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Appropriateness of Empirical Treatment and Outcome in Bacteremia Caused by Extended-Spectrum-β-Lactamase-Producing Bacteria

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We studied clinical characteristics, appropriateness of initial antibiotic treatment, and other factors associated with day 30 mortality in patients with bacteremia caused by extended-spectrum-β-lactamase (ESBL)-producing bacteria in eight Dutch hospitals. Retrospectively, information was collected from 232 consecutive patients with ESBL bacteremia (due to *Escherichia coli*, *Klebsiella pneumoniae*, and *Enterobacter cloacae*) between 2008 and 2010. In this cohort (median age of 65 years; 24 patients were <18 years of age), many had comorbidities, such as malignancy (34%) or recurrent urinary tract infection (UTI) (15%). One hundred forty episodes (60%) were nosocomial, 54 (23%) were otherwise health care associated, and 38 (16%) were community acquired. The most frequent sources of infection were UTI (42%) and intra-abdominal infection (28%). Appropriate therapy within 24 h after bacteremia onset was prescribed to 37% of all patients and to 54% of known ESBL carriers. The day 30 mortality rate was 20%. In a multivariable analysis, a Charlson comorbidity index of ≥3, an age of ≥75 years, intensive care unit (ICU) stay at bacteremia onset, a non-UTI bacteremia source, and presentation with severe sepsis, but not inappropriate therapy within <24 h (adjusted odds ratio [OR], 1.53; 95% confidence interval [CI], 0.68 to 3.45), were associated with day 30 mortality. Further assessment of confounding and a stratified analysis for patients with UTI and non-UTI origins of infection did not reveal a statistically significant effect of inappropriate therapy on day 30 mortality, and these results were insensitive to the possible misclassification of patients who had received β-lactam–β-lactamase inhibitor combinations or ceftazidime as initial treatment. In conclusion, ESBL bacteremia occurs mostly in patients with comorbidities requiring frequent hospitalization, and 84% of episodes were health care associated. Factors other than inappropriate therapy within <24 h determined day 30 mortality.

Extended-spectrum β-lactamases (ESBLs) are enzymes that can hydrolyze penicillins, aztreonam, and cephalosporins. Therefore, ESBL-producing *Enterobacteriaceae* were considered to be resistant to all β-lactam antibiotics except carbapenems. Recently, it has been suggested that cephalosporins (1, 2) and β-lactam–β-lactamase inhibitor combinations (BLBLICs) (3, 4) may still be used to treat infections with ESBL-positive isolates if MICs are below clinical breakpoints. Worldwide, numbers of infections caused by ESBL-producing *Enterobacteriaceae* are increasing in both the hospital and community settings. It is generally assumed that infections with ESBL-producing pathogens have a worse outcome than their non-ESBL-producing counterparts (5, 6).

In the Netherlands, antibiotic resistance levels are low (7), presumably due to the restrictive use of antibiotics (8) and the national infection control policy, including active surveillance and isolation of admitted ESBL carriers (9). However, the proportion of *Escherichia coli* strains resistant or intermediately resistant to third-generation cephalosporins among invasive isolates increased from 0.2% in 2000 to 5.4% in 2010 (7). For *Klebsiella pneumoniae*, these percentages were 3.5% in 2005 and 7.2% in 2010. In most hospitals, empirical antibiotic therapy for sepsis with a urinary, abdominal, pulmonary, or unknown source currently consists of second- or third-generation cephalosporins. Increasing rates of infections caused by ESBL-producing bacteria endanger the appropriateness of such regimens and pose the question of whether empirical treatment should also cover ESBL-producing bacteria. However, it is unknown how frequently initial treatment is truly empirical, as previously obtained culture results may guide initial choices. Naturally, this will occur more frequently in patients with previous hospitalizations or other reasons for microbiological testing than in previously healthy subjects with community-onset infections.

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In eight Dutch hospitals, we performed a retrospective-cohort study of consecutive patients with bacteremia caused by the three most prevalent ESBL-producing pathogens in the Netherlands, i.e., *E. coli*, *K. pneumoniae*, and *Enterobacter cloacae*. Our aim was to determine the characteristics of patients affected and to study which factors, including appropriate initial antibiotic therapy, predict day 30 mortality.

(The results of this study were previously presented at the 22nd European Congress of Clinical Microbiology and Infectious Diseases, London, United Kingdom, 3 April 2012 [10].)

