Urinary Tract Infections Caused by Community-Acquired Extended-Spectrum β-Lactamase-Producing *Enterobacteriaceae* in a Level III Hospital: A Retrospective Study

Infeções Urinárias Causadas por *Enterobacteriaceae* Produtoras de β-Lactamases de Espetro Expandido Adquiridas na Comunidade num Hospital de Nível III: Um Estudo Retrospetivo

Ana SIMÕES✉[1], Margarida LIMA[2], Ana BRETT[1,2], Carolina QUEIROZ[3], Catarina CHAVES[3], Henrique OLIVEIRA[3], Luís JANUÁRIO[1], Fernanda RODRIGUES[1,2]

Acta Med Port 2020 Jul-Aug;33(7-8):466-474 ▪ https://doi.org/10.20344/amp.12338

ABSTRACT

Introduction: The emergence of β-lactamases producing bacteria is a problem worldwide, with increasing importance in community-acquired infections, especially in urinary tract infections. Data regarding the use of non-carbapenem antimicrobials in these infections are scarce. The aim of this study was to analyse the treatment and outcome of urinary tract infections caused by community-acquired β-lactamase-producing bacteria in children.

Material and Methods: Retrospective study performed in a level III paediatric hospital, between June 2007 and December 2017. All children with β-lactamase-producing *Enterobacteriaceae* identified in aseptically collected urine culture were included.

Results: A total of 175 urinary infections caused by β-lactamases producing bacteria were diagnosed, 34 (19%) were community-acquired: 25 *Escherichia coli* (74%), 4 *Klebsiella pneumoniae* (12%), 4 *Proteus mirabilis* (12%) and 1 *Proteus vulgaris* (3%). In 30 (88%) cases, it was the first urinary infection. After identification of the microorganism and antimicrobial susceptibility, 33 (97%) children were re-evaluated and 24 (71%) had a repeat urine culture, which was positive in three (13%). In six (18%) cases, antibiotic treatment was modified. Four (12%) children had another UTI in the following month. In 30 (88%) children, imaging was carried out, with no nephro-urological malformations detected.

Discussion: In the last decade, about 20% of urinary infections caused by β-lactamase-producing *Enterobacteriaceae* were community-acquired with a relatively stable number of cases over the years. No nephro-urological malformations were identified in these children.

Conclusion: Although the number of cases is small, the clinical and microbiological outcomes showed that most were successfully treated with non-carbapenem antibiotics, with low recurrence of new episodes of urinary tract infections.

Keywords: Anti-Bacterial Agents; beta-Lactamases; Child; Community-Acquired Infections; Enterobacteriaceae; Enterobacteriaceae Infections; Urinary Tract Infections

RESUMO

Introdução: A emergência de bactérias produtoras de β-lactamases de espetro expandido é um problema mundial, com importância crescente nas infeções adquiridas na comunidade, nomeadamente nas infeções urinárias. Os dados pediátricos de utilização de antimicrobianos não carbapenemos nestas infeções são escassos. O objetivo do estudo foi analisar a terapêutica antibiótica instituída nas infeções urinárias causadas por estes agentes, assim como a evolução clínica e laboratorial.

Material e Métodos: Estudo retrospetivo efetuado num hospital pediátrico entre junho de 2007 e dezembro de 2017. Foram incluídas todas as crianças com urocultura positiva para *Enterobacteriaceae* produtoras de β-lactamases.

Resultados: Foram diagnosticadas 175 infeções urinárias causadas por *Enterobacteriaceae* produtoras de β-lactamases, das quais 34 (19%) foram adquiridas na comunidade: 25 *Escherichia coli* (74%), 4 *Klebsiella pneumoniae* (12%), 4 *Proteus mirabilis* (12%) e 1 *Proteus vulgaris* (3%). Em 30 (88%) episódios tratou-se da primeira infeção urinária. Após conhecimento do microrganismo e suas suscetibilidades, 33 (97%) crianças foram reavaliadas e 24 (71%) repetiram urocultura, que foi positiva em três (13%). Em seis (18%) casos foi alterado o antimicrobiano. No mês subsequente, quatro (12%) crianças tiveram nova infeção urinária e 30 (88%) crianças realizaram investigação imagiológica, sem deteção de malformações nefro-urológicas.

Discussão: Na última década, cerca de 20% das infeções urinárias causadas por *Enterobacteriaceae* produtoras de β-lactamases foram adquiridas na comunidade, com um número relativamente estável ao longo dos anos. Estas crianças não apresentavam malformações nefro-urológicas.

Conclusão: Embora o número de casos seja pequeno, a evolução clínica e microbiológica mostrou que a maioria foi tratada com sucesso com antimicrobianos não carbapenemos, com baixa ocorrência de novos episódios.

Palavras-chave: Antibacterianos; β-lactamases; Criança; Enterobacteriaceae; Infecções Comunitárias Adquiridas; Infecções por Enterobacteriaceae; Infecções Urinárias

1. Serviço de Urgência e Unidade de Infeciologia. Hospital Pediátrico. Centro Hospitalar e Universitário de Coimbra. Coimbra. Portugal.
2. Faculdade de Medicina. Universidade de Coimbra. Coimbra. Portugal.
3. Serviço de Patologia Clínica. Centro Hospitalar e Universitário de Coimbra. Coimbra. Portugal.
✉ Autor correspondente: Ana Simões. anasofiapediatria@outlook.pt

Recebido: 18 de maio de 2019 - Aceite:04 de novembro de 2019 |

INTRODUCTION

Urinary tract infections (UTI) frequently affect paediatric patients, with a 7% global prevalence in children, even though varying with age, ethnicity and gender.[1] An appropriate treatment is crucial, namely to prevent the development of kidney scars leading to impaired renal function.[2] These are mostly caused by Enterobacteriaceae: *Escherichia coli* (*E. coli*) are responsible for 60-90% of all the cases, followed by *Klebsiella pneumoniae* (*K. pneumoniae*) and *Proteus mirabilis* (*P. mirabilis*).[3]

