Infection and Drug Resistance

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ORIGINAL RESEARCH

Cefuroxime compared to piperacillin/tazobactam as empirical treatment of *Escherichia coli* bacteremia in a low Extended-spectrum beta-lactamase (ESBL) prevalence cohort

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Objectives: On January 18, 2010, a part of the capital region of Denmark shifted the empirical treatment of febrile conditions from cefuroxime to piperacillin/tazobactam. We compare empirical treatment with piperacillin/tazobactam versus cefuroxime for *Escherichia coli* bacteremia with regard to 14 days mortality, in a low prevalence cohort of Extended-spectrum beta-lactamase-producing E. *coli*.

Methods: From January 18, 2010 to December 31, 2012, we conducted a retrospective cohort study including patients with *E. coli* bacteremia from six university hospitals in Copenhagen, Denmark. Clinical and laboratory information was obtained from a bacteremia research database, including information on comorbidity, and we used Cox proportional hazard analysis to asses all-cause 14 days mortality.

Results: A total of 568 patients receiving either cefuroxime (n=377) or piperacillin/tazobactam (n=191) as empirical therapy were included. In the Cox proportional hazard model, cefuroxime treatment was significantly associated with death (mortality rate ratio 3.95, CI 1.12–13.90). Other variables associated with death were health care related infection (MRR 3.20, CI 1.67–6.15), hospital-acquired infection (MRR 2,17, CI 1.02–4.62), admission at intensive care unit (MRR 20.45, 5.31–78.82), and combination therapy with ciprofloxacin (MRR 2.14, CI 0.98–4.68).

Conclusion: Empiric cefuroxime treatment of *E. coli* bacteremia was significantly associated with higher 14 days mortality in comparison with piperacillin/tazobactam.

Keywords: piperacillin/tazobactam, cefuroxime, *E. coli*, bacteremia, mortality

Introduction

Escherichia coli is a common pathogen causing infections in the urinary tract system and the most frequent pathogen causing bacteremia in Denmark.[1] Due to an increasing frequency of Extended-spectrum beta-lactamase (ESBL)-producing *Klebsiella pneumoniae*, a multidisciplinary intervention took place at the beginning of January 2010 in Copenhagen, Denmark. One intervention was to change the empirical treatment of febrile conditions from cefuroxime ± gentamicin to piperacillin/tazobactam (PTZ) ± gentamicin.[2] Since PTZ is documented to be less selective for antimicrobial resistance and therapeutically superior to cephalosporines against ESBL producing *E. coli*, it is often chosen to replace cefuroxime in the empirical treatment of febrile conditions.[3–5] Most *E. coli* strains in Denmark are susceptible to both cefuroxime and PTZ. To our knowledge, there has never been a comparative study of cefuroxime and PTZ against *E. coli*

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bacteremia in a primarily susceptible *E. coli* cohort. This study aims to investigate the difference in mortality for patients with *E. coli* bacteremia treated empirically with PTZ and cefuroxime, in a cohort of *E. coli* with a low prevalence of ESBL.

Materials and methods

Study setting

From January 18, 2010 to December 31, 2012, we conducted a retrospective cohort study of *E. coli* bacteremia patients from six hospitals in the capital region of Denmark (total estimated population: 640,000); Copenhagen University Hospital Hvidovre, Copenhagen University Hospital Amager, Copenhagen University Hospital Bispebjerg, Copenhagen University Hospital Frederiksberg, Copenhagen University Hospital Glostrup and Copenhagen University Hospital Bornholm. The hospitals are all located in Copenhagen and work in collaboration with the same population, and patients are exchanged between the hospitals depending on capacity and specialty. Personnel are widely exchanged, and some departments service several hospitals. The hospitals in the capital region of Denmark refer to the same antimicrobial guidelines, and all the included study hospitals use to the same Department of Clinical Microbiology (DCM) at Hvidovre Hospital. One of the hospitals, Copenhagen University Hospital Bispebjerg (the intervention hospital), did not use cefuroxime after January 18, 2010 due to the ESBL-*K. pneumoniae* outbreak, and restricted the use of fluoroquinolones.[2] We included patients who received either cefuroxime or PTZ as empirical treatment, with or without other antibiotics, typically gentamicin or ciprofloxacin. Patients were excluded if they had received carbapenems or both PTZ and cefuroxime. Local guidelines for dosage of the antibiotics were as follows: Cefuroxime 1.5 g q8h (GFR 10–50 mL/min: 1.5 g q12h or GFR <10 mL/min: 1.5 g q24h); PTZ 4 g/0.5 g q8h (GFR 10–50 mL/min: 4 g/0.5 g q12h or GFR <10 mL/min: 4 g/0.5 g q24h); ciprofloxacin 400 mg q12h (GFR <10 mL/min: 200 mg q12h); gentamicin 5 mg/kg q24h following serum concentration measurements.

