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Svetlana Vakkilainen , Anu Pätäri-Sampo , Harri Saxén

PII: S0163-4453(18)30126-9
DOI: 10.1016/j.jinf.2018.03.009
Reference: YJINF 4090

To appear in: *Journal of Infection*

Received date: 16 March 2018
Accepted date: 17 March 2018

Please cite this article as: Svetlana Vakkilainen , Anu Pätäri-Sampo , Harri Saxén , Outcome of children with ESBL-E. coli acute pyelonephritis treated with cephalosporins, *Journal of Infection* (2018), doi: 10.1016/j.jinf.2018.03.009

Title page

Outcome of children with ESBL-*E. coli* acute pyelonephritis treated with cephalosporins

1) Svetlana Vakkilainen, Children's Hospital, University of Helsinki and Helsinki University Hospital, Helsinki, Finland, svetlanakostjukovitch@gmail.com
2) Anu Pätäri-Sampo, Department of Clinical Microbiology, University of Helsinki and Helsinki University Hospital, HUSLAB, Helsinki, Finland, anu.patari-sampo@hus.fi
3) Harri Saxén, Children's Hospital, University of Helsinki and Helsinki University Hospital, Helsinki, Finland, harri.saxen@hus.fi

* Address all correspondence and requests for reprints to:

Svetlana Vakkilainen; Children's Hospital, Helsinki University Hospital; Stenbäckinkatu 11, PL 281, 00029 HUS, Helsinki, FINLAND, E-mail: svetlanakostjukovitch@gmail.com, Tel. +358 50 427 2994, Fax. 09 471 76712.

Keywords: extended-spectrum beta-lactamase, Escherichia coli, multidrug resistance, urinary tract infections.

Running title: Cephalosporins for ESBL-*E. coli* pyelonephritis

Abstract

Background. Some reports have demonstrated surprising efficacy of cephalosporins in acute pyelonephritis (APN) caused by extended-spectrum beta-lactamase (ESBL)-producing bacteria.

Methods. We analyzed clinical and microbiological data of pediatric ESBL-APN patients treated empirically with cephalosporins. APN was defined as a combination of fever, pyuria >50 x10*6/l, bacteriuria, abnormal C-reactive protein (CRP) and no signs of other focus of infection. For a subgroup of children with no co-morbidities, we selected age- and gender-matched controls with APN caused by a non-ESBL Escherichia coli to compare outcomes.

Results. The study group consisted of 34 children with ESBL-APN (13 boys and 21 girls, median age 1.0 years, range 0.1-9.0 years). The majority of children (88%, 30/34) recovered clinically on the empiric suboptimal antibiotic therapy, being afebrile at ≤48 hours of treatment. Microbiological recovery was documented in seven patients while on therapy with suboptimal antibiotics (64%, 7/11). CRP kinetics, duration of hospitalization, clinical recovery and recurrence rates were similar in children with no co-morbidities in ESBL-APN (n=27) and non-ESBL-APN (n=27) groups.

Conclusions. Most children with ESBL-APN recovered on empiric therapy with cephalosporins. Clinical recovery, duration of hospitalization and recurrence rates were similar in ESBL- and non-ESBL-APN groups of children.

Dear Editor,

We read with interest the recent publication by Moxon and Paulus, outlining the management of infections with *Enterobacteriaceae* producing extended-spectrum beta-lactamase (ESBL) [1]. Treatment options for pediatric ESBL infections often remain limited to carbapenems. We present evidence for the successful use of cephalosporins in the treatment of pediatric acute pyelonephritis caused by ESBL-producing *E. coli* (ESBL-APN). In addition, we report for the first time successful oral treatment of ESBL-APN with the first generation cephalosporins.

This retrospective study was conducted at the tertiary Children's Hospital, Helsinki University Hospital, Finland and was approved by the Institutional Research Board. We used microbiological surveillance system and detected 136 patients aged 0-18.0 years with urine cultures positive for ESBL-*Enterobacteriaceae* during 1.1.2007-31.12.2016. Of them, we selected only children with APN into subsequent analysis (n=37). We defined APN as a combination of fever, pyuria >50 x10*6/l, bacteriuria, abnormal C-reactive protein (CRP) and no signs of other focus of infection. We then excluded three individuals who had received empirical meropenem, ciprofloxacin and piperacillin-tazobactam. The study group thus consisted of 34 patients (13 boys, 21 girls; median age 1.0 years, range 0.1-9.0 years).