Extended-spectrum beta-lactamases (ESBL) are defined as enzymes that are able to hydrolyse and inactivate the β-lactam ring in different types of antibiotics, giving bacteria resistance to penicillin, first, second and third generation cephalosporins and aztreonam. They can also be resistant to aminoglycosides, fluoroquinolones and cotrimoxazole and susceptible to carbapenems[4] and, even though they often show in vitro susceptibility to co-amoxiclav, the use of co-amoxiclav is still controversial in the treatment of these infections.[5]

Strains of ESBL-producing Enterobacteriaceae were for the first time identified in Germany in 1983, involved in nosocomial infections affecting adult patients admitted to intensive care units.[6] The first community-acquired (CA) infections were described in 2000[7] and were first described in children between 1999 and 2003 in France, initially as a cause of invasive disease in neonatal and paediatric intensive care units.[8,9]

These are currently a worldwide issue with an increasing relevance as CA infections, namely as urinary and intra-abdominal infections[10] and an emerging cause of urinary infections in children. This has been occurring in Asia, where around 40% of uropathogenic Enterobacteriaceae are ESBL-producers.[11] However, even though these are more frequent in developing countries, they have also increased in developed countries[12] such as the USA, where the prevalence of infections caused by ESBL-producing bacteria in children, including both CA and healthcare-associated infections, have increased from 0.26% in 2001 to 0.92% in 2010-2011,[13] in line with what has been found in some European countries, such as in France and Germany.[12,14,15]

In addition to longer hospital stays and higher costs when compared to urinary infections caused by other microorganisms,[16] higher mortality, particularly in newborn patients, has also been found in the presence of bacteraemia.[17,18]

Carbapenems are recommended for the treatment of these infections. However, there is an increasing and very worrying prevalence of carbapenemase-producing Enterobacteriaceae associated with high mortality[19] and a reduction in their use is crucial.

Non-carbapenem antibiotics have been successfully used in the treatment of UTIs in adults, showing no differences in clinical and bacteriological cure rates, in 14-day mortality and in the recurrence of these infections, when compared to patients treated with carbapenems.[20-24]

The study was aimed at assessing treatment, clinical (symptom improvement, namely fever and urinary symptoms) and laboratory outcomes (follow-up urine culture) and UTI recurrence. As there is little information on the use of non-carbapenem antibiotics in the treatment of UTIs caused by ESBL bacteria in children, the study was aimed at the assessment of treatment, clinical (resolution of symptoms, namely fever and urinary symptoms) and laboratory (follow-up urine culture results) outcomes and recurrent UTI episodes caused by these CA bacteria.

MATERIAL AND METHODS

Retrospective population-based study

This was a retrospective, descriptive, non-interventional study carried out at the *Hospital Pediátrico - Centro Hospitalar e Universitário de Coimbra* (CHUC), a level-III hospital in the Central region of Portugal providing healthcare to children and young people up to the age of 17 and 364 days, covering 392,112 children and adolescents aged 0-18 (*Instituto Nacional de Estatística*, 2017). On average, 58,550 attendances to Emergency have occurred per year through the study period, up to the age of 13 until 2011 and to the age of 18 from February 2011 onwards. Microbiological data were obtained from the database of the Department of Clinical Pathology / CHUC and included all the patients aged 0-18 presenting between Jun 2007 (at the time when the identification of these microorganisms started) and Dec 2017 (10.5 years) with ESBL-producing gram-negative bacilli isolated from urine.

The study was approved by the Healthcare Ethics Committee of the *Centro Hospitalar e Universitário de Coimbra*.

Microbiological methods

Gram-negative bacilli were isolated from urine culture and the identification and antibiotic susceptibility of *Enterobacteriaceae* were obtained by use of the Vitek-2 (bioMérieux, Marcy L'Etoile, France) compact system and Etest and combined disk tests.

Minimum inhibitory concentrations were interpreted according to the reference values of the European Committee on Antimicrobial Susceptibility Testing (EUCAST).

Inclusion criteria

Infections affecting patients with no risk factors and in whom bacteria were isolated in urine within the initial 48 hours upon admission were considered as CA infections.

Clinical cure was defined as the resolution of symptoms, namely fever and/or urinary symptoms (dysuria, frequent urination, low back pain), while bacteriological cure was defined as the presence of improving parameters in urinalysis (reduction in the number of leukocyte per field, absence of nitrite and bacteria in fresh urine) and negative follow-up urine culture. All the patients were submitted to a laboratory control following 48-72 hours of antibiotic treatment, in case that an ESBL-producing *Enterobacteriaceae* had been

identified.

The following were considered as risk factors: previous hospitalisation, surgical procedure, use of antibiotics or presence of a medical device in the 30 days prior to the episode, renal replacement therapy, use of antibiotic UTI prophylaxis, gastrointestinal colonisation by ESBL-producing *Enterobacteriaceae*, invasive ventilation or long-term corticotherapy within the last 12 months, low birth weight and presence of congenital anomalies of the kidneys and urinary tract and/or recurrent UTIs.[7,25-28]

Only aseptic urine specimens collected via suprapubic bladder aspiration, bladder catheterization or clean-catch midstream were included.

Clinical data

Data on strains and antibiotic susceptibility patterns that were identified in each case were obtained from the Department of Clinical Pathology/CHUC database, with the identification of the patients to be included in the study.

The following information was obtained from clinical records: age, gender, date of specimen collection, collection method, final diagnosis (cystitis or pyelonephritis), presence of risk factors, empirical therapy, antibiotic switch, need for hospital-based treatment, follow-up urine culture as well as imaging, recurrent UTI in the following six months.

Definitions of acute pyelonephritis and acute cystitis were based on local clinical guidelines.

Any UTI episodes affecting patients under the age of two, regardless of the presence of fever or patients with low back pain, regardless of the presence of fever and of all ages were diagnosed as acute pyelonephritis, while nonfebrile UTI episodes affecting children aged two and older were considered as acute cystitis. Two acute pyelonephritis episodes or three or more acute cystitis episodes, or one acute pyelonephritis associated with one episode of acute cystitis were considered as recurrent UTI.

Nonspecific clinical signs usually occur in children under the age of 24 months, with fever being the main clinical sign. After this age, the presence of fever and/or low back pain suggests the presence of inflammation of the renal parenchyma (acute pyelonephritis), while the presence of urinary symptoms such as dysuria, polyuria or incontinence suggests an inflammation of the lower urinary tract (acute cystitis).

