ARTIGO ORIGINAL / *ORIGINAL ARTICLE*

Enterobacteriaceas produtoras de β-lactamases de espectro alargado em idade pediátrica: fatores de risco para infeção recorrente

Risk factors for recurrent extended-spectrum β-lactamase producing Enterobacteriacae *infections in children*

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Patrocínios:
O presente estudo não foi patrocinado por qualquer entidade.

Artigo recebido em
19/09/2018

Artigo aceite para publicação em
01/10/2018

/ Resumo

Introdução: A incidência de infeções por *Enterobacteriaceas* produtoras de β-lactamases de espectro alargado (ESBL-PE) tem aumentado, tanto associadas aos cuidados de saúde (IACS) como à comunidade. Objetivo: caracterizar e identificar fatores de risco clínico para infeção recorrente por ESBL-PE.

Métodos: Estudo retrospetivo descritivo analítico de infeções por ESBL-PE em crianças (<18 anos) sintomáticas observadas no Serviço de Urgência de um hospital nível III, entre 2013 e 2016 (4 anos). Foi também avaliada a antibioterapia e factores de risco para a recorrência.

Resultados: Obtiveram-se 65 isolamentos. Incluíram-se 41 infeções (40 infeções do trato urinário – ITU – e uma urosépsis) de 28 doentes (idade mediana 3 anos [1 mês – 17 anos]). Em 25%, não havia antecedentes de ITU recorrente nem de patologia malformativa. Não houve diferença significativa entre IACS e infeções da comunidade. A exposição prévia a ESBL-PE não foi mais frequente nas IACS (65% vs. 53%, p=0.53). *Escherichia coli* foi o agente mais frequente (68%). Não se observou resistência a carbapenemes e 85% eram sensíveis à nitrofurantoína. Em 66%, a antibioterapia empírica foi inadequada.

Nove doentes (32%), tiveram recorrência e o cateterismo vesical intermitente mostrou ser fator de risco independente (p=0.029; R^2 0.42).

Conclusões: As estirpes ESBL-PE têm emergido na comunidade pediátrica, sendo frequente a antibioterapia inadequada. É fundamental determinar fatores de risco para evitar a recorrência.

Palavras-chave: ESBL, cateterismo vesical, infeção urinária

/ Abstract

Introduction: *Extended-spectrum β-lactamase producing Enterobacteriaceae infections (ESBL-PEI) have emerged in recent years, both community and healthcare-associated infections (HCAI). We aim to characterize ESBL-PEI episodes and to identify recurrence risk factors.*

Methods: *Retrospective data analysis of symptomatic children with a positive ESBL-PE strain, identified at the emergency department of a tertiary care paediatric hospital between 2013-2016. Antibiotic treatment and recurrence risk factors for were also analysed.*

Results: *Sixty-five isolates were identified. Forty-one ESBL-PEI were included (40 urinary tract infections and one urosepsis) from 28 patients, median age 3 years old [1 month – 17 years]. In 25% there was no history of recurrent UTI's or malformations. HCAI and community ESBL-PEI were equally frequent. Previous ESBL exposure was not more frequent in HCAI (65% vs. 53%, p=0.53). Escherichia coli was found in 68%. No resistance to carbapenems was found and 85% were susceptible to nitrofurantoin. Empiric therapy was inappropriate in 66%.*

Comparing the recurrent group (9 patients, 32%), clean intermittent catheterization was recognized as an independent risk factor (p=0.029; R^2 0.42).

Conclusion: *Paediatric ESBL infections have spread to the community, compromising antibiotics choice. To prevent recurrence, risk factors identification is crucial.*

Keywords: *ESBL, Urinary tract infection, clean intermittent catheterization*

/ Introduction

Extended-spectrum β-lactamase producing *Enterobacteriaceae* infections (ESBL-PEI) have emerged in the last years, both community-associated (CA) and healthcare-associated (HCA). A pooled prevalence of 9% is reported for bloodstream paediatric ESBL-PEI[1] and 1% to 11% for urinary tract infections (UTI).[2,3,4,5,6,7] Inappropriate empirical therapy is occurring more often,[8] which may lead to higher mortality and morbidity,[9] longer hospitalizations, worse outcome and, eventually, to colonization and recurrence. Recurrent UTI's may cause long-term consequences such as renal scars, hypertension and chronic kidney disease.

