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treated with cephalosporins

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Letter to the Editor

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

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 x 10^6/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 antibiotics. 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 defervesence in ≤ 48 h. Of the remaining four patients who defevered within 72 h, 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 x 10^6/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 Fig. 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 Fig. 1).

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.
The good response to cefalosporins in the therapy of ESBL-E. coli APN can be partly explained by the high concentration of cephalosporins in urine. 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.

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 cefalosporin therapy. We do not recommend treating ESBL-APN with cefalosporins, however, if such patients have been cured with this therapy, further parenteral treatment with broad-spectrum antibiotics such as carbapenems may not be necessary.

Funding

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Conflict of Interest

All authors: no conflicts.

Acknowledgments

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jinf.2018.03.009.

References


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Leprosy in the Pisan fresco “Triumph of Death” (1336–1341)

In current times leprosy is a disease widespread especially in the tropical and sub-tropical environments of developing countries\(^1\), where it still represents a relevant public health problem. However, in the past this disease also involved the European territory. During the 12–14th centuries, leprosy had a remarkable diffusion in the Western World at the time of Crusades. The large number of leprosaria founded almost all over Europe, and the osteoarchaeological cases of leprosy, are eloquent evidences of the well-established presence of the disease in late Medieval Europe.\(^2\)

Although leprosy is characterised by a low grade of infectivity, in Medieval collective imagery its deforming impact on the body raised terror and repugnance towards the patients affected. Lepers were a sort of living dead, considered unclean or morally corrupt by Medieval society. They had to wear special clothes, to carry a bell announcing their presence, and they were segregated in lazaret houses outside the urban centres.\(^3\)

Leprosy, or Hansen’s disease, is a chronic infection caused by Mycobacterium leprae, characterised by involvement of skin, mucous membranes, and nerves. The disease has been classified into a number of clinical types, the most severe of which is its lepromatous form, in which the immune response is poor. Transmission occurs through the airborne spread of nasal secretion.

The organism has a predilection for the cooler parts of the body and, therefore, the most affected regions are the nose and the extremities. The result is deformity of the face with resorption of the nasal cartilage and loss of sensory perception in the fingers and toes. Peripheral anaesthesia can lead to the atrophy of muscle activity with resorption of the tubular bones of hands and feet, which can eventually fall off for secondary infections or involuntary trauma. Lesions can also affect the conjunctivae, causing keratitis, iridocyclitis, up to blindness.\(^4\)

Medieval iconography is not exempt from representations of lepers which, even so, are generally very stereotyped, with the disease simply symbolised through dots spread over the body.\(^5\) However, a famous Tuscan fresco of the first half of the 14th century offers the first realistic representation of the disease (Fig. 1).

The “Triumph of Death” of the Monumental Cemetery of Pisa, a pictorial masterpiece of Italian Medieval art dated back to the years 1336–1341, is attributed to Buonamico Bufalumacco.\(^6\) In the fresco, which occupies a wall of 5.6 × 15 m, the author follows a pictorial address characterised by expressionist realism. In the centre of the scene Death, personified in a sort of winged demon with bat wings and sickle, and about to invest a group of wealthy young people on the right, totally ignores a bunch of beggars on the left of the fresco, who invoke her as the liberation of their sorrows. A cartouche, almost a comic, gives voice to the group of beggars, who thus reproach the Grim Reaper: “As prosperity has left us, oh Death, medicine of all evil, come and give us the last supper”.

Among the group of beggars who invoke death as extreme consolation to their disasters, the figure of a leper is clearly defined, appearing as an individual with the typical Facies leprosa. The man shows atrophy of the nasal region where the nasal cartilage is totally lacking, and probably blindness, since the eye is without the pupil and seems obscured. The upper limbs, stretched towards Death, appear as two stumps totally deprived of the hands at the level of the wrists. Another beggar in the group appears blind, with his eyes covered by a bandage, and his right hand reduced to a stump, wrapped in a rag closed by a string at the wrist. It is in both cases the iconographic description of a rather typical and advanced stage of the pathology.

Leprosy constitutes a sort of archetypal disease for the Medieval world; the leper is seen as a shameful being, struck by a disease that is a kind of divine curse. In the case of Pisa, we observe a diascopic representation, like a figurative sermon that fits well with the search for greater realism aimed at impressing the observer: in the fresco the leper is the exemplar model of the sinner.\(^7\)

The remarkable fact that distinguishes the lepers of the cemetery of Pisa is, indeed, the highly realistic style of representation for the first time so accentuated in Western art, as the result of a probably direct observation of the disease, and not a stereotyped figuration, as Medieval art has usually been up to that time.