MATERIALS AND METHODS

Patients. In this retrospective study, all consecutive patients with bacteremia caused by ESBL-producing *E. coli*, *K. pneumoniae*, and *E. cloacae* present in laboratory information system databases in eight Dutch hospitals (three university hospitals and five teaching hospitals) were included. The inclusion period ranged from 1 January 2008 to 31 December 2010 (36 months) in six hospitals and to 1 July 2010 (30 months) in two hospitals. Per patient, only the first episode of bacteremia caused by ESBL-producing *Enterobacteriaceae* within the study period was included. The study was approved by the institutional review board at the University Medical Center Utrecht.

Medical records were reviewed for the clinical data described in Table 1, such as Charlson comorbidity index (11), immunosuppression, urinary tract disease, recent invasive procedures, previous hospital admission abroad, known ESBL carriage at bacteremia onset, and previous use of antibiotics. Data for variables from each bacteremic episode were also collected (most of which are shown in Table 2), including origin of bacteremia (nosocomial, health care associated, or community onset), Pitt bacteremia score (12), presumed bacteremia source, use of antibiotics (including start and stop dates and route of administration), and interval between bacteremia onset and start of appropriate therapy. Outcome data were all-cause mortality 30 days after bacteremia onset (primary outcome), length of hospital stay, and intensive care unit (ICU) admission within 1 week after bacteremia onset (secondary outcomes). If no outpatient visit records were available, patients discharged within 30 days in an apparently healthy state were assumed to have survived the follow-up period.

Microbiological methods. Seven centers used the Vitek 2 system (bioMérieux SA, Marcy l'Etoile, France) and one center used the Phoenix system (BD, Franklin Lakes, NJ, USA) for identification. Susceptibility to antibiotics was determined by Vitek or Phoenix reports in all but one center, which used disk diffusion tests. All centers used CLSI interpretation criteria applicable at that point in time, e.g., CLSI criteria in 2007 (13). ESBL detection was done according to national guidelines, which have high positive and negative predictive values for detecting ESBLs (14). In short, screen-positive isolates (MIC of cefotaxime or ceftazidime of $\geq$1 mg/liter or an ESBL warning by an automated system) were subjected to confirmation tests using ESBL Etests (AB Biodisk, Solna, Sweden) or combination disk diffusion tests (BD, MAST, Bootle, United Kingdom, or ROSCO, Taastrup, Denmark), with cefotaxime and ceftazidime with and without clavulanic acid for *E. coli* and *K. pneumoniae* and with cefepime with and without clavulanic acid for *E. cloacae*.

Definitions. Bacteremia onset was the day on which the first ESBL-positive blood culture was drawn. Bacteremia was considered nosocomial if this culture was taken $\geq$48 h after hospital admission. Health care-related bacteremia was defined as described previously by Friedman et al. (15). Recurrent urinary tract infections (UTIs) implied at least three UTIs needing antibiotic treatment in the year prior to bacteremia. Severe sepsis and septic shock were defined according to criteria described previously (16). We defined recurrent UTIs, obstructive urinary tract disease, hospital admission in the previous year, antibiotic use in the year prior to bacteremia, and antibiotic use or hospitalization in a country with high ESBL prevalence as risk factors for ESBL acquisition (17–20).

The time periods between the drawing of the first positive blood culture and the start of appropriate therapy were categorized as <24 h, 24 to 48 h, 48 to 72 h, and >72 h. Initial therapy was defined as therapy given in the first 24 h after blood culture drawing. Appropriateness of non-β-lactam antibiotics and carbapenems was based on susceptibility reports to the clinic, according to CLSI interpretive criteria, which remained unchanged between 2007 (13) and 2010 (2). We considered oral fluoroquinolones and cotrimoxazole to be appropriate if isolates tested susceptible and if the clinical condition at the time of blood culture was considered nonsevere sepsis. Initially, all β-lactam antibiotics apart from carbapenems were considered inappropriate. In a secondary analysis, appropriateness of BLBLICs and ceftazidime was adjusted according to susceptibility test results, using CLSI interpretive criteria from 2010 (2). Appropriate therapy also required administration of appropriate agents on $\geq$7 consecutive days, except if interrupted by the death of a patient. A switch from appropriate to inappropriate therapy within 7 days was classified as inappropriate therapy.