Several independent risk factors associated with ESBL UTI's have been reported in children,[3,6,10] but few have explored ESBL-PEI recurrence risk factors.[11]

Moreover, few studies on ESBL producing *Enterobacteriacea* among paediatric patients in Portugal have been published.[12]

This study aims to characterize ESBL-PE infections that presented to our emergency department, to assess antibiotic ESBL-PE sensibilities and clinical responses to empiric therapy. We also intended to determine the incidence and independent risk factors for ESBL-PEI recurrence.

/ Materials And Methods

We performed a retrospective observational data analysis of symptomatic children (< 18 years old) that presented to the emergency department at a tertiary care paediatric Portuguese hospital, from January 2013 to December 2016.

Antibiotic susceptibility was determined by automated susceptibility system (VITEK2; bioMerieux®), according to EUCAST guidelines. Nitrofurantoin susceptibility was not tested for *K. pneumoniae* isolates after 2016, according to EUCAST guidelines.

Inclusion criteria

Only patients with a positive ESBL-PE isolate identified in a usually sterile site were included. Regarding urine cultures, only those collected by catheterization, ureterostomy or clean-catch midstream in symptomatic children[13,14] with a suggestive urine analysis (positive leukocyte esterase, ≥10 white blood cells/mm^3 or a positive nitrite test) and more than 10^5 colony-forming units/mL of a single pathogen, were included. Catheter-associated UTI was defined according to Hooton et al.[14] criteria and only patients with pyuria and suggestive symptoms (fever, rigors, altered mental status, malaise or lethargy with no other identified cause; flank pain; acute haematuria; pelvic discomfort) were included.

Definitions

Health-care associated infections (HCAI) were categorized by Friedman et al. proposed criteria:[15] invasive procedures or exposure to a hospital in the previous 30 days, hospitalization for more than two days in the previous 90 days, treatment with broad spectrum antibiotics in the last 30 days. Otherwise episodes were classified as community-associated infections.

A history of ESBL-PE exposure was considered positive in case of asymptomatic ESBL-PE identification by urine culture in the 12 preceding months.

Empiric antibiotic therapy was considered inappropriate in case of *in vitro* resistance. If combined therapy was prescribed, inappropriateness was considered if there was *in vitro* resistance to both antibiotics.

Reinfection was defined as new ESBL-PE infection within 30 days after the first episode and relapse in case the same organism was identified.

Data analysis

Clinical data (gender, age, clinical presentation, co-morbidities, previous antibiotic treatment, ESBL carriage/infection in the last 12 months, hospitalizations in the last 12 months, recurrent UTI (>2), use of clean intermittent catheterization (CIC), microbiological data, treatment and evolution data (antibiotherapy, clinical response, recurrence) were obtained from the patient medical record.

Patients were classified as ESBL-PEI single infection or recurrent (more than one episode during the study period) and the two groups were compared to determine recurrence risk factors.

SPSS Statistics® version 22 was used to perform data analysis. P<0.05 was considered statistically significant. Chi-square test or Fisher's exact test was used to evaluate categorical variables.

Logistic regression analysis was performed to determine independent risk factors for recurrent ESBL-PEI.

/ Results

Population

Sixty-four ESBL isolates were obtained but 23 were excluded. Therefore, 41 ESBL-PE infections from 28 patients were included: 40 UTI's and one urosepsis – same agent identified in blood and urine cultures. No significant variation on case numbers per year was observed (Fig. 1). Median age was 3 years old (1 month – 17 years). A summary of the patient's clinical characteristics is shown in Table I. In total, 25% had neither history of recurrent UTI's nor structural malformations. The urosepsis case was an eleven-month old patient with a primary obstructive megaureter.

TABLE I – MAIN CHARACTERISTICS

PATIENTS CHARACTERISTICS	N=28 (%)
Male gender	14 (50)
No underlying disease	7 (25)
Recurrent UTI (>2) without anatomic abnormalities	4 (14)
Urinary tract and/or anorectal malformation	11 (39)
Neurogenic bladder	6 (21)
EPISODES OF INFECTION	**N=41 (%)**
Previous antibiotic therapy	
Within 12 months	36 (88)
Within 3 months	28 (68)
Within 30 days	24 (58)