The diagnosis of UTI in children was based on rapid urine test strips (nitrites and leukocytes) or urine analysis (nitrites, leukocytes and bacteria) and urine culture.[1]

Diagnosis was confirmed with a positive urine culture (suprapubic bladder - positive with ≥ 103 bacteria/mL, bladder catheterisation - positive with ≥ 104 bacteria/mL or clean-catch midstream - positive with ≥ 105 bacteria/mL).[29,30]

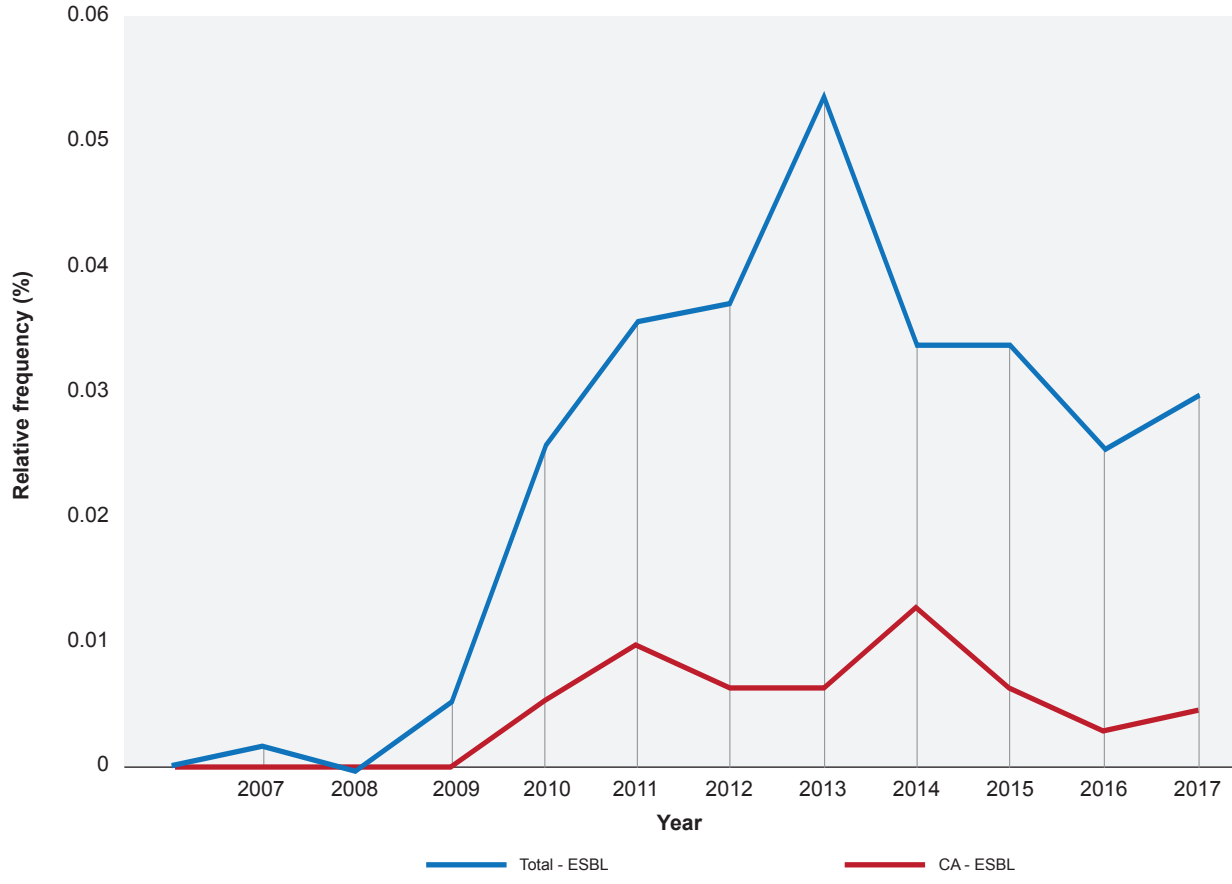

Figure 1 – Relative frequency (%) of community-acquired UTIs caused by ESBL-producing bacteria (2007 to 2017)

Data were recorded and processed through Microsoft Office Excel 2016® software. Descriptive statistical analysis was carried out (median in quantitative variables and relative frequency in nominal variables). Descriptive charts (2D bar charts, 2D line charts) and tabular presentations were used to illustrate the results.

A line chart representing relative frequencies of UTIs caused by ESBL-producing bacteria over time was used to show the changes between 2007 and 2017, while a frequency histogram was used to show the frequency of CA UTIs caused by ESBL-producing bacteria distributed by age cohorts and a bar chart was used to represent the rate of resistance of ESBL-producing bacteria against the antibiotics that were tested.

RESULTS

Relative frequency distribution and trend of CA UTIs caused by ESBL-producing bacteria throughout the study period

A total of 175 UTI episodes caused by ESBL-producing bacteria were diagnosed during the study period, from which 34 (19%) were CA infections. The relative frequencies over time are shown in Fig. 1.

A sustained increase in the total number of UTI episodes caused by ESBL-producing bacteria up to 2013 is worth mentioning (the year in which the maximum value was found), which has remained relatively stable from then onwards. CA UTI episodes caused by these bacteria were initially diagnosed in 2010 and, despite some variability, the numbers remained low and stable over the years, with a median of four episodes/year (maximum of eight in 2014 and minimum of two in 2016).

Demographic and clinical characteristics of the episodes of CA UTI caused by ESBL-producing bacteria

Eighteen episodes involved female patients (53%) and a median two-year and five months median age has been found (range 1 month – 16 years). This was the first UTI episode in 30 (88%) patients and the distribution per age frequency is shown in Fig. 2.

Urine sampling was obtained by middle-stream in 27 (79%) episodes, by bladder catheterisation in six (18%) and suprapubic in one (3%) and all samples were obtained at the Emergency Department.

A diagnosis of acute pyelonephritis was established in 19 (56%) episodes and cystitis in 15 (44%).

Microbiological data

The identification of *E. coli* was obtained in 25 (74%), *K. pneumoniae* in four (12 %), *P. mirabilis* also in four (12%) and *P. vulgaris* in one episode (3%).

