectively collected. Pathogens, samples of pathogen's isolation and antibiotic resistance profile were recorded. In neonatal cases, an investigation on mothers' ESBL-pE infection/colonization episodes was performed. Informed consent was obtained from parents of all participants included in the study, and the Hospital internal Board gave the ethical approval.
Medical records of children with isolation of ESBL-pE were examined in order to collect demographical characteristics (*e.g.*, age, sex, underlying chronic diseases), clinical and laboratory data useful to differentiate infection from colonization, as well as outcome of the infectious disease episode. Admission ward of the patient at the time of his first ESBL-pE pathogen isolation in a microbiological culture (the "index" culture) was also registered.
To define the types of infection by site and context of acquisition (community-acquired vs healthcare-associated) we referred to the 2013 Centers for Diseases Control and Prevention (CDC) guidelines [2]. Colonization was defined as the bacteria isolation from a specific site with no signs and symptoms of related infectious disease.

Case-control study design
Each child with ESBL-pE isolation became a case in the case-control study; each case was matched with a control patient according to their age at the time of pathogen isolation, type of pathogen isolated (non ESBL-producers in control patients) and sample of isolation (*e.g.*, blood, urine, etc), with a 1:1 ratio.
The following potential risk factors for ESBL-pE acquisition were considered:
- sex;
- mean length of the hospital stay before pathogen isolation;
- hospital admissions in the 90-day period before isolation; if any, mean length of the hospital stay;
- previous antibiotic prescription (type of molecule/duration of therapy) in the 90-day period before bacteria isolation; antibiotic molecules considered were: broad-spectrum penicillins ± beta-lactamase inhibitors, third and fourth-generation cephalosporins, carbapenems, aminoglycosides, fluoroquinolones, cotrimoxazole;
- underlying chronic diseases (first of all, immune system disorders);
- surgical interventions in the 30-day period before pathogen isolation;
- admission to an ICU in the 90-day period before bacteria isolation; if any, mean length of the ICU stay;
- presence and days of permanence of a central venous catheter (CVC)/urinary catheter/naso-gastric tube/endotracheal tube in the 30-day period before isolation;
- prescription of a total parenteral nutrition (NPT) and days of its administration in the 30-day period before isolation.

Microbiological analysis
Identification of ESBL-pE and antimicrobial susceptibility testing were performed through the

VITEK-2 automated system (bioMérieux, Mercy-L'Etoile, France). In case of isolation of Enterobacteriaceae spp. other than *Escherichia coli*, *Klebsiella pneumoniae* or *Klebsiella oxytoca*, the ESBL production would be confirmed by the broth microdilution test if the minimum inhibitory concentration (MIC) indicated intermediate sensitivity or resistance to cefotaxime, cefepime or ceftazidime, as recommended by the European Committee on Antimicrobial Susceptibility Testing breakpoints (EUCAST). All results were interpreted according to EUCAST guidelines [6].

Statistical analysis

Univariate analysis for identification of potential risk factors for ESBL-pE acquisition and infection was performed through a two-tailed Student's t-test for continuous variables, and two-tailed chi-square test for dicotomic variables. A *p*-value <0.05 was considered statistically significant.

Only significant variables were considered for the multivariate analysis, performed through the logistic regression model.

Data were managed through Microsoft Excel 2007 for Windows. Statistical analysis was performed through SPSS software (version 20) for Windows.

RESULTS

During the study period, out of 83 children (37 males, mean age 4.7 ± 5.46 years), 45 were identified as infected (54.2%) and 38 as colonized (45.8%) by ESBL-pE. Characteristics of the study population are listed in Table 1. Fifty-height patients (70%) had relevant co-morbidities, which predisposed them to repeated hospitalizations. The onco-haematological ward accounted for the great majority of ESBL-pE isolations (22, 30.1%), followed by paediatric specialties (17, 23.3%) and neonatal units (12, 16.4%).

Strictly according to 2013 CDC definitions, 29 (64.4%) infectious disease episodes were categorized as community-acquired, 16 (35.6%) as healthcare-associated (Table 2) [3].

Escherichia coli was the commonest ESBL-producing pathogen isolated (52, 62.7%), followed by *Klebsiella pneumoniae* (17, 20.5%) and *Enterobacter cloacae* (6, 7.2%). Patterns of antimicrobial resistance in cultured ESBL-pE are summarized in Table 3: mostly isolated bacilli retained susceptibility to amikacin and nitrofurantoin, and partially to piperacillin/tazobactam. They were all carbapenems-susceptible, supporting the choice