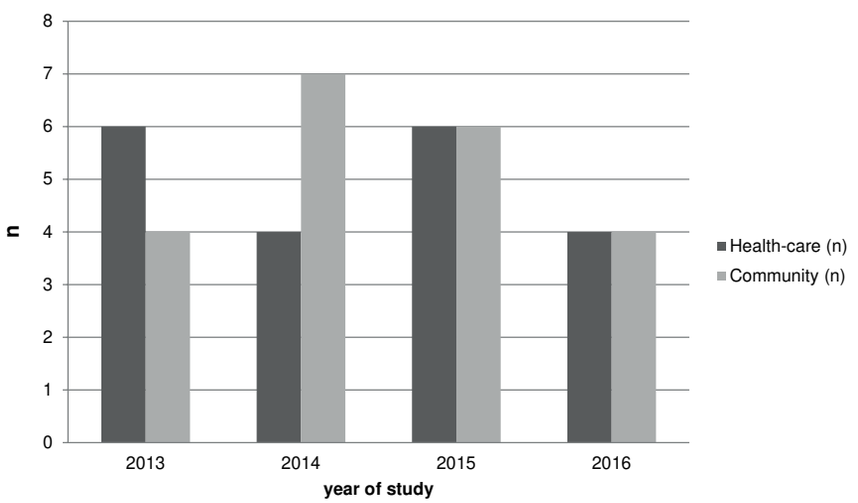

Figure 1 – Incidence of ESBL-PEI (2013-2016)

Infection characteristics

HCAI and community ESBL-PEI episodes were equally frequent (49% *vs.* 51%).

Escherichia coli was the most frequent pathogen (68%), followed by *Klebsiella pneumoniae* (32%). Antibiotic susceptibilities are presented in Table II. Co-resistance rates to ciprofloxacin, co-trimoxazole, ceftazidime and gentamicin were high. Furthermore, 29% were simultaneously resistant to these three antimicrobial groups. No resistance to carbapenems was found. The association between co-resistance and recurrence was not statistically significant. No difference (p=0.53) was observed regarding previous ESBL exposure in HCAI (65%) and community infections (53%).

Empiric therapy (Fig. 2) was inappropriate in 66% of the episodes (27/41), both in community (52%) and HCAI (48%).

Among these, 48% (13/27) were asymptomatic after 48-72 hours (Fig. 3) and 52% (14/27: eight symptomatic patients and six asymptomatic) switched antibiotherapy according to antimicrobial susceptibility testing: seven to meropenem, three to beta-lactam/beta-lactamase inhibitor, three to co-trimoxazole and one to cefotaxime.

In the appropriate therapy group, 21% (3/14) remained symptomatic after 48-72h. Three patients in this group also switched antibiotics (two for persistent symptoms and one asymptomatic patient that showed resistance to one of the two antibiotics prescribed): meropenem to piperacillin-tazobactam, amoxicillin/clavulanate to piperacillin-tazobactam, amoxicillin/clavulanate to meropenem.

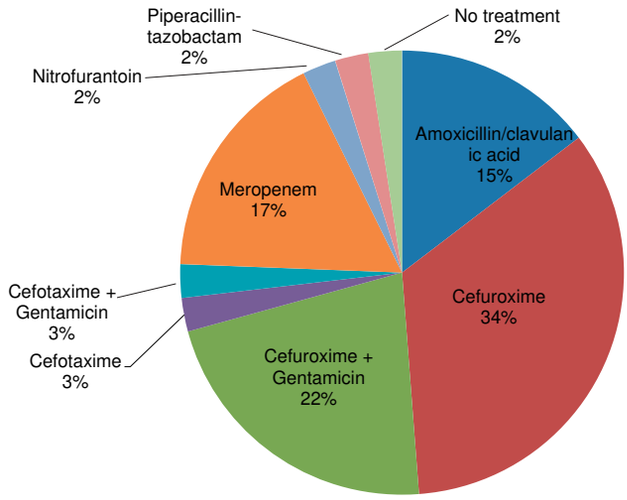

Figure 2 – Empiric antibiotic treatment

In total, 41% (17/41) switched antibiotics and thus 68% were receiving adequate therapy after 72 hours.

After 30 days, UTI relapse was observed in five patients (Fig. 3). Analysing the initial episode, three patients had received adequate treatment (two after 48h switching) and two didn't (one was asymptomatic and regardless of the *in vitro* resistance continued treatment and the other was not revaluated after 48h, remaining with the same antibiotic). The only patient that received initial appropriate antibiotic therapy and had become asymptomatic had