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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.

\(^1\) Funding: None.

\(^2\) Declarations of interest: None

\(^3\) Authorship: All authors had access to the data and played a role in writing this manuscript.
Fig. 1. "The Triumph of Death" of Buonamico Bufalìmacco in the Monumental Cemetery of Pisa (years 1336–1441). Particular of the group of beggars with two lepers [The photographic reproduction is taken from the photo library of the Federico Zeri Foundation].

References


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**What is the criterion of ‘high’ pentraxin-3 (PTX-3) cutoff in patients with sepsis?**

Dear Editors

We read with great interest, the recently published meta-analysis by Lee et al., who concluded that pentraxin-3 (PTX-3) significantly predicted disease severity and mortality in sepsis. However, we wish to raise some questions about the study.

First, Lee et al. aimed to evaluate the predictive value of PTX-3 in the population with sepsis; however, some studies analyzed in the meta included patients who were not septic, the predictive values of PTX-3 from the non-septic population were not separated from the whole population, thus we were afraid that biases may exist and make the final result inaccurate.

Second, Lee et al. claimed they searched PubMed and EMBASE for eligible studies by using the following terms: [pentraxin-3 mortality sepsis]. However, we are afraid that this search strategy may not be systematic or accurate, some important researches may be missed. For example, one study investigated the predictive value of PTX-3 in the septic population and could be retrieved in the Pubmed, but it had not been incorporated into the meta-analysis though it should be.

Third, some data in the meta-analysis need to be checked again in Table 1, the unit of following up time should be day rather than month. The sample size of the population with cirrhosis in Fan’s study should be 156 (48 ± 108) rather than 277, while the sample size of the population with acute kidney injury in critically ill in Schilder’s study should be 42 rather than 13, the number of males in Bastrup-Birk’s study should be 139 rather than 138, and so on.

Fourth, in Fig. 1 of the meta, the difference in means/median of the study by Huttunen et al. should be 41.5 rather than 38.4 as the latter value was the difference in maximum value between the survivors and non-survivors. In Fig. 2, the lower limit and upper limit of 95% confidence interval (CI) of hazard ratio (HR) for high PTX-3 levels and risk of mortality in Kim et al. study should be (2.46, 15.85) rather than (2.82, 18.17). Besides, odds ratio (OR) is totally different from hazard ratio (HR), the authors of the meta may mix up the two notions (OR and HR) in the study carried by Wagenaar et al. in Fig. 2.

Fifth, there is no clear definition and limit for “more severe sepsis and less severe sepsis” in the meta-analysis, it can be several different compared groups such as “severe sepsis and sepsis”, “septic shock and severe sepsis” and “septic shock and sepsis” which can cause variable results if not specified as two specific groups. Besides, Fig. 2 lists the studies which investigate the relationship between ‘high’ PTX-3 and risk of mortality. Nevertheless, there are different criterion of ‘high’ PTX-3 value in different studies in the meta-analysis, varying from 3.35 ng/ml to 140 ng/ml, obviously, ‘high’ PTX-3 concentration in one study may be deemed as ‘low’ in others studies, different cutoffs of ‘high’ PTX-3 should have different predictive value for death, so we suggest the authors provide a unified criterion for ‘high’ PTX-3 value or just indicate different cutoff of ‘high’ PTX-3 in each study.

Sixth, systemic levels of PTX3 are well known to be influenced by the age of the patients and underlying disease, as this meta-analysis contains adult and pediatric studies together and infectious diseases in different severity, we strongly suggest the authors carry out subgroup analysis according to the age and the severity of illness.

Finally, we appreciate Lee et al. for their innovative work, but further rigorous validating studies are still needed.

**Conflict of interest**

The authors declare that there are no conflicts of interest.

**Financial support**

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**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; (PTX-3), pentraxin-3; (CI), confidence interval; (HR), hazard ratio; (OR), odds ratio.

**The work of this submission was conducted at the Emergency Department, Guangdong Provincial Hospital of Chinese Medicine, Guangzhou, 510120, China.**
### Table 1
Characteristics of the nine studies included in this meta-analysis.