Table 1 - Characteristics of the study population

	Cases (number/percentage)	*Controls (number/percentage)*
Patients enrolled	83	77
Age (mean ± SD, years)	4.7±5.46	1.76±3.57
Males	37 (44.6)	40 (51.9)
Co-morbidities		
Acute lymphoid or myeloid leukemia/lymphomas	13 (15.7%)	4 (5.2%)
Solid organ tumor	4 (4.8%)	1 (1.3%)
Allogenic HSCT	6 (7.2%)	3 (3.9%)
SOT	2 (2.4%)	0
Immunodeficiency (congenital/iatrogenic)	2 (2.4%)	0
Congenital malformation syndromes	13 (15.7%)	6 (7.8%)
Other chronic diseases	18 (21.7%)	12 (15.6%)
No co-morbidities	25 (30.1%)	51 (66.2%)
Inpatients/outpatients (at the moment of the "index" culture)	73/10	72/5
Admission wards (at the moment of the "index" culture)		
General Medical Units	10 (13.7)	34 (47.2)
Specialized Medical Units	17 (23.3)	5 (6.9)
Onco-haematological Department (Stem Cell Transplantation Unit included)	22 (30.1)	4 (5.6)
Surgical Units	8 (11)	6 (8.3)
ICU	4 (5.5)	4 (5.6)
Neonatal Units (Neonatal Intensive Care Units included)	12 (16.4)	19 (26.4)

Legend: HSCT = haematopoietic stem cell transplantation; SOT = solid organ transplantation; ICU = intensive care unit.

Table 2 - ESBL-pE isolated and type of infection/colonization by site.

	Cases (number/percentage)	*Controls (number/percentage)*
Enterobacteriaceae species isolated		
Escherichia coli	52 (62.7)	50 (64.9)
Klebsiella pneumoniae	17 (20.5)	15 (19.5)
Klebsiella oxytoca	5 (6)	4 (5.2)
Proteus mirabilis	1 (1.2)	1 (1.3)
Enterobacter cloacae	6 (7.2)	5 (6.5)
Enterobacter aerogenes	1 (1.2)	1 (1.3)
Citrobacter freundii	1 (1.2)	1 (1.3)
Infection/colonization by sample		
All cultures	45/38 (54.2/45.8)	48/29 (62.3/37.7)
Urine cultures	26/22	30/18
Blood cultures	6/0	5/0
Nasal/pharyngeal swab	3/8	5/5
Peritoneal fluid	5/0	5/0
Surgical wound swab	3/1	1/0
Gastric fluid	0/5	1/4
Tracheal fluid	1/1	0/1
Bronchoalveolar fluid	1/1	1/1
Infections by site		
Urinary tract infection	26 (57.9)	30 (62.5)
Bloodstream infection	5 (11.1)	5 (10.4)
Upper respiratory tract infection	3 (6.7)	6 (12.5)
Lower respiratory tract infection (pneumonia excluded)	2 (4.4)	1 (2.1)
Pneumonia	1 (2.2)	0 (0)
Intra-abdominal infection	5 (11.1)	5 (10.4)
Surgical site infection	2 (4.4)	1 (2.1)
Bedsore infection	1 (2.2)	0 (0)
Infection acquisition setting		
Healthcare associated	16 (35.6)	13 (27.1)
Community acquired	29 (64.4)	35 (72.9)

Table 3 - Resistance patterns of ESBL-producing isolates (No = 83).

Antibiotics	*ESBL-producing isolates No (%)*
Amikacin	13 (15.7)
Gentamycin	38 (45.8)
Amoxicillin/clavulanate	65 (78.3)
Ampicillin	83 (100)
Cefepime	56 (67.5)
Cefotaxime	75 (90.4)
Ceftazidime	61 (73.5)
Ciprofloxacin	42 (50.6)
Carbapenems*	0 (0)
Nitrofurantoin	2/51 (3.9)
Piperacillin/tazobactam	35 (42.2)
Cotrimoxazole	50 (60.2)

*Carbapenems: meropenem, imipenem and ertapenem included.

of carbapenems as targeted treatment. ESBL-pE were mainly isolated in urine samples (48, 57.8%), so that the urinary tract appeared the most infectious disease site involved (26, 57.9%). Likewise, it was recognized as the principal site of ESBL-pE colonization (22).

During the study period, 5 bloodstream infections (BSIs) by ESBL-producing pathogens were recorded: four episodes regarded immunocompromised hosts (2 onco-haematological patients, 1 haematopoietic cells transplanted child, 1 renal transplanted infant), and one affected a child during his ICU stay after cardiac surgery for tetralogy of Fallot. No death occurred. Later on, the ESBL-producing rod was persistently isolated in one oncological patient.

ESBL-pE were isolated in 9 neonates: 7 were preterm neonates (4 very low birth weight - VLBW, 1 low birth weight - LBW), 2 were born at term but presented congenital chronic diseases

(congenital myopathy, methylmalonic acidemia). None of their mothers had previous or concomitant ESBL-pE isolation. At the time of isolation, all the babies were in a neonatal or paediatric ICU. Seven have been previously treated with prolonged antibiotic therapies (mean 10 ± 5.6 days). Four had developed a urinary tract infection (UTI) and one a lower respiratory tract infection, but all presented a favorable outcome of the infectious disease episode.