Data analysis. For each study year and within each of the three included species, we calculated the ratio of ESBL-positive isolates to all blood culture isolates for that specific species. Within a single patient, we used a deduplication window of 2 weeks. This analysis could be performed for 5 hospitals only (2 university hospitals and 3 teaching hospitals).

Characteristics of patients receiving appropriate versus inappropriate therapy within <24 h were compared by χ^2 tests, Fisher exact tests, or Mann-Whitney U tests. Determinants associated with inappropriate therapy with a P value of <0.20 were selected for a multivariable logistic regression model using forward stepwise regression based on the Wald statistic. To study the association between inappropriate therapy within <24 h and day 30 mortality, eight covariates that were clinically deemed important confounders or effect modifiers of this association were selected. They were dichotomized or grouped in a manner that best reflected the association between the covariate and mortality. Stratum-specific odds ratios (ORs) for inappropriate therapy within <24 h were calculated, and these were pooled by the Mantel-Haenszel method. Different multivariable logistic regression models explaining day 30 mortality were constructed: a forward stepwise regression with inclusion in the case of a P value of <0.05 for the score test and removal in the case of a P value of <0.10 for the likelihood ratio statistic, incorporating the relevant confounders and with inappropriate therapy initially forced into the model; sensitivity analyses by the above-mentioned reconsideration of appropriateness of BLBLICs and ceftazidime, constructing separate models for UTI and non-UTI bacteremia sources, excluding patients not receiving intravenous therapy <24 h after onset, and assessing appropriateness of therapy for <48 instead of <24 h; and a model starting with inappropriate therapy only, followed by the stepwise addition of variables changing the regression coefficient of inappropriate therapy >10%. The association between inappropriate therapy within <24 h and the secondary outcomes was studied univariably and in forward stepwise regression analyses also incorporating the eight covariates. A P value of <0.05 was considered statistically significant. All analyses were performed with SPSS Statistics 20.0 (IBM, Armonk, NY, USA).

RESULTS

Prevalence of ESBL bacteremia. During the study period of 276 hospital months, there were 238 patients with an episode of ESBL bacteremia, 6 of whom were excluded due to an absence of clinical data. The total number of included episodes ranged from 9 to 74 per hospital. In the five hospitals with prevalence data available, ESBL prevalences among blood culture isolates were 6.6%, 8.7%, and 10.0% for *E. coli*, *K. pneumoniae*, and *E. cloacae*, respectively. The overall ESBL prevalences among these three species were 7.0%, 7.2%, and 7.6% in 2008, 2009, and 2010, respectively.

Patient characteristics. Patient characteristics of the 232 included patients are shown in Table 1. The median age was 65 years. Only 6% of patients had been hospitalized abroad in the year prior