Microbiology and susceptibility testing

The six hospitals in the greater Copenhagen area are served by the DCM at Copenhagen University Hospital Hvidovre. Blood cultures were obtained when clinically indicated. Culturing was obtained by a minimum of 30 mL of blood per blood culture, either with two sets of two blood culture bottles, using BacT/ALERT (bioMérieux, Marcy l'Étoile, France) for five hospitals, or one set comprising three bottles, using BACTEC (Becton-Dickinson, Sparks, MD, USA) for one hospital. Antimicrobial susceptibility testing was performed at the DCM with disc diffusion tests according to EUCAST guidelines (www.EUCAST.org). All data were recorded in a laboratory information system (ADBakt, Autonik, Ramsta, Sweden).

Data source

Patients with *E. coli* bacteremia were identified in ADBakt. The data were obtained from the Danish Collaborative Bacteremia Network (DACOBAN), which is a research database containing microbiological data from positive blood cultures from three major clinical microbiology departments in Denmark.[6] Each positive blood culture is linked to a unique civil registration number, given to all Danish residents. This unique number enables DACOBAN to link the vital status (alive or date of death), disappearance or emigration, of all patients from the Danish Civil Registration System (CRS).[7] The vital status was obtained on September 27, 2013. Similarly, DACODAN also extracts data on comorbidity based on the Charlson Comorbidity Index (CCI) from the Danish National Patient Registry (DNPR).[8,9] The DNPR contains hospital discharge diagnoses and surgical procedures from all non-psychiatric inpatients since 1977. The information obtained included date of admission, date of discharge, and type of diagnosis (International Classification of Diseases, revision 10). Data on empirical antimicrobial therapy were linked to DACODAN through the physicians' supplementary variables retrieved from electronic databases at each department of microbiology.[6]

Definitions

E. coli bacteremia was defined as any positive blood culture with *E. coli*. Polymicrobial bacteremia was defined as isolation of another pathogenic microorganism from the blood cultures. Resistant strains were defined as any resistance to cefpodoxime, PTZ, gentamicin or ciprofloxacin. A new positive blood culture >30 days after the initial positive blood culture was defined as a new episode and included as a new case. Positive cultures obtained 48 hrs after admission were classified as hospital-acquired, and within 48 hrs of admission, they were classified as community-acquired, except if patients regularly visited the hospital (eg, HD or chemotherapy) or had been hospitalized 30 days before and were classified as health care related.[10] CCI was calculated at the

time of hospitalization and was divided into three levels: Low (a score of 0), medium (1–2), and high (≥3).[8,11] Intensive care unit was defined as admission to an intensive care unit at the time of blood culturing. Empirical antibiotic therapy was defined as the antibiotic treatment given on the day of blood culturing. Cefuroxime 1.5 g q8h and PTZ 4 g/0.5 g q8h was regarded as adequate empirical treatment, unless the dosage was adjusted to the weight and/or kidney function. Time to death was calculated from the day the first blood culture was drawn.