TABLE II – ANTIMICROBIAL RESISTANCE TESTING

ANTIBIOTIC RESISTANCE	TOTAL N (%)	*E. COLI* N=28 (%)	*K. PNEUMONIAE* N=13 (%)
Amoxicillin/clavulanic acid	30/41 (73)	18/28 (64)	12/13 (92)
Cefuroxime	41/41 (100)	28/28 (100)	13/13 (100)
Ceftazidime	24/41 (59)	15/28 (54)	9/13 (69)
Piperacillin-tazobactam	16/41 (39)	9/28 (32)	7/13 (54)
Gentamicin	21/41 (51)	9/28 (32)	12/13 (92)
Amikacin	2/41 (9)	1/28 (4)	1/13 (8)
Tobramycin	21/41 (51)	11/28 (39)	10/13 (77)
Ciprofloxacin	21/41 (51)	15/28 (54)	6/13 (46)
Co-trimoxazole	32/41 (78)	22/28 (79)	10/13 (77)
Nitrofurantoin	5/38* (13)	2/28 (7)	3/10 (30)
Meropenem	0/41 (0)	0/28 (0)	0/13 (0)

* Nitrofurantoin susceptibility was not tested for *K. pneumoniae* isolates after 2016, according to EUCAST guidelines.

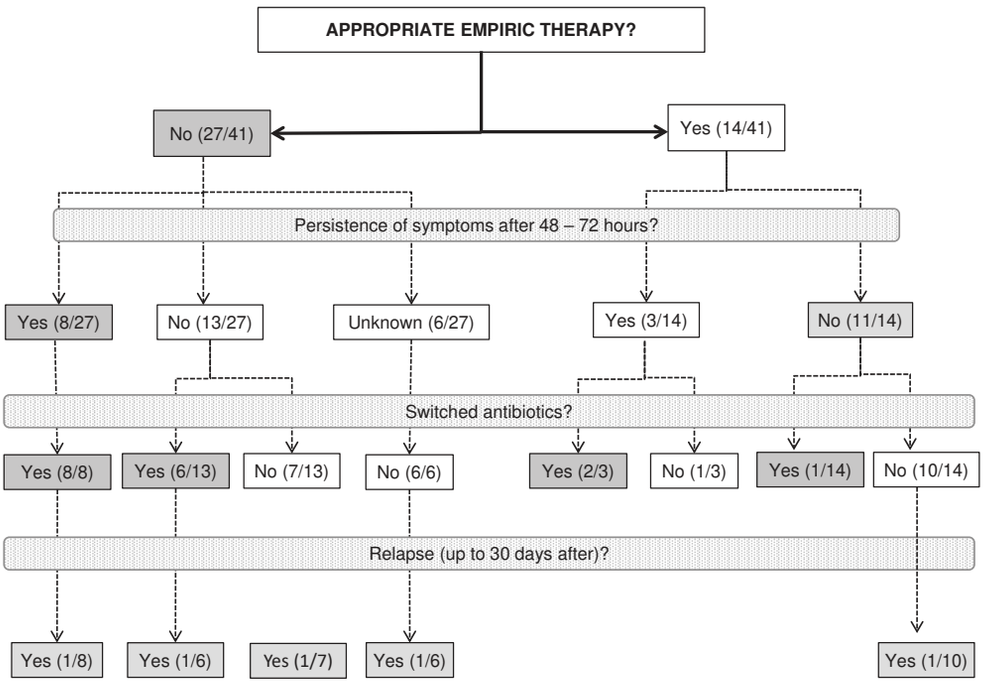

Figure 3 – Clinical evolution up to 30 days after ESBL-PEI

an uro-rectal malformation but didn't use CIC and was not previously colonized with ESBL-PE.

Initial antibiotic therapy and relapse had no statistical significance (p=0.412).

Recurrence and risk factors

Throughout the study, 9 patients (38%) had more than one ESBL-PE episode: eight had comorbidities, three were evacuated from African countries and six had no previous ESBL isolation before the first episode.

This group had in total 22 episodes: 68% HCAI, mean 76 days between episodes [12 – 245]).

Exposure to antibiotics in the 12 months preceding the ESBL-PE infection was identified in 88% and in 58% up to 30 days before (Table I). A broad-spectrum antibiotic was used in the 30 days preceding ESBL-PE infection in 54%.

Comparing the recurrent with single ESBL-PEI groups, use of antibiotics in the last three months and last 30 days, hospitalization in the previous three months and CIC were associated with recurrence by univariate analysis (Table III). On logistic regression analysis, CIC was identified as an independent risk factor (p=0.029; R^2 Cox&Snell 0.42). Also, the recurrent ESBL-PEI group had more than one antibiotic cycle (median 4) in the 12 months preceding the infection (p=0.017, Mann-Whitney test).