Seventy-seven patients were enrolled as controls (40 males, mean age 1.76 ± 3.57 years). For 6 case-patients, no adequate control-subjects could be found.

In the univariate analysis (Table 4), risk of ESBL-pE acquisition was found to be significantly consistent in immunocompromised children and in patients with a prolonged hospital stay in the 90-day period before pathogen isolation. Carrying a CVC and a urine catheter, or receiving a NPT in the previous 30 days before ESBL-pE isolation were otherwise recognized as potential risk factors for ESBL-pE acquisition. Both the general antibiotic prescription and the use of specific

Table 4 - Univariate analysis: risk factors for ESBL-producing Enterobacteriaceae infection/colonization.

Variables	*Cases (Total=83)*	*Controls (Total=77)*	*p-value*
Male gender, n (%)	37 (44.6)	40 (51.9)	0.439
Mean length of the hospital stay (mean ± SD, days)	15.72±32.36	10.76±27.78	0.3015
Mean length of hospital stay in the previous 90-day period (mean ± SD, days)	11.34±19.96	5.45±13.08	0.0276
Mean duration of antibiotic therapies[1] in the previous 90-day period (mean ± SD, days)	28.95±28.40	4.31±7.63	<0.001
Mean duration of broad-spectrum penicillins therapies in the previous 90-day period (mean ± SD, days)	11.35±18.38	1.86±3.42	<0.001
Mean duration of 3rd-4th generation cephalosporin therapies in the previous 90-day period (mean ± SD, days)	6.89±12.93	1.25±3.34	<0.001
Mean duration of aminoglycosides therapies in the previous 90-day period (mean ±SD, days)	2.89±4.30	0.88 ± 2.42	<0.001
Mean duration of fluoroquinolones therapies in the previous 90-day period (mean ±SD, days)	1.38±5.06	0.26±2.28	0.0768
Mean duration of cotrimoxazole therapies in the previous 90-day period (mean ± SD, days)	7.51±14.53	1.18±4.88	<0.001
Immunodepression, n (%)	27 (32.5)	8 (10.4)	0.0014
Other underlying chronic diseases, n (%)	31 (37.3)	18 (23.4)	0.0811
Surgical interventions in the previous 30-day period n (%)	8 (9.6)	4 (5.2)	0,4437
Admission to an ICU in the previous 90-day period, n (%)	9 (10.8)	5 (6.5)	0.4883
Mean length of ICU stay in the previous 90-day period (mean ± SD, days)	2.11±10.44	0.47±2.07	0.1778
CVC carriage in the previous 30-day period, n (%)	37 (44.6)	22 (28.6)	0.05325
Mean length of CVC stay in the previous 30-day period (mean ± SD, days)	11.64±15.97	5,05±10.19	0.0024
Urinary catheter carriers in the previous 30-day period, n (%)	12 (14.5)	4 (5.2)	0.0914
Mean length of urinary catheter stay in the previous 30-day period (mean ± SD days)	2.02±6.88)	0.15±0.89	0.0192
Endotracheal tube carriage in the previous 30-day period, n (%)	13 (15.7)	8 (10.4)	0.4516
Mean length of endotracheal tube stay in the previous 30-day period (mean ± SD, days)	1.36±4.52	0.46±1.83	0.1056
Total parenteral nutrition in the previous 30-day period, n (%)	22 (26.5)	10 (13)	0.05259
Mean duration of total parenteral nutrition in the previous 30-day period (mean ±SD, days)	4.36±8.41	1.79±5.52	0.0248

Legend: [1]=broad-spectrum penicillins, 3rd-4th generation cephalosporins, carbapenems, aminoglycosides, cotrimoxazole; ICU = intensive care unit; CVC = central venous catheter.

molecules (β-lactams, third and forth generation cephalosporins, aminoglycosides and cotrimoxazole) in the 3 month-period before the "index" culture were found significantly associated with ESBL-pE isolation.
In the multivariate analysis (Table 5), prolonged hospitalization in the 90-day period before bacteria identification, prolonged exposition to broad-spectrum penicillins and to III and IV generation cephalosporins were both confirmed as independent risk factors for ESBL-pE acquisition in the pediatric age.