Statistical analysis

All the data are represented in medians and interquartiles. Continuous variables were analyzed regarding normal distribution. Comparisons of independent normally distributed data were performed using the Student's *t*-test. Non-normally distributed data were compared using the Mann–Whitney test and categorical data were analyzed with the Fisher's Exact test with odds ratios presented with 95% confidence intervals (CIs). We chose all-cause 14 days mortality as an outcome, as we lacked information regarding definitive antibiotic treatment. Cox proportional hazards regression analysis was used to compute mortality rate ratios (MRRs) with 95% CIs and survival curves. The proportionality assumption was tested visually for categorical variables and by Schoenfeld residuals for numerical variables. The multivariate model was evaluated for confounders by stepwise excluding variables to detect changes in the MRRs. The adjusted model was fitted by excluding variables that changed the MRR less than 0.1 points each from the full model. The final cox proportional hazard model included treatment with cefuroxime, acquisition, CCI, intensive care unit, intervention hospital, polymicrobial bacteremia and combination with ciprofloxacin. Two-sided significance was tested with the assumption of $P<0.05$ as significant. The statistical analysis was performed by the Statistical Package for Social Sciences (version 23.0; SPSS, IBM).

Ethical and data protection approval

The study was approved by the local ethics committee and the Danish Data Protection Agency (no.: 03064, ID: AHH-2014–012).

Results

A total of 707 patients with *E. coli* bacteremia were identified (Figure 1). Of them 628 patients were treated with either cefuroxime or PTZ. Six patients had polymicrobial infections not covered with cefuroxime or PTZ (one *E. faecium*, two *M. morganii*, and three *B. fragilis*) and were excluded, as well as 54 patients who did not receive an antibiotic to which the *E. coli* isolate was susceptible. Hence, a total of 568 patients with *E. coli* bacteremia remained.

Antimicrobial therapy

General characteristics of the *E. coli* bacteremia regarding the empirical antibiotic treatment are summarized in Table 1. Sixteen patients had polymicrobial bacteremia: Six *K. pneumoniae*, three *Proteus mirabilis*, two *Klebsiella oxytoca*, and one *Streptococcus dysgalactiae*, all fully susceptible to both cefuroxime and PTZ. In the last four cases, the other microbe present was a coagulase-negative staphylococcus in all cases considered contaminations. Three children were in the cohort (age 0, 8, and 16 years), and they were all treated with cefuroxime. In no cases were both gentamicin and ciprofloxacin administered. Cefuroxime treatment was significantly associated with combination therapy using gentamicin (17.0% vs 9.9%, $P=0.03$), whereas PTZ treatment was significantly associated with combination therapy with ciprofloxacin (24.9% vs 42.4%, $P<0.01$). There was no significant difference in the crude data regarding mortality.

Differences between hospitals

Table 2 shows the differences between the intervention hospital and the five other hospitals. The only significant differences were the empiric antibiotic therapy with cefuroxime and combination with ciprofloxacin (both $P<0.01$).

Mortality

Overall mortality in the cohort was 10.7% (67/628) 14 days and 15.8% (99/628) 30 days after blood culturing. Table 3 shows the differences between non-survivors and survivors on day 14. In the crude analysis, health care related (MRR 3.07, CI 1.59–5.92) and hospital acquisition (MRR 2.37, CI 1.11–5.04) as well as a high CCI (MRR 2.11, CI 1.02–4.39) and intensive care unit (MRR 8.87, CI 1.75–44.93) were significantly associated with 14 days mortality.

Survival analysis

Included in the adjusted multivariate Cox regression model were acquisition, CCI, intensive care unit, intervention hospital, polymicrobial bacteremia, resistant strain, combination