TABLE 1 Characteristics of patients with ESBL bacteremia

Variable[d]	Value for group			
		Therapy within 24 h that was deemed:		
	All patients (n = 232)	Appropriate (n = 85; 37%)	Inappropriate (n = 147; 63%)	P value[a]
No. (%) of patients of age (yr)				0.17
1–17	24 (10)	13 (15)	11 (7)	
18–64	87 (38)	29 (34)	58 (39)	
≥65	121 (52)	43 (51)	78 (53)	
No. (%) of male patients	140 (60)	51 (60)	89 (61)	1.00
Median (IQR) LOS before onset (days)	7.5 (1–21)	6 (1–25)	8 (1–20)	0.83
No. (%) of patients with comorbidity				
Malignancy	78 (34)	37 (44)	41 (28)	0.02
Obstructive urinary tract disease	43 (19)	18 (21)	25 (17)	0.48
Biliary disease	17 (7)	7 (8)	10 (7)	0.80
Recurrent UTI				0.71
Yes	35 (15)	14 (17)	21 (14)	
Unknown[b]	41 (18)	15 (18)	26 (18)	
Solid-organ transplant	25 (11)	9 (11)	16 (11)	1.00
Stem cell transplant	14 (6)	6 (7)	8 (5)	0.78
No. (%) of patients with Charlson comorbidity index of:				0.10
0	44 (19)	9 (11)	35 (24)	
1–2	102 (44)	41 (48)	61 (42)	
3–4	46 (20)	18 (21)	28 (19)	
≥5	40 (17)	17 (20)	23 (16)	
No. (%) of patients with immune suppression caused by:				
Immunosuppressant use	52 (22)	20 (24)	32 (22)	0.87
Neutropenia	25 (11)	14 (17)	11 (8)	0.05
No. (%) of patients with invasive procedures in last 4 wk				
Surgical procedure (n = 230)	78 (34)	31 (37)	47 (32)	0.57
Urologic procedure (n = 218)	48 (22)	23 (28)	25 (19)	0.13
No. (%) of patients with invasive devices at bacteremia onset				
Mechanical ventilation (n = 229)	32 (14)	13 (16)	19 (13)	0.70
CVC/arterial catheter (n = 218)	78 (36)	33 (42)	45 (32)	0.19
No. (%) of patients with previous antibiotic use				
No. of courses previous yr:				
≥3	100 (43)	42 (49)	58 (39)	0.21
Unknown	58 (25)	19 (22)	39 (27)	
2/3GCs in previous 2 mo (n = 227)	77 (34)	30 (37)	47 (33)	0.67
β-Lactams in previous 2 mo (n = 226)	146 (65)	59 (72)	87 (60)	0.09
Fluoroquinolones in previous 2 mo (n = 225)	76 (34)	31 (38)	45 (31)	0.31
No. (%) of patients with known hospitalization abroad previous yr	13 (6)	4 (5)	9 (6)	0.77
No (%) of patients known to be ESBL carriers at bacteremia onset (n = 227)	71 (31)	38 (46)	33 (23)	<0.01
No. (%) of patients at hospital				
University	139 (60)	60 (71)	79 (54)	0.01[c]
1	27 (12)	13 (15)	14 (10)	
2	38 (16)	16 (19)	22 (15)	
3	74 (32)	31 (36)	43 (29)	
Non-university	93 (40)	25 (29)	68 (46)	
1	19 (8)	3 (4)	16 (11)	
2	18 (8)	4 (5)	14 (10)	
3	33 (14)	14 (16)	19 (13)	
4	9 (4)	2 (2)	7 (5)	
5	14 (6)	2 (2)	12 (8)	

[a] P value of comparison between patients with appropriate and those with inappropriate therapy, calculated with Pearson's chi-squared, Fisher's exact, or Mann-Whitney U test when applicable.

[b] Unknown cases were included in the group not having recurrent UTI.

[c] Comparison of university hospital versus non-university hospital patients.

[d] 2/3GC, second- or third-generation cephalosporin; CVC, central venous catheter; IQR, interquartile range; LOS, length of stay; UTI, urinary tract infection.

TABLE 2 Characteristics of ESBL bacteremia episodes

Variable[d]	Value for group			*P* value[a]
		Therapy within 24 h that was deemed:		
	All patients ($n = 232$)	Appropriate ($n = 85$; 37%)	Inappropriate ($n = 147$; 63%)	
No. (%) of patients with origin of bacteremia				0.14
Community onset	38 (16)	10 (12)	28 (19)	
Health care associated	54 (23)	25 (29)	29 (20)	
Nosocomial[b]	140 (60)	50 (59)	90 (61)	0.53
On medical ward	58 (42)	24 (48)	34 (39)	
On surgical ward	45 (33)	14 (28)	31 (35)	
On ICU	35 (25)	14 (24)	21 (26)	
No. (%) of patients with definitive bacteremia source[c]				0.03
Primary or unknown	24 (10)	7 (8)	17 (12)	
Urinary tract infection	97 (42)	38 (45)	59 (40)	
Pneumonia	11 (5)	0 (0)	11 (7)	
Vascular catheter infection	20 (9)	9 (11)	11 (7)	
Intra-abdominal infection	64 (28)	22 (26)	42 (29)	
Surgical wound infection	5 (2)	3 (4)	2 (1)	
Skin/soft tissue infection	6 (3)	2 (2)	4 (3)	
Other	5 (2)	4 (5)	1 (1)	
No. (%) of patients with species isolated				0.27
E. coli	163 (70)	65 (76)	98 (67)	
K. pneumonia	44 (19)	12 (14)	32 (22)	
E. cloacae	25 (11)	8 (9)	17 (12)	
No. (%) of patients with polymicrobial bacteremia	22 (9)	8 (9)	14 (10)	1.00
No. (%) of patients with severe sepsis/septic shock ($n = 226$)	75 (33)	31 (37)	44 (31)	0.38
No. (%) of patients with Pitt score of:				
≥3	81 (35)	29 (34)	52 (35)	0.88
Unknown	42 (18)	19 (22)	23 (16)	
No. (%) of patients with outcome				
ICU admission				0.47
No ICU admission	168 (72)	58 (68)	110 (75)	
Already in ICU	35 (15)	13 (15)	22 (15)	
Within 2 days after onset	22 (9)	10 (12)	12 (8)	
Within 2–7 days after onset	7 (3)	4 (5)	3 (2)	
In-hospital mortality ($n = 230$)	54 (23)	24 (28)	30 (21)	0.20
Day 30 mortality ($n = 231$)	46 (20)	16 (19)	30 (21)	0.87
Median (IQR) LOS after onset (days)	15 (9–30)	16 (10–34)	14 (7–27)	0.09