<table>
<thead>
<tr>
<th>First author/year</th>
<th>Population</th>
<th>Sample size (n)</th>
<th>Age (yrs)</th>
<th>SD</th>
<th>No. of males</th>
<th>Follow-up (months)</th>
<th>Variables in multivariate model</th>
<th>Ref.</th>
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</thead>
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<td>Jie (2017)</td>
<td>ICU septic shock</td>
<td>112</td>
<td>59</td>
<td>20</td>
<td>55</td>
<td>28</td>
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<td>Kim (2017)</td>
<td>Sepsis</td>
<td>83</td>
<td>71</td>
<td>10</td>
<td>47</td>
<td>28</td>
<td></td>
<td>13</td>
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<tr>
<td>Caironi (2016)</td>
<td>Severe sepsis</td>
<td>958</td>
<td>70</td>
<td>15</td>
<td>563</td>
<td>90</td>
<td></td>
<td>8</td>
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<tr>
<td>Hansen (2016)</td>
<td>Necrotizing soft tissue infections</td>
<td>135</td>
<td>61</td>
<td>13</td>
<td>84</td>
<td>510</td>
<td>ICU stay, hypotension, use of vaspressors, acute renal insufficiency, disseminated intravascular coagulation, decreased Glasgow Coma Scale, need of mechanical ventilation, severe sepsis, MOF, plasma CRP levels, plasma procalcitonin levels, white cell count, platelet count APACHE II score, CPIS, SOFA score, PO2/FiO2, creatinine, plasma levels of CRP on day of admission</td>
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<td>Fan (2016)</td>
<td>Cirrhosis</td>
<td>277</td>
<td>54</td>
<td>26</td>
<td>139</td>
<td>90</td>
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<td>Schilder (2015)</td>
<td>Acute kidney injury in septicemia</td>
<td>13</td>
<td>70</td>
<td>45</td>
<td>7</td>
<td>30</td>
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<td>Acute leukaemia in septicemia</td>
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<td>39</td>
<td>7</td>
<td>28</td>
<td>3</td>
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<td>Akin (2014)</td>
<td>Neonatal sepsis</td>
<td>28</td>
<td>0.6</td>
<td>0.1</td>
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<td>–</td>
<td>(Univariate)</td>
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<td>Bastrup-Birk (2013)</td>
<td>Systemic inflammatory</td>
<td>261</td>
<td>63</td>
<td>18</td>
<td>138</td>
<td>873</td>
<td>Age and sex</td>
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<td>Uusitalo-Seppälä (2013)</td>
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<td>64</td>
<td>21</td>
<td>310</td>
<td>365</td>
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<td>Lin (2013)</td>
<td>Ventilator-associated pneumonia</td>
<td>136</td>
<td>64</td>
<td>12</td>
<td>80</td>
<td>28</td>
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<td>Bacteraemia</td>
<td>132</td>
<td>62</td>
<td>19</td>
<td>70</td>
<td>30</td>
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<td>61</td>
<td>15</td>
<td>56</td>
<td>28</td>
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<td>Severe leptospirosis</td>
<td>52</td>
<td>45</td>
<td>17</td>
<td>37</td>
<td>14</td>
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<td>Sprong (2009)</td>
<td>Severe meningococcia disease</td>
<td>26</td>
<td>3</td>
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<td>Muller (2001)</td>
<td>Critically ill (SIRS, sepsis, severe sepsis, septic shock)</td>
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#### Mean difference of PTX-3: non-survivors vs. survivors

<table>
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<tr>
<th>Study name</th>
<th>Difference in means</th>
<th>Standard error</th>
<th>Variance</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>Z-Value</th>
<th>p-Value</th>
<th>Difference in means 95% CI</th>
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<td>Jie, 2017</td>
<td>63.900</td>
<td>6.717</td>
<td>45.120</td>
<td>50.736</td>
<td>77.096</td>
<td>9.513</td>
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<td>Kim, 2017</td>
<td>164.000</td>
<td>18.846</td>
<td>365.184</td>
<td>127.962</td>
<td>201.838</td>
<td>8.760</td>
<td>0.000</td>
<td>(Univariate)</td>
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<td>46.000</td>
<td>7.940</td>
<td>61.469</td>
<td>28.635</td>
<td>60.365</td>
<td>5.740</td>
<td>0.000</td>
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<td>139.300</td>
<td>23.990</td>
<td>570.251</td>
<td>92.496</td>
<td>186.104</td>
<td>5.633</td>
<td>0.000</td>
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<td>15.287</td>
<td>250.459</td>
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<td>0.668</td>
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<td>4.847</td>
<td>8.760</td>
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<td>5.035</td>
<td>0.000</td>
<td>(Univariate)</td>
</tr>
</tbody>
</table>

**Fig. 1.** Mean difference of PTX-3: non-survivors vs. survivors.
Fig. 2. High PTX-3 levels and risk of mortality.

References


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