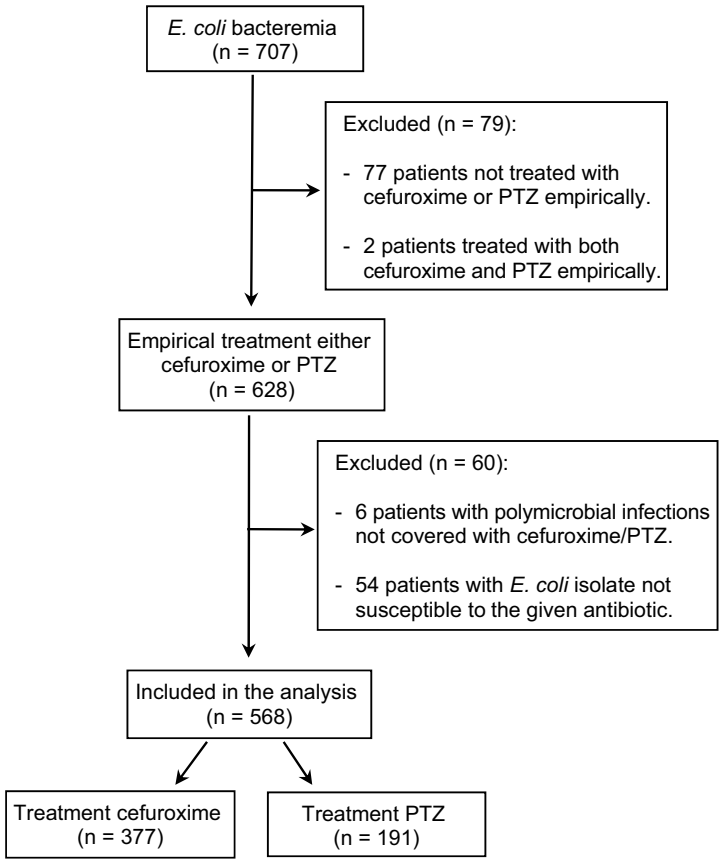

Figure 1 Flow diagram presenting the inclusion and exclusion procedure for patients with *Escherichia coli (E. coli)* bacteremia.
Abbreviation: PTZ, piperacillin/tazobactam.

with ciprofloxacin and treatment with cefuroxime (Table 3). Significant risk factors associated with death were a health care related infection (MRR 3.20, CI 1.67–6.15), hospital-acquired infection (MRR 2.17, CI 1.02–4.62), admission at intensive care unit (MRR 20.45, 5.31–78.82), combination therapy with ciprofloxacin (MRR 2.14, CI 0.98–4.68), and empiric antibiotic treatment with cefuroxime (MRR 3.95, CI 1.12–13.90). Figure 2 shows the individual survival curves for cefuroxime and PTZ treatment based on the Cox proportional hazard model.

Subgroup analysis where strains resistant to ciprofloxacin or gentamicin were excluded from the analyses did not alter the results (data not shown). However, when excluding cases where either ciprofloxacin or gentamicin was given as combination therapy, MRR of empiric antibiotic treatment with cefuroxime increased to 9.34 (CI 1.02–85.93, P=0.03).

Discussion

Our study shows that empiric antibiotic treatment of susceptible *E. coli* with cefuroxime leads to higher 14 days mortality rates compared to PTZ. To our knowledge, this is the first time such a result has been reported for susceptible *E. coli*.

Guidelines in study hospitals, except the intervention hospital, reserved PTZ for more severe cases. At the intervention hospital, a carbapenem would be used as a second line drug instead. This difference in second line antibiotics should be in favor of cefuroxime. Hence, we have reason to believe that the difference we find is conservative. Furthermore, patients at the intervention hospital significantly more often received ciprofloxacin and were less likely to receive gentamicin than the patients at the other hospitals. Again, this should not act in favor of PTZ, since local guidelines stated that fluoroquinolones, instead of gentamicin, should only be added in case of septic shock. Fluoroquinolones had in general been restricted to the treatment of septic shock at the intervention hospital.[2] This also explains the association between combination therapy with ciprofloxacin and death. Comparing cefuroxime and PTZ, more female patients were treated with cefuroxime empirically, and gentamicin was more often given in combination with cefuroxime. One explanation could be guidelines stating

Table 1 Characteristics of *Eshericha coli* bacteremia cases regarding antimicrobial therapy from 2010 to 2012