Bacterial resistances to different antibiotics are shown in Fig. 3. In vitro susceptibility to carbapenem (meropenem/imipenem) agents has been found in all the episodes and resistance to gentamicin was found in nine episodes (26%). Resistance to co-amoxiclav has been found in eight (47%) out of the 17 episodes in which this was included in the test, while resistance to ciprofloxacin was found in 13 (41%) out of the 32 tested samples.

Treatment and clinical progression of the CA UTI episodes caused by ESBL-producing bacteria

An empirical treatment with cefuroxime axetil was used in 19 (56%) episodes and with co-amoxiclav in 15 (44%), according to the clinical guidelines that are in force at the *Hospital Pediátrico-CHUC*.

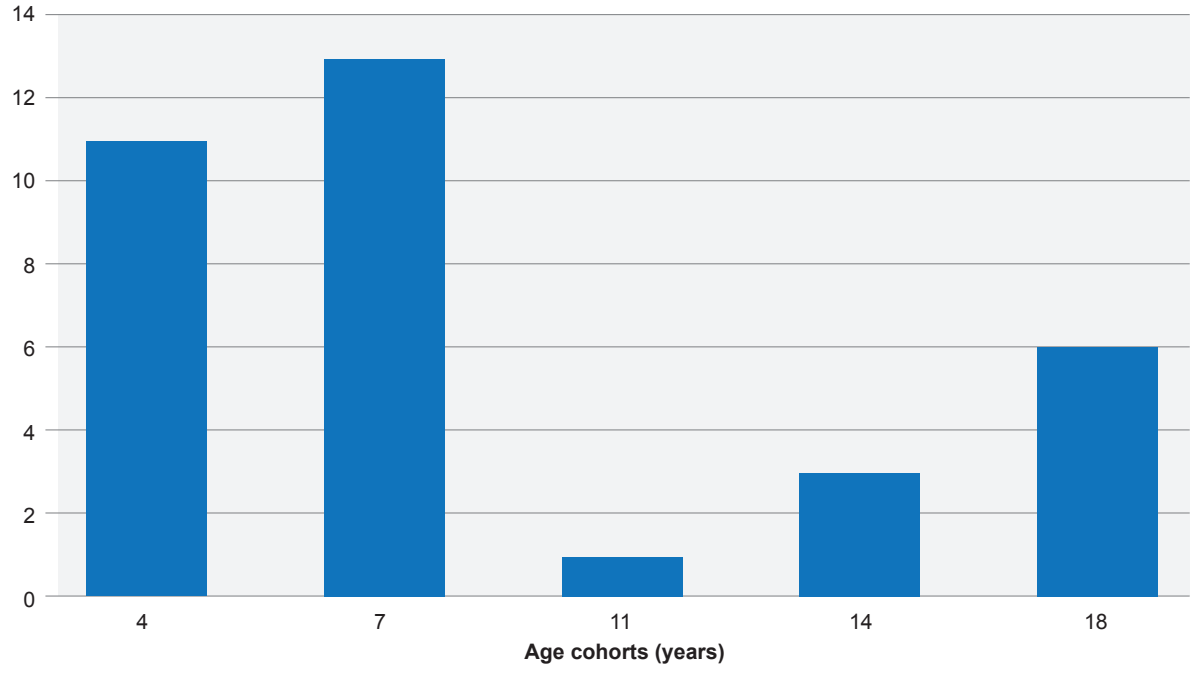

Figure 2 – Frequency histogram. Graphic representation of the frequency of CA-UTIs caused by ESBL-producing bacteria and their distribution by age cohorts

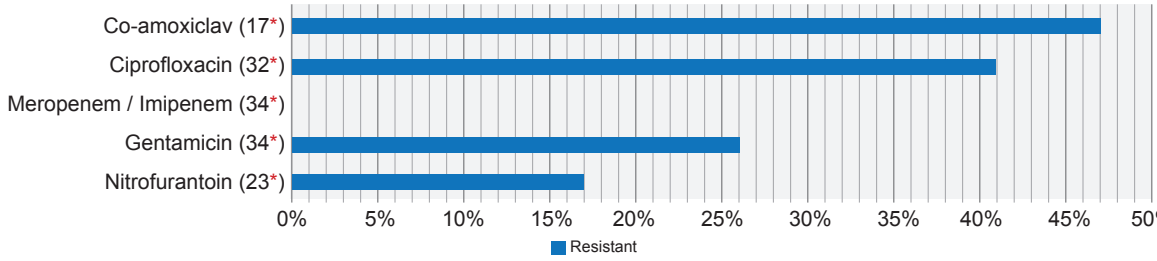

Figure 3 – Resistance rate of ESBL-bacteria to the tested antibiotics
* The number of tested strains for each antibiotic is shown in brackets

Thirty-three patients (97%) were re-evaluated: 30 (91%) were asymptomatic and three (9%) still presented with symptoms; a urine culture was repeated in 24/33 (73%), with a positive result found in three (13%). Clinical outcomes and follow-up cultures are shown in Fig. 4. Considering the three symptomatic cases, two presented with a positive follow-up urine culture and only one patient out of the 21 who were asymptomatic presented with a positive follow-up urine culture.

Three episodes with a positive follow-up urine culture were found, as shown in Table 1, including two patients with symptoms; all were diagnosed with pyelonephritis and were treated with cefuroxime axetil. The initial antibiotic was switched in these two patients: one to cotrimoxazole and the other one to a carbapenem agent (meropenem), with a negative follow-up urine culture and with no symptoms at follow-up.

Four patients presented with a negative follow-up urine culture and their treatment was switched upon knowing the result of the antibiogram: one of the patients was switched to a carbapenem agent due to clinical worsening and the remaining three patients to cotrimoxazole, even though they had no symptoms.

Twenty-seven (96%) patients from the 28 who were treated with β-lactam antibiotics alone were re-examined and all had no symptoms at follow-up.

A hospital-based treatment was required for three patients (all infants) with a mean 4.3-days hospital stay (2-9 days).

No congenital anomalies of the kidneys and urinary tract were found in 30 (88%) patients who were submitted to imaging assessment.

