

Analysis of 4758 *Escherichia coli* bacteraemia episodes: predictive factors for isolation of an antibiotic-resistant strain and their impact on the outcome

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Received 10 October 2008; returned 1 November 2008; revised 16 November 2008; accepted 18 November 2008

Objectives: To describe the predictive factors for the isolation of fluoroquinolone-resistant or extended-spectrum β -lactamase (ESBL)-producing *Escherichia coli* and their impact on bacteraemia outcome.

Methods: Analysis of *E. coli* bacteraemia episodes prospectively collected through a blood culture surveillance programme from January 1991 to December 2007.

Results: Out of 18 080 episodes, 4758 (26%) *E. coli* bacteraemias were reported in the period of study. Mortality was noted in 440 cases (9%). Fluoroquinolone-resistant strains were reported in 1300 (27%) cases and ESBL-producing strains in 211 cases (4%). One hundred and seventy-eight strains out of 211 (84%) ESBL-producing *E. coli* were isolated since 2001. The two main independent risk factors for mortality were shock (OR: 10.28, $P < 0.001$) and inappropriate empirical therapy (OR: 4.83, $P < 0.001$). Inappropriate empirical therapy was significantly more frequent for infections caused by fluoroquinolone-resistant strains ($n = 203$, 16%, $P < 0.001$) and ESBL-producing strains ($n = 110$, 52%, $P < 0.001$). Independent factors associated with the isolation of a fluoroquinolone-resistant strain were: nosocomial origin (OR: 1.61, $P < 0.001$); urinary catheterization (OR: 2.44, $P < 0.001$); and previous therapy with a fluoroquinolone (OR: 7.41, $P < 0.001$). The independent risk factors associated with the isolation of an ESBL-producing strain were: nosocomial origin (OR: 1.68, $P = 0.03$); urinary catheterization (OR: 1.88, $P = 0.001$); and previous β -lactam antibiotic therapy (OR: 2.81, $P < 0.001$).

Conclusions: Inappropriate empirical therapy was the strongest independent factor that we could modify to improve mortality in *E. coli* bacteraemia and was more frequent in cases caused by fluoroquinolone-resistant or ESBL-producing strains. Nosocomial acquisition, urinary catheterization and previous therapy with a fluoroquinolone or β -lactam were predictive factors for infection with an antibiotic-resistant strain.

Keywords: *E. coli* bacteraemia, fluoroquinolone resistance, extended-spectrum β -lactamases, outcome, empirical treatment

Introduction

Escherichia coli is the most frequent Gram-negative microorganism causing bacteraemia worldwide and several studies have been focused on the prognostic factors of these bloodstream infections.^{1–7} Over the last decade, there has been a marked increase in infections caused by antibiotic-resistant *E. coli* that could have changed the outcome in patients with bacteraemia. Fluoroquinolone-resistant *E. coli* and, particularly, extended-

spectrum β -lactamase (ESBL)-producing *E. coli* are of great concern due to their increased incidence and their frequent associated resistance to other groups of antimicrobial agents.^{8–10} This increasing resistance limits treatment options and may affect the prognosis of the *E. coli* infections.^{11–15} Promptness of adequate antibiotic therapy can influence the outcome of bloodstream infections. Growing resistance to antibiotics may lead to an increase in inappropriate empirical antimicrobial treatment of infections with a delay in the correct therapy.^{16–18}

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This study was undertaken to describe the source, resistance rate to fluoroquinolone and β -lactam antibiotics and mortality of *E. coli* bacteraemia episodes reported during the 1991–2007 period in a single institution and to identify the predictive factors for the isolation of fluoroquinolone-resistant or ESBL-producing strains.

Patients and methods

Setting and data collection

The setting was the Hospital Clínic in Barcelona, a 700 bed university tertiary centre that provides specialized and broad medical, surgical and intensive care for an urban population of 500 000 people. This hospital has followed a blood culture surveillance programme since 1990. Briefly, one infectious disease specialist and one microbiologist review the charts of patients with positive blood cultures and recommend antibiotic therapy, according to the clinical context and the results of the Gram stain, organism identification and susceptibilities. The patient is then followed until discharge or death. Data regarding the episode of bacteraemia are thus collected prospectively and entered in a database designed specifically for the blood culture surveillance programme.

Study design and inclusion criteria

The type of study was an analysis of cases of *E. coli* bacteraemia prospectively collected through the previously described blood culture surveillance programme from January 1991 to December 2007. The Ethics Committee of the hospital approved the study. Written informed consent was obtained from patients.

Microbiological methods

Between 1991 and 1997, blood samples were processed by the BACTEC NR-730 system (Becton-Dickinson Microbiology Systems) and maintained routinely for 7 days. Since 1998, we have used the BACTEC 9240 system (Becton-Dickinson Microbiology Systems), with an incubation period of 5 days. Isolates were identified by standard techniques.¹⁹ Antimicrobial susceptibility testing was performed by a microdilution system (Microscan, Dade Behring, West Sacramento, CA, USA, or Sensititre, Trek Diagnostic Systems, East Grinstead, West Sussex, UK, or Phoenix System, Becton Dickinson, Franklin Lakes, NJ, USA). MICs observed with the three systems were interpreted using CLSI guidelines.²⁰ The recommendations advocated in the CLSI documents were also followed to detect the production of an ESBL. Microorganisms reported as intermediate were considered resistant.