	All patients (%)	Cefuroxime (%)	Piperacillin/tazobactam (%)	OR (95% CI)	*P*-value
	n=568	n=377	n=191		
Age [median (25–75 percentiles)]	76 (62–84)	75 (61–84)	77 (62–84)		0.38
Gender (female)	318 (56.0)	220 (58.4)	98 (51.3)	1.33 (0.94–1.89)	0.13
Acquisition (n=503)					
Community-acquired	331 (61.8)	211 (62.8)	100 (59.9)	1.00	
Health care related	110 (21.9)	70 (20.8)	40 (24.0)	0.83 (0.53–1.31)	0.42
Hospital-acquired	82 (16.3)	55 (16.4)	27 (16.2)	1.04 (0.62–1.74)	0.89
Charlson Comorbidity Index					
Low	157 (27.6)	105 (27.9)	52 (27.2)	1.00	
Medium	207 (36.4)	143 (37.9)	64 (33.5)	1.11 (0.71–1.72)	0.66
High	204 (35.9)	129 (34.2)	75 (39.3)	0.85 (0.55–1.32)	0.47
Intensive care unit	6 (1.1)	3 (0.8)	3 (1.6)	0.50 (0.10–2.51)	0.41
Intervention hospital	175 (30.8)	7 (1.9)	168 (88.0)	0.003 (0.001–0.006)	**<0.01**
Polymicrobial bacteraemia (n=503)	16 (3.2)	9 (2.3)	7 (4.2)	0.65 (0.24–1.78)	0.43
Resistant strain	38 (6.7)	21 (5.6)	17 (8.9)	0.60 (0.31–1.17)	0.16
Combination therapy with gentamicin	83 (14.6)	64 (17.0)	19 (9.9)	1.85 (1.07–3.19)	**0.03**
Combination therapy with ciprofloxacin	175 (30.8)	94 (24.9)	81 (42.4)	0.45 (0.31–0.65)	**<0.01**
14 days mortality	60 (10.6)	45 (11.9)	15 (7.9)	1.5 (0.86–2.93)	0.09
30 days mortality	88 (15.5)	61 (16.2)	27 (14.1)	1.17 (0.72–1.92)	0.31

Note: *P*<0.05 shown in bold.

cefuroxime and gentamicin should be used for a urinary tract focus and females more often have a urinary tract infection. We would expect a urinary tract focus to be relatively uncomplicated and a susceptible site for antibiotics to reach high concentrations compared to an abdominal focus. Hence, this should again be an advantage to cefuroxime. The subgroup analysis excluding cases with combination therapy of ciprofloxacin or gentamicin confirmed these findings with a further increased MRR associated with cefuroxime therapy.

In Denmark, the incidence of ESBL producers in blood culture positive *E. coli* has increased from 2% in 2003 to 9% in 2010,[12] and has thereafter stabilized.[1] Samples from the primary health care who were forwarded to a DCM showed an incidence of cefuroxime resistance at 6%.[1] However, compared to some southern European countries this is still a relatively low incidence. In our study, we have shown a lower mortality rate when PTZ was administered compared to cefuroxime despite the *E. coli* strains being susceptible to cefuroxime. This result questions the place of cefuroxime in the treatment of any severe *E. coli* infection. A clinical randomized trial has previously shown no difference in the outcome between PTZ and cefuroxime/metronidazole in the treatment of intraabdominal infections.[13] In this study, there was a great diversity in the bacterial strains, making it difficult to extrapolate the results in *E. coli* bacteremia. Recent studies concerned with the treatment of *E. coli* infections have focused on the challenges with more resistant strains, eg, ESBL producing *E. coli*.[14,15] However, these studies do not provide any information regarding cefuroxime treatment in a susceptible population such as the present study.