[a] *P* value of comparison between patients with appropriate and those with inappropriate therapy, calculated with Pearson's chi-squared, Fisher's exact, or Mann-Whitney U test when applicable.
[b] For two nosocomial cases, the ward type is unknown.
[c] Divided into urinary tract infections, intra-abdominal infections, pneumonias, other sources, and unknown/primary sources for multivariable analysis for prediction of inappropriate therapy.
[d] ICU, intensive care unit; IQR, interquartile range; LOS, length of stay.

to bacteremia, but 37% patients had a Charlson index of ≥3, and 15% had recurrent UTIs. At least 43% of patients had received more than three antibiotic courses during the last year, and 34% had used second- or third-generation cephalosporins in the two preceding months. In 31% of episodes, prior ESBL-positive culture results were available at bacteremia onset. Most bacteremia episodes were nosocomial (60%) or health care associated (23%) (Table 2). Of the community-acquired episodes, 68% originated from the urinary tract. Most patients (at least 71%) with community-onset ESBL bacteremia had one or more of the predefined risk factors for ESBL acquisition. Overall, UTI was the most frequent source of bacteremia (42%) (Table 2), and 68% of these patients suffered from obstructive urinary tract disease, had recurrent UTIs, had recently undergone urological procedures, or had a urinary catheter at bacteremia onset.

Antimicrobial susceptibility. For non-β-lactam antibiotics, MICs were available from seven hospitals. According to CLSI interpretive criteria from 2010 (2), rates of coresistance were 75/193 (39%) for gentamicin, 112/200 (56%) for ciprofloxacin, and 156/200 (78%) for trimethoprim-sulfamethoxazole. For

TABLE 3 Initial antimicrobial therapy according to appropriateness of therapy within 24 h[a]

Initial therapy[c]	No. (%) of patients in group		
		Therapy within 24 h that was deemed:	
	All patients ($n = 232$)	Appropriate ($n = 85$; 37%)	Inappropriate ($n = 147$; 63%)
Monotherapy			
Amoxicillin	1 (0)	0 (0)	1 (1)
BLBLIC	24 (10)	0 (0)	24 (16)
2GC	14 (6)	0 (0)	14 (10)
3GC	29 (13)	0 (0)	29 (20)
Aminoglycoside	3 (1)	1 (1)	2 (1)
Fluoroquinolone	7 (3)	2 (2)[b]	5 (3)
Cotrimoxazole	2 (1)	0 (0)	2 (1)
Carbapenem	62 (27)	57 (67)	5 (3)
Combination therapy			
Amoxicillin + aminoglycoside	5 (2)	2 (2)	3 (2)
Amoxicillin + fluoroquinolone	4 (2)	0 (0)	4 (3)
BLBLIC + aminoglycoside	12 (5)	4 (5)	8 (5)
BLBLIC + fluoroquinolone	2 (1)	1 (1)[b]	1 (1)
1GC + aminoglycoside	1 (0)	0 (0)	1 (1)
2GC + aminoglycoside	16 (7)	9 (11)	7 (5)
2GC + fluoroquinolone	1 (0)	1 (1)[b]	0 (0)
3GC + aminoglycoside	6 (3)	3 (4)	3 (2)
3GC + fluoroquinolone	3 (1)	0 (0)	3 (2)
β-Lactam + cotrimoxazole	3 (1)	0 (0)	3 (2)
Aminoglycoside + fluoroquinolone	1 (0)	0 (0)	1 (1)
Cotrimoxazole + aminoglycoside + fluoroquinolone	1 (0)	1 (1)	0 (0)
β-Lactam + aminoglycoside + fluoroquinolone	7 (3)	4 (5)	3 (2)
No antimicrobial therapy	5 (2)	0 (0)	5 (3)
Therapy started after 24 h	23 (10)	0 (0)	23 (16)