A recurrent UTI episode has been found in 4/34 (12%) patients on follow-up at six months, within the first 30 days upon the initial episode, as shown in Table 2. These patients were treated with β-lactam antibiotics, with clinical and laboratorial resolution after the first episode. Non-ESBL-producing microorganisms were identified in three of these episodes and an ESBL-producing E. coli was isolated in one patient presenting with acute pyelonephritis. The new infection episodes presented with the same diagnosis as those of the initial episode: three patients with acute cystitis and one with acute pyelonephritis.

DISCUSSION

The 10.5-year experience of a paediatric centre in the treatment of CA UTIs caused by ESBL-producing bacteria was shown in this study.

These infections were first found at the Paediatrics Department of the CHUC in 2010 and their number remained relatively stable over the study period. Most patients were treated with non-carbapenem β-lactam antibiotics, with a high clinical and microbiological cure rate and low recurrence rate.

A worrying increase in the identification of ESBL-producing bacteria has been found in the past few years, both regarding healthcare-associated and CA infections. An increasing incidence of UTIs caused by these bacteria has been found in paediatric patients and is a cause for concern regarding antibiotic treatment.[25]

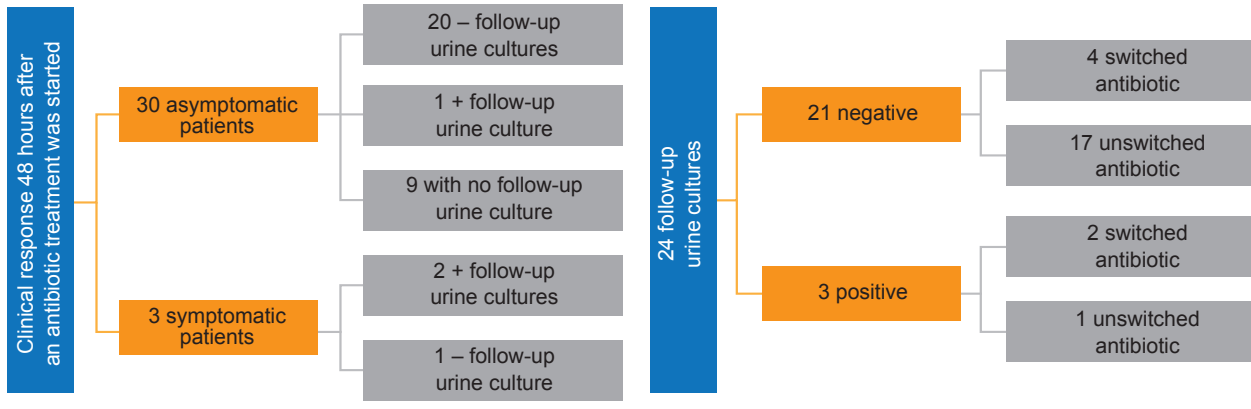

Figure 4 – Clinical outcomes and follow-up urine culture collected 48 hours after an empirical antibiotic treatment was started

Table 1 – Antibiotic treatment and outcomes of patients with positive follow-up urine culture

Isolated bacteria in the first UTI episode	Initial empirical antibiotic treatment	First follow-up urine culture	Antibiotic used	Second follow-up urine culture
Klebsiella pneumoniae	Cefuroxime-axetil	*K. pneumoniae*	Meropenem	Negative
Escherichia coli	Cefuroxime-axetil	*E. coli*	Cotrimoxazol	Negative
Escherichia coli	Cefuroxime-axetil	*E. coli*	Unswitched treatment	Negative

Table 2 – Clinical and microbiological characteristics of the patients presenting with a recurrent UTI episode within the six months following the first episode

Type of UTI	Age (years)	ESBL--producing bacteria in the first UTI episode	Antibiotic treatment used in the first UTI episode	Antibiotic switch in the first UTI episode	Bacteria identified in the second UTI episode	Congenital anomalies of the kidneys and the urinary tract
Cystitis	3	*Proteus mirabilis*	Co-amoxiclav	No	ESBL negative *Klebsiella pneumoniae*	No
Cystitis	13	*Escherichia coli*	Co-amoxiclav	No	ESBL negative *Escherichia coli*	With no imaging assessment
Cystitis	3	*Proteus mirabilis*	Co-amoxiclav	No	ESBL negative *Proteus mirabilis*	With no imaging assessment
Pyelonephritis	15	*Escherichia coli*	Cefuroxime-axetil	No	ESBL negative *Escherichia coli*	No

ESBL: Extended-spectrum ß-lactamases

These infections are more frequent in the Southern and Eastern Europe. According to the Annual Report of the European Antimicrobial Resistance Surveillance Network (EARS-Net) published in 2017, a 16.1% prevalence of E. coli resistant to third-generation cephalosporins has been found in Portugal in the triennium 2013 - 2016, above the European average (12.4%) and showing a 0.4% increase between 2014 and 2016. A 46.7% resistance rate has been found in Portugal as regards invasive *K. pneumoniae* strains, above the 25.7% European average,[12] including strains isolated from both adults and children and caused by healthcare-associated and CA infections.

In a case-control study carried out at the Paediatrics Department - CHUC from 2007 to 2009 aimed at assessing the risk factors and infections caused by healthcare-associated and CA ESBL-producing bacilli, 39.1% (n = 9) regarded UTIs, mostly CA infections (n = 6).[25] A 9.2% prevalence rate of CA UTIs caused by ESBL-producing E. coli has been found in a Spanish study carried out from 2015 to 2016 in children aged 14 years and younger (n = 21/229),[31] while a 1% prevalence rate of ESBL-producing *E. coli* (n = 6/562) and 0.4% of Klebsiella spp. (n = 2/562) have been found in a Israeli paediatric hospital from 2003 to 2010.[32]

The prevalence rate of UTIs caused by ESBL-producing microorganisms was not assessed in this study, even though a 19% (n = 34) rate of CA UTIs caused by ESBL-producing microorganisms has been found. In this group, the ESBL phenotype was more often identified among E. coli strains, in line with other studies.[32]