DISCUSSION

Epidemiology, clinical manifestations and antibiotic resistance profile of ESBL-pE found in our case series are overall comparable to those described in literature, both for adult and paediatric populations [1]. As in the majority of reported hospital outbreaks, the more frequently isolated ESBL-pE were *Escherichia coli* and *Klebsiella pneumoniae*, mainly responsible for UTIs. No deaths occurred in our study, even if 5 cases of BSIs were described, and reported mortality rates related to these pathogens are consistently higher [8,12].
The antibiotic susceptibility profiles reflected a MDR resistance pattern, demonstrating a high rate of co-resistance with fluoroquinolones and cotrimoxazole, making almost unfeasible the oral treatment option. All the strains isolated maintained susceptibility to carbapenems, confirming these antibiotics as the agents of choice for the treatment of ESBL-pE infections in the paediatric age [12]. Although residual sensitivity was observed, we didn't treat any patient with the association β-lactam/β-lactamase inhibitor ± aminoglycoside in order to preserve carbapenems, as its application is still controversial particularly in the pediatric age [4, 8, 9].
Throughout this observational, case-control study, we would like to focus the attention on the predisposing conditions which may pose children at risk for ESBL-pE acquisition.
The ESBL-pE infected population of our case-control study can be considered the result of the two major causative determinants of the ESBL-pE worldwide spread: the patient's overexposure to antibiotics and the ESBL-pE cross-transmission [17].
Our case patients received significantly more antibiotics than the controls, as prolonged expositions to broad-spectrum penicillins and to III/IV generation cephalosporins in the previous 90 days were found as independent risk factors associated with ESBL-pE infection/colonization. Multiple and prolonged antibiotic courses are closely related with multiple and prolonged hospitalizations: the duration of hospitalizations in the previous 90-day period before ESBL-pE isolation was equally found as a considerable and independent risk factor for ESBL-pE acquisition. It's worth considering that more than a half of our study patients had relevant co-morbidities (mainly onco-haematological diseases) and therefore required major medical devices: immunodepression, length of the CVC/urinary catheter stay and NPT prolonged use were identified as predisposing conditions to infectious complications and consequent exposure to further antimicrobial treatments. In neonates, as no maternal colonization was found, major risk factors for ESBL-pE acquisition are prolonged

Table 5 - Logistic regression model: risk factors for ESBL-producing Enterobacteriaceae infection/colonization.

Variables	*p-value*
Mean length of hospital stay in the previous 90-day period	0.043
Mean duration of broad-spectrum penicillins therapies in the previous 90-day period	0.002
Mean duration of 3rd-4th generation cephalosporin therapies in the previous 90-day period	0.014
Mean duration of aminoglycoside therapies in the previous 90-day period	0.41
Mean duration of co-trimoxazole therapies in the previous 90-day period	0.059
Immunodepression	0.496
Mean length of CVC stay in the previous 30-day period	0.07
Mean length of urinary catheter stay in the previous 30-day period	0.184
Mean duration of total parenteral nutrition in the previous 30-day period	0.082

Legend: CVC = central venous catheter.

NICU stay, prolonged CVC carriage and multiple antibiotic therapies [5, 12, 16].

In spite the type of risk factors identified, we should interpret the 64.4% of ESBL-pE infectious disease episodes as community-acquired, strictly according to 2013 CDC criteria. We know that prolonged hospitalizations increase the risk of ESBL-pE acquisition, selection and dissemination among hospitalized adults and children, and can potentially create a considerable number of human reservoirs. Recently discharged children could carry ESBL-pE in the stool for many months after hospitalization (6 to 24 months), being potential sources for communitarian transmission [7, 12, 15].

There are various evidences of ESBL-pE person-to-person transmission, both within the child's family and within schoolmates, as resistance to β-lactams and other antibiotics is mostly associated with plasmidic elements, easily transferrable between species and carriers [10, 14, 16]. This may be a possible explanation for ESBL-pE acquisition by those children with no relevant co-morbidities included in our study population. However, many "community-acquired" cases regarded patients with chronic co-morbidities and those risk factors (*e.g.*, recent hospitalizations and recent antibiotic therapies, performed in any moment of the 90-day period before ESBL-pE isolation) were identified as predisposing conditions for ESBL-pE acquisition. These patients had reasonably a "hospital-related" ESBL-pE acquisition, and this consideration raises perplexities in considering these ESBL-pE infectious disease episodes strictly as "community-acquired". The "14 window period" identified in the new 2015 CDC criteria will open new perspectives on HAI definitions [3].

Application of effective antimicrobial stewardship programs could limit the ESBL-pE spread [13]. The thoughtful selection of empiric antimicrobial therapies both in the hospital and in the communitarian setting could primarily represent an adoptable strategy in order to prevent the emergence of ESBL-pE infection/colonization. Moreover, careful recognition of patients at risk for ESBL-pE acquisition and promptly carriers' isolation, together with application of standard contact precautions in the hospital setting, could reduce ESBL-pE selection and cross-transmission.

COMPLIANCE WITH ETHICAL STANDARDS

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Ethical Approval. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent. Informed consent was obtained from all individual participants in the study.

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