TABLE III – RISK FACTORS FOR RECURRENCE

UNIVARIATE ANALYSIS	N (%)	p	ODDS RATIO
Antibiotic exposure			
last 12 months	36 (87)	0.129	1.3 (1.004-1.598)
last 3 months	28 (68)	0.009	2.1 (1.314-3.391)
last 30 days	24 (58)	0.001	3.2 (1.634-6.138)
Hospitalization < 3 months	18 (44)	0.001	5.6 (1.943-16.311)
Clean Intermittent catheterization (CIC)	7 (25)	0.001	5.3 (1.256 – 22.171)

/ Discussion

Rising rates of ESBL-PE infections have been observed worldwide in the last decade.[16,17] Chronic medical conditions, frequent or recent hospital admission, catheters and medical devices and recent antibiotic exposure are described as risk factors for long-term ESBL colonization and community-onset infection in adults and children.[10,11] Similar to Blaschke et al.,[18] most children in our study had chronic medical issues, reflecting the specificity of patients followed at our hospital. Still, 51% were considered community-infections. Among these was an eleven-month old patient with a primary obstructive megaureter that presented with a life-threatening infection (urosepsis). Thus, early recognition of patients at risk for an ESBL-PEI is crucial to an effective initial therapy choice.

Previous documentation of colonization may guide the initial approach at the emergency department, particularly in those with previous use of β-lactam/β-lactamase inhibitor and CIC, as Goulenok et al. observed in his retrospective study.[19] In our cohort, we found that 58% had previous ESBL-PE isolation, a higher prevalence than Blaschke et al. (23%) and Asakura et al. (35%). Moreover, although high (65.8%), we found a lower rate of inappropriate initial therapy than these authors (Blaschke 86%, Asakura 66.7%), suggesting that this was maybe taken into consideration before the prescription.

Inappropriate empiric therapy was more frequent in CA infections, as cefuroxime is part of our empiric treatment protocol, in monotherapy for uncomplicated UTI's and combined with an aminoglycoside for patients with urogenital disease. Furthermore, the majority of infections were gentamicin resistant. Still, 48% of the inappropriate group became asymptomatic in the first 48 hours. On the other hand, three patients (21%) with appropriate treatment remained symptomatic after 48 hours. No deaths were reported and clinical cure was achieved in all 17 patients after treatment change. In another study (Jacmel et al.),[3] 32% showed a favourable clinical course two days after beginning treatment, before any treatment change. Toubiana et al.[4] also obtained clinical cure in 94% of UTI's, even with 63% inappropriate empiric therapy, thought 88% of patients received appropriate antibiotic therapy after 72 hours. This *in vivo* and *in vitro* clinical evolution dissociation was also observed in our study, especially in the relapse paradigm patients, emphasizing the difficulty to choose an empiric regimen. Furthermore, high resistance levels to multiple antibiotic classes are common in ESBL. Our results also support the awareness raised by these authors, suggesting minimizing carbapenems use in paediatric patients, to avoid resistances emergence. Like Dayan et al.,[5] we also observed a low nitrofurantoin resistance, which could be an interesting option for uncomplicated CA ESBL-PE cystitis in our children.

ESBL-UTI's recurrence was frequent (32%). Possible associated risk factors were former use of antibiotics, hospitalization in the previous three months and CIC, in agreement with previous studies that analysed ESBL-PEI risk factors.[3,5,6,10] In 2010, Kizilca et al.[21] showed that the proportion of paediatric patients who underwent CIC was significantly higher in the ESBL-PE group, but did not prove it as an independent risk factor. More recently, in the study by Aksu et al.,[10] CIC was an independent risk factor ($p=0.012$) for ESBL-PE infections. In our study, CIC was the only factor independently associated with recurrence ($p=0.029$). This may be in relation to the specificity of our sample and points out the increased infectious risk using invasive devices.

Indeed, our study has some limitations. First, it's retrospective nature without a non-ESBL group control. Second, it reports the local population and antibiotic susceptibility of a tertiary care university hospital with complex paediatric cases. Third, the recurrence's subgroup very small sample size that limits the power of the recognized risk factors. Nevertheless, to our knowledge, it is the first report about ESBL-PE infections at an emergency paediatric Portuguese department and supplies additional information about risk factors for recurrent ESBL-PEI.

In **conclusion**, paediatric infections caused by ESBL-producing organisms have spread to the community, which compromises the choice of antibiotics used. Although ESBL-PE were resistant to many antibiotics and inappropriate therapy occurred in the majority of cases, they were still not associated with a more severe clinical evolution. CIC, hospitalization and antibiotherapy in the last 3 months should be considered risk factors for recurrent ESBL-PEI, but further investigations are needed.

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