The risk factors for the colonisation by ESBL-producing microorganisms, as well as the risk factors associated with CA UTIs caused by these bacteria have been described in adults, while data in paediatric patients are scarce. The performance of antibiotic treatment within the last 30 days and the presence of chronic pathology in need for multiple hospital-based treatment were identified as risk factors in the abovementioned case-control study. Invasive ventilation within the last 30 days proved to be an independent risk factor, probably due to an increasing impact on the colonisation with these microorganisms.[25] In a Turkish case-control study carried out from 2004 to 2006, involving children presenting with UTI caused by these bacteria, it was also found that the presence of a chronic illness and hospital admission within the last three months corresponded to independent risk factors for these infections.[33] Recurrent UTI, congenital anomalies of the kidney and the urinary tract, antibiotic prophylaxis with cephalosporins and previous UTIs caused by Klebsiella spp. strains, even with non-ESBL-producing strains were also described as risk factors.[26]

Paediatric UTIs are associated with higher morbidity related both to the acute episode and also to a long-term risk for the development of high blood pressure and chronic kidney disease.[34] Renal scarring affect a small number of patients, yet it is the most important cause of complications.[35] A retrospective cohort study involving a group of patients aged two months to six years with a first or second UTI episode, based on two previous North-American longitudinal studies and with a two-year follow-up, found a relationship between delayed antibiotic therapy in children with febrile UTI and the development of renal scarring.[36]

In this study, the antibiogram results were in line with literature regarding the limited treatment options. Despite the resistance to carbapenems described in several studies,[37,38] we found that all isolated strains were susceptible.

Carbapenem antibiotics are first-line treatment for UTIs caused by ESBL-producing bacteria. However, these should

be used carefully due to an increasing worldwide incidence of carbapenemase-resistant Enterobacteriaceae.[39] One explanation for the development of carbapenemases is that the use of carbapenems induces mutations in bacterial outer membrane proteins, also leading to the selection of β-lactamases capable of hydrolysing them.[37] Prior exposure to antibiotics, mainly cephalosporins, appears to be an independent and consistent risk factor for the emergence of ESBL- and carbapenemase-producing bacteria.[38]

Non-carbapenem antibiotics have been successfully used to treat these infections in adults, with relevant impact on daily clinical practice. Local host defence mechanisms, in addition to high urinary concentrations of some antibiotics that are excreted in urine, have been described by some authors as major facilitators of a favourable outcome.[40,41] However, there are few studies on the use of these antibiotics in paediatric patients for the treatment of UTIs caused by ESBL-producing bacteria.

The minimum inhibitory concentration (MIC) is one of the pharmacodynamic parameters used as indicator for the selection of an antibiotic, even though this is an in vitro parameter. The assessment of the clinical response should also be used in therapeutic decisions upon the use of the antibiotic in vivo.[41]

In a Finnish retrospective study carried out in a tertiary care hospital from 2007 to 2016, including 34 patients under the age of 18 presenting with UTI caused by ESBL-producing bacteria, it was found that 88% (n = 30) of these infections were successfully treated with cephalosporins.[42]

In addition, another retrospective study conducted in Tokyo between 2006 and 2016, including patients presenting with febrile UTI caused by ESBL-producing E. coli, found that 80% of these (n = 12/15) were successfully treated with non-carbapenem antibiotics.[41]

Recently, other non-carbapenem antibiotics such as fosfomycin have been successfully used to treat UTIs caused by ESBL-producing bacteria in adults. A systematic review published in 2010 found favourable clinical outcomes with the use of fosfomycin in patients presenting with cystitis caused by these strains (93.8%, n = 75/80), particularly E. coli strains.[43] Although clinical evidence is still limited, this antibiotic may also be a treatment option in UTIs caused by these microorganisms.

Aminoglycosides have shown variable efficacy, the most promising being amikacin.[44] A 96% cure rate (n = 51/53) has been found in a retrospective study carried out in 2015-2016 in patients aged 2-18 and presenting with cystitis caused by CA ESBL-producing E. coli strains.[45]

A South-Korean retrospective study found no statistically significant differences between children presenting with UTIs caused by ESBL-producing Enterobacteriaceae and treated with non-carbapenem antibiotics (cefotaxime, piperacillin-tazobactam and amikacin) *vs.* carbapenems.[40]

In our study, a 91% clinical cure rate has been found (n = 30/33) with the use of an initial empirical treatment with cefuroxime-axetil (56%) or co-amoxiclav (46%), while a 95% rate of laboratorial cure has been found in those who were submitted to a follow-up urine culture (n = 20/21). Empirical antibiotic therapy was not switched in one patient after knowing the absence of in vitro susceptibility, due to a favourable clinical progression.

Most patients in our group underwent renal and bladder ultrasound imaging and no anomalies of the kidneys and the urinary tract were found.

In this study, four patients presented with a new UTI episode within six months following the first episode. In one of the cases, the new infection was again caused by an ESBL-producing E. coli strain. The empirical antibiotic therapy was not switched in the first episode, as there was a favourable clinical response.

There is very little information on the recurrence rate of these infections, according to the antimicrobial therapy used. A South-Korean retrospective study comparing the outcomes of UTIs caused by ESBL bacteria treated with non-carbapenem *vs.* carbapenem antibiotics over a five-year period found no statistically significant differences in the recurrence of UTIs between both groups.[40]

The fact that only UTI cases with aseptic urine collection and that clinical reassessment occurred in almost all the patients are worth mentioning as strengths of the study, while the fact that it was based on a retrospective analysis, with a relatively small sample should be considered as limitations. In addition, not all the patients in our group underwent a follow-up urine culture.

Based on the results of the study, the local resistances and current scientific knowledge, it seems appropriate to maintain the initial empirical treatment with β-lactam antibiotics as a guideline, with clinical and laboratory control in cases where a resistant microorganism is identified in vitro and the same antibiotic may remain unswitched whenever clinical and laboratory cure occurs.

Microbiological surveillance of these bacteria is a crucial measure and other Portuguese hospitals and patients with risk factors should be included in further studies. The knowledge on the susceptibility to fosfomycin, which was tested in a reduced number of cases, will provide relevant data, as this could be a relevant option in the treatment of cystitis caused by these microorganisms.

CONCLUSION

Around 20% of the UTI caused by ESBL-producing *Enterobacteriaceae* were community-acquired infections affecting patients with no congenital anomalies of the kidneys or the urinary tract, with unchanged prevalence over the years. Despite a small group of patients has been included in the study, the clinical and microbiological outcomes have shown that most of the patients were successfully treated with non-carbapenem β-lactam antibiotics, with a low rate of recurrence within the following six months.