Our findings could be related to differences in pharmacokinetic and pharmacodynamic activity between the drugs. It applies to beta lactams that the amount of time the free concentration of the antibiotic exceeds the minimal inhibitory concentration ($fT > MIC$) is the best pharmacokinetic/pharmacodynamic predictor. Optimally plasma drug concentration would be above MIC 50% of the time. Both cefuroxime and piperacillin have clinical breakpoints at MIC 8 mg/L.[16] Usually cefuroxime is administered 1.5 g q8h, which is also the case in this cohort. Viberg et al, showed that 23% of *E. coli* infections

Table 2 Characteristics of *E. coli* bacteremia cases regarding hospitals from 2010 to 2012

	Intervention hospital (%)	Other hospitals (%)	OR (95% CI)	*P*-value
	n=175	n=393		
Age [median (25–75 percentiles)]	77 (64–84)	75 (61–84)		0.24
Gender (female)	92 (52.6)	226 (57.5)	0.82 (0.57–1.17)	0.31
Acquisition (n=553)				
Community-acquired	96 (63.2)	215 (61.3)	1.00	
Health care related	34 (22.4)	76 (21.7)	1.00 (0.63–1.61)	0.99
Hospital-acquired	22 (14.5)	60 (17.1)	0.82 (0.48–1.42)	0.48
Charlson Comorbidity Index				
Low	45 (25.7)	112 (28.5)	1.00	
Medium	61 (34.9)	146 (37.2)	0.96 (0.61–1.52)	0.87
High	69 (39.4)	135 (34.4)	1.27 (0.81–2.00)	0.30
Intensive care unit	1 (0.6)	5 (1.3)	0.45 (0.05–3.85)	0.67
Polymicrobial bacteraemia (n=503)	8 (5.3)	8 (2.0)	2.25 (0.83–6.08)	0.17
Resistant strain	15 (8.6)	23 (5.9)	1.51 (0.77–2.97)	0.28
Combination with gentamicin	19 (10.9)	64 (16.3)	0.63 (0.36–1.08)	0.10
Combination with ciprofloxacin	68 (38.9)	107 (27.2)	1.70 (1.17–2.48)	**<0.01**
Treatment with cefuroxime	7 (4.0)	370 (94.1)	0.003 (0.001–0.006)	**<0.01**
14 days mortality	14 (8.0)	46 (11.7)	0.66 (0.35–1.23)	0.24
30 days mortality	24 (13.7)	64 (16.3)	0.82 (0.49–1.36)	0.46

Note: *P*<0.05 shown in bold.

did not reach the target T>MIC 50% for wild-type distribution MIC, when using 1.5 g q8h at creatinine clearance (CLcr) >80 mL/min.[17] Carlier et al, reported similarly that 1.5 g q8h did not reach their target MIC 8 mg/L in critically ill patients when CLcr≥50 mL/min.[18] Both studies reported the need for a shorter dosing interval with increased CLcr. Patients with sepsis are likely to have an increased CLcr, as a response to treatment.[19] One approach could be to increase the regime to cefuroxime 1.5 g q6h for patients with a normal kidney function. Another possible solution is continuous infusion. We do not know whether the difference in mortality between PTZ and cefuroxime is related specifically to cefuroxime or cephalosporins as a class. Further studies are required.

The study has several strengths. It is based on a large population and all included data are highly validated. Furthermore, we had a high statistical precision, indicated by the relatively narrow CIs. Our study, however, also has some important limitations that should be taken into consideration. Firstly, the study design was observational, which in contrast to randomized clinical trials has a risk of confounding by indication when evaluating treatment; we do not know if the physician systematically treated one category of patients with cefuroxime and another category with a PTZ. However, only gender and antibiotic treatment showed significant differences between the two groups. Secondly, the intervention hospital was responsible for 88% of the cases with PTZ treatment. Therefore, there could be a risk that the difference between the drugs was a difference between the hospitals. As demonstrated in Table 2, nothing indicated that there was a difference in the populations between the intervention hospital and the other study hospitals. As previously described, the hospitals work in collaboration were patients and personnel are exchanged and the hospitals use the same guidelines. This makes the hospitals comparable, and the difference in the physical site does not explain the difference we found. Thirdly, information regarding definitive antibiotic therapy was missing. We took this into consideration by investigating 14 days mortality instead of 30 days mortality. However, when the empirical treatment is evaluated to be adequate and in line with local guidelines, it is likely to be continued and therefore be identical with the definitive treatment. Hence, in most of these cases, the empirical and definitive treatment would be the same although we cannot document this. Fourthly, the study lacked information regarding the anatomic focus of the infection and the severity of the