All urine samples were obtained for culture at the hospital and collected into BD Vacutainer® Preservative tubes (Becton Dickinson and Company, Franklin Lakes, New Jersey, USA). Urine samples were collected from either urine bags (n=17) or voided midstream (n=17), and in most children (71%, 24/34) two subsequent samples were obtained prior to commencement of antibacterials. Standard urine culture was performed. *E. coli* was detected in urine samples of all children, and one patient was co-infected with non-ESBL *Klebsiella pneumonia*. All blood cultures remained negative. Antimicrobial susceptibility categorization was done by disc testing (Oxoid, Cambridge, UK) according to the EUCAST methodology and clinical breakpoints for SIR interpretation (www.eucast.org). Of the tested *E. coli* isolates, 100% (34/34) demonstrated susceptibility to carbapenems and to fosfomycin (19/19), 94% (32/34) to nitrofurantoin, 88% (29/33) to netilmycin, 64% (21/33) to tobramycin, 63% (17/27) to ciprofloxacin and 29% (10/34) to trimethoprim-sulfamethoxazole. The ESBL production was confirmed with a combination disc test according to the manufacturer (Mast Group, Bootle, UK).

The majority of children (79%, 27/34) presented with the first-time UTI and had no co-morbidities and no abnormalities on urinary tract ultrasound. Others had a documented history of previous UTI (n=4), structural abnormalities of the urinary tract (n=3), kidney transplants (n=2), and neurogenic bladder (n=1).

Fifteen children (44%, 15/34) were treated as inpatients and their mean duration of hospitalization was 4.3 days (standard deviation (SD) 2.71 days). Initial empiric therapy included oral cefalexin (n=9, 27%), intravenous (i/v) cefuroxime (n=12, 35%) or parenteral ceftriaxone (n=13, 38%). After the data on antimicrobial susceptibility became available, patients were treated with either oral nitrofurantoin (n=11), carbapenems (n=7), oral trimethoprim-sulfamethoxazole (n=5), oral ciprofloxacin (n=4) or i/v netilmycin (n=2). The therapy of five patients was not changed, despite the microbiological resistance data.

The majority of patients (88%, 30/34) recovered clinically while receiving empiric cephalosporin therapy. Clinical recovery was defined as defeverscence in ≤ 48 hours. Of the remaining four patients who defeverced within 72 hours, three had their therapy switched according to the microbiological resistance data, while one continued to receive oral cefalexin.

Altogether, two children (6%) experienced a recurrence caused by ESBL-*E. coli*, 2 and 4 weeks after the initial ESBL-APN episode. One of them had received ertapenem as the definitive treatment of the initial ESBL-APN episode (first treated empirically with i/v ceftriaxone), while other had been treated with oral cefalexin only. Control urine samples were obtained in 59% (20/34) of patients from three days to four weeks after the commencement of therapy. Of these 20 samples, 15 tested (75%) negative and five (25%) were positive for ESBL-*E. coli*. However, despite positive cultures, 2 of the 5 samples showed no pyuria and leukocyte counts were low (6-7 cells x10*6/l) in another 2 samples. Seven patients (64%, 7/11) demonstrated microbiological recovery while still on inappropriate therapy.

Subgroup of children with no co-morbidities. For the 27 children with first-time APN and with no co-morbidities, we selected 27 controls with non-ESBL-APN who were matched for age, gender and the absence of co-morbidities. *Supplementary Table 1* presents the comparison of their clinical, laboratory and outcome data, while *Figure 1* demonstrates the rates of clinical and microbiological recovery in patients

and controls. Ethnic background differed significantly among patients and controls, as more patients of non-Finnish origin had ESBL-APN (p=0.001). The rate of clinical recovery appeared identical in both groups, which is in conjunction with previous studies [2]. Recurrences were actually more common in the non-ESBL-APN group (4/27 vs 1/27 in ESBL-APN group). The mean duration of hospitalization was 3.0 days (SD 1.48 days) in patients with ESBL-APN (n=11) and 2.8 (SD 1.14 days) in those with non-ESBL-APN (n=10, p=0.731). The kinetics of CRP appeared similar in both groups (see *Supplementary Figure 1*).

The good response to cephalosporins in the therapy of ESBL-*E. coli* APN can be partly explained by the high concentration of cephalosporins in urine [3]. Furthermore, some children with UTI may be able to control the infection spontaneously and recover without proper treatment, as has been shown in some patients with bacterial pneumonia [4].