HUMAN AND ANIMAL PROTECTION

The authors declare that the followed procedures were according to regulations established by the Ethics and Clinical Research Committee and according to the Helsinki

Declaration of the World Medical Association.

DATA CONFIDENTIALITY

The authors declare that they have followed the protocols of their work centre on the publication of patient data.

CONFLICTS OF INTEREST

The authors declare that there were no conflicts of interest in writing this manuscript.

FINANCIAL SUPPORT

The authors declare that there was no public or private financial support in writing this manuscript.

REFERENCES

1. Balighian E, Burke M. Urinary tract infection in children. Pedsinreview. 2018;39:3-12.
2. Lagree M, Bontemps S, Dessein R, Angoulvant F, Madhi F, Martinot A, et al. Extended-spectrum β-lactamase-producing Enterobacteriaceae, national study of antimicrobial treatment for pediatric urinary tract infection. Med Mal Infect. 2018;48:193-201.
3. Oliveira G, Saraiva J. Lições de pediatria Vol. I e II. Coimbra: Imprensa da Universidade de Coimbra; 2017.
4. Jacoby GA. Extended-spectrum beta-lactamases and other enzymes providing resistance to oxyimino-beta-lactams. Infect Dis Clin North Am. 1997;11:875-87.
5. Rodríguez-Baño J, Alcalá JC, Cisneros JM, Grill F, Oliver A, Horcajada JP, et al. Community infections caused by extended-spectrum-β-lactamase-producing Escherichia coli. Arch Intern Med. 2008;168:1897-902.
6. Cantón R, Novais A, Valverde A, Machado E, Peixe L, Baquero F, et al. Prevalence and spread of extended-spectrum-β-lactamase-producing Enterobacteriaceae in Europe. Clin Microbiol Infect. 2008;14:S144–53.
7. Calbo E, Romaní V, Xercavins M, Gómez L, Vidal CG, Quintana S, et al. Risk factors for community-onset urinary tract infections due to Escherichia coli harbouring extended-spectrum beta-lactamases. J Antimicrob Chemother. 2006;57:780–78.
8. Lukac PJ, Bonomo RA, Logan LK. Extended-spectrum β-lactamase-producing Enterobacteriaceae in children: old foe, emerging threat. Clin Infect Dis. 2015;60:1389-97.
9. Raymond J, Nordmann P, Doit C, Vu Thien H, Guibert M, Ferroni A, et al. Multidrug-resistant bacteria in hospitalized children: a 5-year multicenter study. Pediatrics. 2007;119:e798-803.
10. Park SY, Kang CI, Wi YM, Chung DR, Peck KR, Lee NY, et al. Risk factors and molecular epidemiology of community-onset, multidrug resistance extended-spectrum β-lactamase-producing. Korean J Intern Med. 2017;32:146-57.
11. Flokas ME, Detsis M, Alevizakos M, Mylonakis E. Prevalence of ESBL-producing Enterobacteriaceae in paediatric urinary tract infections: a systematic review and meta-analysis. J Infect. 2016;73:547-57.
12. European Centre for Disease Prevention and Control. Antimicrobial Resistance Surveillance in Europe 2016. Annual Report of the European Antimicrobial Resistance Surveillance Network (EARS-Net). [consultado 2018 nov 5]. Disponível em: https://ecdc.europa.eu/en/publications-data/antimicrobial-resistance-surveillance-europe-2015.
13. Logan LK, Braykov NP, Weinstein RA, Laxminarayan R; CDC Epicenters Prevention Program. Extended-spectrum β-lactamase–producing and third-generation cephalosporin-resistant Enterobacteriaceae in children: trends in the United States, 1999–2011. J Pediatric Infect Dis Soc. 2014;3:320–8.
14. Martin D, Fougnot S, Grobost F, Thibaut-Jovelin S, Ballereau F, Gueudet T, et al. Prevalence of extended-spectrum beta-lactamase producing Escherichia coli in community-onset urinary tract infections in France in 2013. J Infect. 2016;72:201-6.
15. Leistner R, Schröder C, Geffers C, Breier AC, Gastmeier P, Behnke M. Regional distribution of nosocomial infections due to ESBL-positive Enterobacteriaceae in Germany: data from the German National Reference Center for the Surveillance of Nosocomial Infections (KISS). Clin Microbiol Infect. 2015;21:255.e1-5.
16. Nieminen O, Korppi M, Helminen M. Healthcare costs doubled when children had urinary tract infections caused by extended-spectrum β-lactamase-producing bacteria. Acta Paediatr. 2017;106:327-33.
17. Flokas ME, Karanika S, Alevizakos M, Mylonakis E. Prevalence of ESBL-producing enterobacteriaceae in pediatric bloodstream infections: a systematic review and meta-analysis. PLoS One. 2017;12:e0171216.
18. Blomberg B, Jureen R, Manji KP, Tamim BS, Mwakagile DS, Urassa WK, et al. High rate of fatal cases of pediatric septicemia caused by gram-negative bacteria with extended-spectrum beta-lactamases in Dar es Salaam, Tanzania. J Clin Microbiol. 2005;43:745-9.
19. Apisarnthanarak A, Hsu LY, Khawcharoenporn T, Mundy LM. Carbapenem-resistant Gram-negative bacteria: how to prioritize infection prevention and control interventions in resource-limited settings? Expert Rev Anti Infect Ther. 2013;11:147-57.
20. Aris P, Boroumand MA, Rahbar M, Douraghi M. The activity of fosfomycin against extended-spectrum beta-lactamase-producing isolates of enterobacteriaceae recovered from urinary tract infections: A single-center study over a period of 12 years. Microb Drug Resist. 2018;24:607-12.
21. Liu HY, Lin HC, Lin YC, Yu SH, Wu WH, Lee YJ. Antimicrobial susceptibilities of urinary extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella pneumoniae to fosfomycin and nitrofurantoin in a teaching hospital in Taiwan. J Microbiol Immunol Infect. 2011;44:364-8.
22. Doi A, Shimada T, Harada S, Iwata K, Kamiya T. The efficacy of cefmetazole against pyelonephritis caused by extended-spectrum beta-lactamase-producing Enterobacteriaceae. Int J Infect Dis. 2013;17:e159-6.
23. Asakura T, Ikeda M, Nakamura A, Kodera S. Efficacy of empirical therapy with non-carbapenems for urinary tract infections with extended-spectrum beta-lactamase-producing Enterobacteriaceae. Int J Infect Dis. 2014;29:91-5.
24. Álvarez J, Rojas Á, Carvajal C, Revello J, Meza P, Guggiana P, et al. Evaluación de susceptibilidad y respuesta al tratamiento con piperacilina/tazobactam en pacientes con infecciones por Escherichia coli productoras de β-lactamasas de espectro extendido (BLEE) CTX-M. Rev Chilena Infectol. 2018;35:343-50.
25. Dias A, Oliveira G, Oliveira H, Marques M, Rodrigues F. Bacilos gram negativos produtores de ß-lactamases de espectro expandido num hospital pediátrico. Acta Med Port. 2011;24:S197-206.
26. Dayan N, Dabbah H, Weissman I, Aga I, Even L, Glikman D. Urinary tract infections caused by community-acquired extended-spectrum β-lactamase-producing and nonproducing bacteria: a comparative study. J Pediatr. 2013;163:1417-21.
27. Haverkate MR, Platteel TN, Fluit AC, Cohen Stuart JW, Leverstein-van Hall MA, Thijsen SF, et al. Quantifying within-household transmission of extended-spectrum β-lactamase-producing bacteria. Clin Microbiol Infect. 2017;2346.e1-.e7.
28. Herindrainy P, Rabenandrasana MA, Andrianirina ZZ, Rakotoarimanana FM, Padget M, de Lauzanne A, et al. Acquisition of extended spectrum beta-lactamase-producing enterobacteriaceae in neonates: a community based cohort in Madagascar. PLoS One. 2018;13:e0193325.
29. Direção-Geral de Saúde. Diagnóstico e tratamento da infeção do trato urinário em idade pediátrica. Norma nº 8, 2012. Lisboa: DGS: 2012.
30. Reaffirmation of AAP Clinical Practice Guideline: The Diagnosis and Management of the Initial Urinary Tract Infection in Febrile Infants and Young Children 2-24 Months of Age. Pediatrics. 2016;138:e20163026.
31. Pérez Heras I, Sanchez-Gomez JC, Beneyto-Martin P, Ruano-de-Pablo L, Losada-Pinedo B. Community-onset extended-spectrum β-lactamase producing Escherichia coli in urinary tract infections in children from 2015 to 2016: prevalence, risk factors, and resistances. Medicine. 2017;96:e8571.
32. Sakran W, Smolkin V, Odetalla A, Halevy R, Koren A. Community-acquired urinary tract infection in hospitalized children: etiology and antimicrobial resistance. A comparison between first episode and recurrent infection. Clin Pediatr). 2015;54:479-83.
33. Topaloglu R, Er I, Dogan BG, Bilginer Y, Ozaltin F, Besbas N, et al. Risk factors in community-acquired urinary tract infections caused by ESBL-