[a] Appropriateness of therapy was judged according to *in vitro* susceptibility, duration of therapy, and, for oral fluoroquinolones or cotrimoxazole, severity of sepsis (see description in Materials and Methods).
[b] In 3 instances, oral therapy with fluoroquinolones was deemed appropriate: once as monotherapy, once combined with an intravenous BLBLIC, and once combined with an intravenous second-generation cephalosporin.
[c] 1GC, first-generation cephalosporin; 2GC, second-generation cephalosporin; 3GC, third-generation cephalosporin; BLBLIC, β-lactam–β-lactamase inhibitor combination.

β-lactam antibiotics, we analyzed MICs from six hospitals (56% of the total study population). All isolates were susceptible to imipenem and/or meropenem. For amoxicillin-clavulanic acid or piperacillin-tazobactam, MICs below susceptibility breakpoints were demonstrated in 37/127 (29%) and 95/126 (75%) ESBL isolates, respectively. For ceftriaxone and cefotaxime, MICs below breakpoints were measured in 0/79 and 1/33 (3%) cases, respectively, whereas 71/127 (56%) isolates had ceftazidime MICs of ≤4 mg/liter.

Antibiotic treatment. Eighty-five patients (37%) received appropriate therapy within <24 h. Of these patients, 67% received carbapenems and 28% received aminoglycoside mono- or combination therapy (Table 3). Of the 71 known ESBL carriers, 38 (54%) received appropriate therapy within <24 h. Proportions of patients receiving appropriate therapy after bacteremia onset were 37% ($n = 85$) within <24 h, 59% ($n = 137$) within <48 h, and 74% ($n = 171$) within <72 h. Twenty patients received appropriate therapy within >72 h, 30 received inappropriate treatment only, and 11 patients died before receiving appropriate therapy.

In Tables 1 and 2, predictors of appropriate initial therapy on a univariable level are shown. In the multivariable analysis, known ESBL carriers (OR, 4.22; 95% confidence interval [CI], 2.10 to 8.49), patients with neutropenia (OR, 2.77; 95% CI, 1.04 to 7.37), patients having had a urological procedure (OR, 2.55; 95% CI, 1.18 to 5.51), and patients admitted to a university hospital (OR, 2.41; 95% CI, 1.17 to 4.96) received appropriate therapy within <24 h more often.

Day 30 mortality. For patients who received appropriate therapy within <24 h, <48 h, and <72 h, the day 30 mortality rates were 19% (16/85), 18% (24/137), and 16% (30/170), respectively, whereas for people treated inappropriately within these time periods, day 30 mortality rates were 21% (30/146), 23% (22/94), and 31% (19/61), respectively. In the univariable analysis, inappropriate therapy within <24 h was not associated with day 30 mortality (OR, 1.12; 95% CI, 0.57 to 2.19) (Table 4). Based on stratum-specific ORs, the strongest effect modification of the association between inappropriate therapy and mortality was seen for length of stay (LOS) before bacteremia onset, but for none of the strata was inappropriate therapy within <24 h significantly associated with day 30 mortality.

In multivariable analysis, a Charlson index of ≥3, patient age of ≥75 years, staying in the ICU at bacteremia onset, bacteremia source outside the urinary tract, and presence of severe sepsis or septic shock were independent predictors for day 30 mortality.

TABLE 4 Association of appropriateness of therapy within 24 h and possible confounders with day 30 mortality[c]