We acknowledge that the retrospective nature of our study complicated the appropriate follow-up of the patients. It is possible, but unlikely, that recurrences may have been treated in other hospitals. Further, the relatively small number of patients resulted from the low prevalence of ESBL in Finland. Blood cultures were negative in all our patients, thus our results should not be extrapolated to children with severe bacteremic ESBL-APN. In addition, empiric therapy was changed in many patients after the microbiological susceptibility data became available, thus the definitive therapy may have affected the rate of recurrences.

In conclusion, children with APN caused by ESBL-*E. coli* showed good response to suboptimal cephalosporin therapy. We do not recommend treating ESBL-APN with cephalosporins, however, if such patients have been cured with this therapy, further parenteral treatment with broad-spectrum antibiotics such as carbapenems may not be necessary.

Abbreviations

CRP C-reactive protein

ESBL extended-spectrum beta-lactamase

ESBL-APN acute pyelonephritis caused by ESBL-producing bacteria

i/v intravenous

SD standard deviation

UTI urinary tract infections

Funding

No funding was obtained for this study.

Conflict of Interest

All authors: no conflicts.

Acknowledgments

We acknowledge the help of infection control nurse Leena Simons in retrieving data from microbiological surveillance system.

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Figure legends

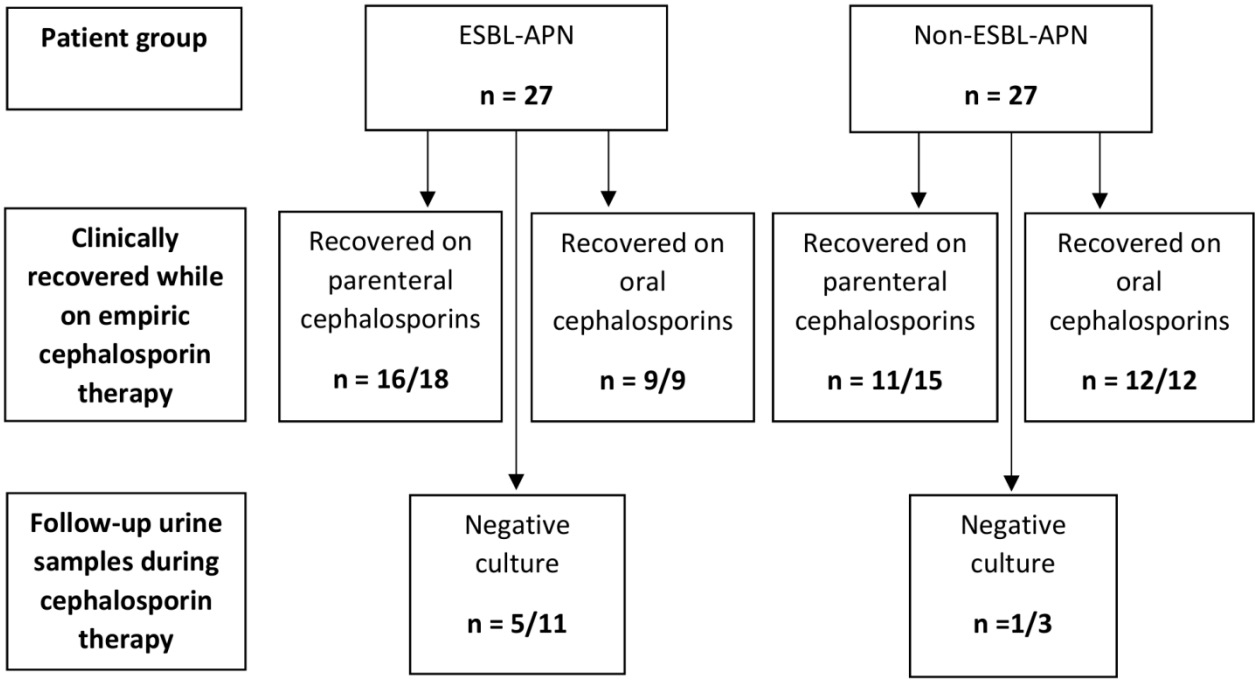

Figure 1. Clinical and microbiological recovery rates in the study patients while on inappropriate empiric therapy with cephalosporins. Subgroup of patients with acute pyelonephritis (APN) caused by extended-spectrum beta-lactamase producing (ESBL)-*E. coli* and with no co-morbidities is compared to their age- and gender-matched controls with non-ESBL-*E. coli* APN.

ESBL-APN = acute pyelonephritis caused by extended-spectrum b-lactamase producing *E. coli*; n=number.