producing bacteria in children. Pediatr Nephrol. 2010;25:919-25.
34. Stein R, Dogan HS, Hoebeke P, Kočvara R, Nijman RJ, Radmayr C, et al. Urinary tract infections in children: EAU/ESPU guidelines. Eur Urol. 2015;67:546-58.
35. Westwood ME, Whiting PF, Cooper J, Watt IS, Kleijnen J. Further investigation of confirmed urinary tract infection (UTI) in children under five years: a systematic review. BMC Pediatr. 2005;5:2.
36. Shaikh N, Mattoo TK, Keren R, Ivanova A, Cui G, Moxey-Mims M, et al. Early antibiotic treatment for pediatric febrile urinary tract infection and renal scarring. JAMA Pediatr. 2016;170:848-54.
37. Tamma PD, Rodriguez-Bano J. The use of noncarbapenem β-lactams for the treatment of extended-spectrum β-lactamase infections. Clin Infect Dis. 2017;64:972-80.
38. Marchaim D, Chopra T, Bhargava A, Bogan C, Dhar S, Hayakawa K, et al. Recent exposure to antimicrobials and carbapenem-resistant Enterobacteriaceae: the role of antimicrobial stewardship. Infect Control Hosp Epidemiol. 2012;33:817-30.
39. Han SB, Lee SC, Lee SY, Jeong DC, Kang JH. Aminoglycoside therapy for childhood urinary tract infection due to extended-spectrum β-lactamase-producing Escherichia coli or Klebsiella pneumoniae. BMC Infect Dis. 2015;15:414.
40. Lee B, Kang SY, Kang HM, Yang NR, Kang HG, Ha IS, et al. Outcome of antimicrobial therapy of pediatric urinary tract infections caused by extended-spectrum β-lactamase-producing enterobacteriaceae. Infect Chemother. 2013;45:415-21.
41. Abe Y, Inan-Erdogan I, Fukuchi K, Wakabayashi H, Ogawa Y, Hibino S, et al. Efficacy of non-carbapenem antibiotics for pediatric patients with first febrile urinary tract infection due to extended-spectrum beta-lactamase-producing Escherichia coli. J Infect Chemother. 2017;23:517-22.
42. Vakkilainen S, Pätäri-Sampo A, Saxén H. Outcome of children with ESBL-E. coli acute pyelonephritis treated with cephalosporins. J Infect. 2018;77:75-81.
43. Falagas ME, Kastoris AC, Kapaskelis AM, Karageorgopoulos DE. Fosfomycin for the treatment of multidrug-resistant, including extended-spectrum beta-lactamase producing, Enterobacteriaceae infections: a systematic review. Lancet Infect Dis. 2010;10:43-50.
44. Madhi F, Jung C, Timsit S, Levy C, Biscardi S, Lorrot M, et al. Febrile urinary-tract infection due to extended-spectrum beta-lactamase-producing Enterobacteriaceae in children: a French prospective multicenter study. PLoS One. 2018;13:e0190910.
45. Polat M, Kara SS. Once-daily intramuscular amikacin for outpatient treatment of lower urinary tract infections caused by extended-spectrum β-lactamase-producing. Infect Drug Resist. 2017;10:393-9.