Table 3 Analysis of 14-day mortality with unadjusted and adjusted cox proportional hazards regression model

	Deaths (%)	Survivors (%)	Unadjusted		Adjusted	
	n=60	n=508	Mortality rate ratio (95% CI)	*P*-value	Mortality rate ratio (95% CI)	*P-value(P<0.05 in bold)*
Age [median (25–75 percentiles)]	74 (66–84)	71 (61–84)	1.01 (0.99–1.03)	0.26		
Gender (female)	29 (48.3)	289 (56.9)	0.71 (0.41–1.21)	0.22		
Acquisition (n=503)						
Community-acquired	21 (39.6)	290 (64.4)	1.00		1.00	
Health care related	20 (37.7)	90 (20.0)	3.07 (1.59–5.92)	**<0.01**	3.39 (1.77–6.49)	**<0.01**
Hospital-acquired	12 (22.6)	70 (15.6)	2.37 (1.11–5.04)	**0.03**	2.17 (1.02–4.62)	**<0.05**
Charlson Comorbidity Index						
Low	11 (18.3)	146 (28.7)	1.00		1.00	
Medium	21 (35.0)	186 (36.6)	1.50 (0.70–3.21)	0.30	1.47 (0.65–3.32)	0.35
High	28 (46.7)	176 (34.6)	2.11 (1.02–4.39)	**<0.05**	1.93 (1.05–3.53)	0.06
Intensive care unit	3 (5.0)	3 (0.6)	8.87 (1.75–44.93)	**0.02**	20.45 (5.31–78.82)	**<0.01**
Intervention hospital	14 (23.3)	161 (31.7)	0.66 (0.35–1.23)	0.24	0.60 (0.32–1.59)	0.15
Polymicrobial bacteraemia (n=503)	2 (3.3)	14 (2.8)	1.05 (0.24–4.72)	1.00	1.75 (0.50–6.05)	0.35
Resistant strain	17 (28.3)	94 (18.5)	1.31 (0.49–3.49)	0.58		
Combination with gentamicin	8 (13.3)	75 (14.8)	0.88 (0.41–1.95)	1.00		
Combination with ciprofloxacin	25 (41.7)	150 (29.5)	1.71 (0.99–2.95)	0.08	2.14 (0.98–4.68)	**0.04**
Treatment with cefuroxime	45 (75.0)	332 (65.4)	1.59 (0.86–2.93)	0.15	3.95 (1.12–13.90)	**0.02**

Note: *P*<0.05 shown in bold.

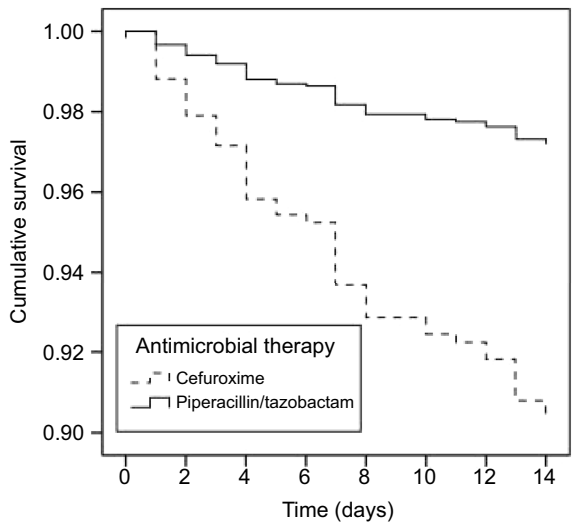

Figure 2 Cox regression survival curves for 14-day survival after antibiotic treatment onset.

bacteremia at onset. Yet, as previously described we would expect PTZ more often to be given in case of a difficult anatomic focus and in more severe cases. Therefore, this lack of information could underestimate the difference between PTZ and cefuroxime treatment.

In conclusion, empirical treatment with cefuroxime of *E. coli* bacteremia in a low ESBL cohort was significantly associated with a higher mortality than PTZ.

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Disclosure

The authors report no conflicts of interest in this work.

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