Variable	Mortality [no. of patients who died/total no. of patients (%)]	Unadjusted OR for mortality (95% CI) in univariable analysis	Association model[a]		Adjusted OR for mortality[b] (95% CI) in multivariable analysis
			Stratum-specific OR (95% CI) for appropriate therapy-mortality	MH pooled OR (95% CI)	
Appropriate therapy within <24 h					
Yes	16/85 (19)	1.12 (0.57–2.19)			1.53 (0.68–3.45)
No	30/146 (21)				
Charlson index					
<3	22/145 (15)	2.16 (1.13–4.16)*	1.15 (0.44–3.04)	1.18 (0.59–2.34)	2.80 (1.21–6.51)*
≥3	24/86 (28)		1.20 (0.46–3.17)		
Patient age (yr)					
<75	29/177 (16)	2.35 (1.17–4.72)*	1.46 (0.61–3.53)	1.21 (0.61–2.42)	3.81 (1.55–9.39)*
≥75	17/54 (31)		0.86 (0.27–2.72)		
LOS before onset (days)					
<21	33/169 (20)	1.09 (0.53–2.25)	0.79 (0.36–1.72)	1.12 (0.57–2.19)	
≥21	13/62 (21)		2.95 (0.72–12.04)		
Hospital ward at bacteremia onset					
Other	31/196 (19)	3.99 (1.85–8.64)*	1.26 (0.56–2.86)	1.13 (0.56–2.27)	2.88 (1.05–7.85)*
ICU	15/35 (43)		0.81 (0.20–3.22)		
Bacteremia source					
UTI	8/96 (8)	4.31 (1.91–9.71)*	1.10 (0.25–4.90)	1.05 (0.52–2.11)	4.79 (1.74–13.16)*
Other	38/135 (28)		1.04 (0.47–2.29)		
Bacteremia origin					
CO	5/38 (13)	1.78 (0.65–4.85)	1.50 (0.15–15.28)	1.16 (0.59–2.29)	
HC	41/193 (21)		1.13 (0.55–2.31)		
Severe sepsis					
No	14/150 (9)	7.24 (3.53–14.71)*	0.70 (0.23–2.15)	1.34 (0.65–2.74)	5.24 (2.36–11.60)*
Yes	32/75 (43)		2.10 (0.81–5.47)		
Neutropenia					
No	40/206 (19)	1.31 (0.49–3.50)	1.12 (0.54–2.33)	1.15 (0.58–2.27)	
Yes	6/25 (24)		1.38 (0.22–8.67)		

[a] Stratum-specific ORs to study confounding and effect modification of the association between appropriate therapy and mortality by the eight other variables.
[b] Adjusted OR from forward stepwise logistic regression analysis, with appropriate therapy initially forced into the model (including 225 patients).
[c] CO, community onset; HC, nosocomial or health care associated; ICU, intensive care unit; LOS, length of stay; MH, Mantel-Haenszel; UTI, urinary tract infection. *, *P* value of <0.05 determined by Pearson's chi-squared test or Wald test.

Forcing inappropriate therapy within <24 h into this model failed to reveal a statistically significant association (OR, 1.53; 95% CI, 0.68 to 3.45) (Table 4). When interaction terms between each variable and appropriateness of therapy were added to the latter model, none of them appeared significant. By calculating Mantel-Haenszel pooled ORs, the strongest confounding effect was seen for severe sepsis (Table 4). Further analysis of confounding revealed that no other covariate influenced the regression coefficient for adequacy of therapy by >10% after inclusion of sepsis severity, patient age, and neutropenia, and the association between adequacy of therapy and mortality remained nonsignificant (OR, 1.65; 95% CI, 0.76 to 3.59).

Thirty-seven patients did not receive appropriate therapy within <24 h in the primary analysis but received a regimen with a BLBLIC or ceftazidime initially, which, taking into account the criterion for duration of appropriate treatment, could potentially form part of appropriate therapy provided that the isolate was susceptible. Of these patients, 8 (22%) had MICs of the concerned agent below CLSI 2010 clinical breakpoints. Classification of these episodes as receiving appropriate therapy within <24 h, together with the 6 patients (16%) for whom no MICs were available, did not change the association between inappropriate therapy and day 30 mortality (data not shown). When patients with urinary and nonurinary bacteremia sources were analyzed separately, results for inappropriate therapy in multivariable models did not change appreciably, nor did they change after exclusion of patients not receiving intravenous therapy in the first 24 h (data not shown). Also, inappropriate therapy within <48 h was not associated with day 30 mortality in a multivariable model (OR, 1.92; 95% CI, 0.89 to 4.16).

Secondary outcomes. Inappropriate therapy within <24 h was associated with neither ICU admission within 1 week of bacteremia onset nor length of hospital stay after bacteremia onset in patients who were discharged alive, by both univariable and multivariable analyses (data not shown).

DISCUSSION

This study demonstrates that, in the Netherlands, 84% of bacteremia episodes caused by ESBL-producing *E. coli*, *K. pneumoniae*, or *E. cloacae* are nosocomial or otherwise health care associated, that ESBL carriage is known at bacteremia onset in 31% of episodes, that 63% of patients still receive inappropriate antimicro-

bial therapy in the first 24 h after bacteremia onset, and that the day 30 mortality rate of ESBL bacteremia is 20%. Comorbidity, patient age, source of bacteremia, presence of severe sepsis or septic shock, and ICU stay at bacteremia onset, but not adequacy of antibiotic treatment within <24 h or <48 h after bacteremia onset, were associated with day 30 mortality.

The population of patients with ESBL bacteremia in Dutch hospitals is characterized by high prevalences of malignancies, recurrent UTIs, previous antibiotic use, and long hospital stay before bacteremia onset, which is typical for patients at risk for multiresistant bacterial infections, as reported by others (21). UTIs and intra-abdominal infections are the major sources of bacteremia. Even most patients with community-onset bacteremia had comorbidities requiring frequent hospital visits or had recently visited a country with a high prevalence of ESBL carriage.

Inappropriate empirical antibiotic therapy is the most feared consequence of the increasing incidences of infections caused by ESBL-producing bacteria. As shown, the prevalence of ESBL-producing bacteria is still low in our country. Prediction rules might be helpful in identifying those patients who should (or should not) be empirically treated with carbapenems or other appropriate combinations of antibiotics. In this study, only half of patients with known ESBL carriage received appropriate therapy within <24 h. Apparently, patient records with microbiology results were either not consulted or neglected before initiation of empirical therapy. Currently, Dutch national sepsis guidelines recommend prescribing a combination of a second- or third-generation cephalosporin and aminoglycoside or carbapenem monotherapy if a patient is known to be colonized with an ESBL-producing isolate or has used cephalosporins or fluoroquinolones in the past month (22). In our cohort, 149 patients either had documented ESBL carriage or had used these antibiotics in the past 2 months. Only 65 of them received appropriate initial therapy. Adherence to Dutch national sepsis guidelines, therefore, would increase the proportion of patients receiving appropriate empirical antibiotic treatment.

Inappropriate therapy for sepsis has been shown to increase mortality, especially in critically ill patients (23–25). Indeed, upon univariable analysis, we observed a trend toward higher mortality in the case of inappropriate therapy in severely septic patients (OR of 2.10 for this stratum; 95% CI, 0.81 to 5.47). However, inadequate therapy within <24 h did not increase day 30 mortality in the multivariable analysis. In this ESBL bacteremia cohort, patients might have died due to underlying diseases and an inability to treat severe sepsis or to control the source of bacteremia, for instance, by surgery. Neither the possible misclassification of cephalosporins and BLBLIs as inadequate therapy nor the abundance of comparatively benign urinary tract infections appeared to explain the absence of an effect. In other studies of patients with infections caused by ESBL-producing bacteria, conflicting results were obtained with regard to associations between inappropriate treatment and mortality. Strong effects (adjusted ORs of 5.88 to 6.28) were demonstrated in patients with bacteremia caused by ESBL-producing *E. coli* (26) and *Enterobacteriaceae* (27), whereas no association was reported by others (28–32). However, the effects of inappropriate empirical therapy on patient outcomes were often evaluated in cohorts combining ESBL and non-ESBL bacteremias. The results of these studies were similarly conflicting (33–36).

Our study has several limitations. First of all, due to its retrospective nature, some data, such as the exact number and duration of the previous use of antibiotics and Pitt scores, could not be retrieved for all patients. Second, the study was performed in eight Dutch hospitals, which may reduce generalizability to other countries. Similarly, inclusion of three out of eight university hospitals in the country may curtail generalizability for the non-university hospitals in the Netherlands. However, the annual proportions of ESBL-producing isolates among *Enterobacteriaceae* were comparable to those reported for the Netherlands in the EARSS database (7), and characteristics of patients were comparable to those reported in another Dutch study on ESBL bacteremia (37). Finally, we did not perform genetic typing of isolates and hence could not assess the role of specific pathogenic clones, such as *E. coli* ST131 and *K. pneumoniae* ST258, as a determinant of mortality in bacteremia.

In conclusion, 84% of ESBL bacteremia episodes in these Dutch patients were nosocomial or otherwise health care associated. Most patients had comorbidities requiring frequent hospital visits. Although inappropriate therapy was not associated with day 30 mortality, adequacy of initial treatment may be improved in a significant number of patients by consultation of previous culture results.

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