Patient characteristics

The following data were obtained for all patients: age, sex, pre-existing co-morbidities, prognosis of the underlying disease, prior antibiotic therapy, prior surgery (within the last month), current administration of ≥ 20 mg of corticosteroids every day, current administration of anti-neoplastic chemotherapy, source of bacteraemia, leucocyte count, origin of the infection (community-acquired or nosocomial, including last conventional hospitalization or outpatient visit), length of hospitalization before diagnosis of bacteraemia, ICU admission, need for mechanical ventilation, empirical and definitive antibiotic treatment, susceptibility to antibiotics of the microorganism isolated, presence of shock, and mortality.

Definition of terms

Significant bacteraemia was defined as one or more blood cultures positive for *E. coli* and clinically apparent signs and symptoms of sepsis (as described previously).²¹ An episode of *E. coli* bacteraemia was thought to be nosocomial if it took place ≥ 72 h after admission, or if the patient had been hospitalized within 2 weeks before the current admission or had received long-term healthcare (healthcare-related); otherwise, the bacteraemia was considered community-acquired. The source of infection was determined by a senior infectious disease specialist, who considered the patient's medical history, physical examination and the results of other microbiological tests and complementary imaging exploration. Definitions of the source of bacteraemia, such as pneumonia, urinary tract infection, surgical site infection or another, were as described previously.^{22,23} An intravenous catheter was considered to be the source of bacteraemia when, in the absence of any other clinically apparent focus, any of the following criteria was present: local inflammatory signs or suppuration at the insertion site; a positive culture of the catheter tip where the *E. coli* with the same susceptibility pattern as that isolated in peripheral blood was grown; at least 2 h difference in the time of growth between catheter and a venepuncture-drawn blood culture; and, finally, spontaneous resolution of sepsis within 24 h after catheter withdrawal without antibiotic treatment.^{24,25} When no focal infection could be demonstrated, the source was categorized as unknown.

Co-morbidity was defined as a disease or therapy that could predispose patients to infection, alter defence mechanisms or cause functional impairment, such as the following: diabetes; liver cirrhosis; renal failure; alcoholism (> 100 g of alcohol every day); injecting drug users; active neoplastic disease; severe chronic obstructive pulmonary disease; severe cardiac disease with symptomatic heart failure; severe dementia; and administration of immunosuppressive drugs (≥ 20 mg of corticosteroids every day on a regular basis or anti-neoplastic chemotherapy). Prognosis of the underlying disease was classified, according to a modification of the criteria of McCabe and Jackson, as rapidly fatal (when death was expected within ≤ 3 months), ultimately fatal (when death was expected within a period of > 3 months but < 5 years) and non-fatal (when life expectancy was ≥ 5 years).²⁶

Prior antibiotic therapy was defined as the use of any antimicrobial agent for ≥ 3 days during the month prior to the occurrence of the bacteraemic episode. Antibiotic treatment, either empirical or definitive (before or after the microbiological results and susceptibilities were known, respectively), was considered appropriate if at least one of the antibiotics involved had *in vitro* activity against the bacteria and the dose and route of administration were adequate. Shock was defined as a systolic pressure of < 90 mmHg that was unresponsive to fluid treatment or required vasoactive drug therapy.²¹

Death was considered related to the bloodstream infection if it occurred before the resolution of symptoms or signs or within 7 days of the onset of bacteraemia, and if there was no other explanation; otherwise, death within 30 days of the onset of bacteraemia was considered unrelated to the episode.

Follow-up

Patients were observed from the diagnosis of bacteraemia until 30 days afterwards, until death in hospital or until discharge.

Statistical analysis

Statistical analyses were carried out using the program SPSS (version 14.0; SPSS, Chicago, IL, USA). Continuous variables are expressed as mean \pm SD or median (range) according to their homogeneity. Categorical variables were compared using the χ^2 test or Fisher's

exact test (when necessary). The quantitative variables were compared using the Student–Fisher *t*-test or ANOVA. Non-parametric tests were used when the application conditions were not applicable. Statistical significance was defined as a two-tailed *P* value <0.05.

Variables with *P* ≤ 0.2 in the univariate analysis were further analysed by using a stepwise non-conditional (logistic regression) multivariate analysis to find out the independent factors associated with mortality. For analysis purposes, we considered related and unrelated mortality (within 30 days of bloodstream infection) together.

Results

During the period of study, 4758 *E. coli* bacteraemia episodes out of 18 080 (26%) bloodstream infections were reported. *E. coli* isolation occurred in 40% of community-acquired and

14% of nosocomial bacteraemia episodes. Table 1 shows the epidemiological and clinical characteristics of episodes. There were 1399 (29%) cases of nosocomial acquisition. In 349 (7%) cases, the empirical therapy was inappropriate. One thousand and three hundred strains (27%) were resistant to fluoroquinolones and 211 cases (4%) were ESBL-producing strains. Mortality was noted in 440 cases (9%).

The more frequent sources of bacteraemia are reported in Table 2. Pneumonia, intra-abdominal infection, skin and soft tissue infection and unknown focus were the bacteraemia sources with a higher mortality (37%, 26%, 18% and 15%, respectively). On the other hand, catheter-related bacteraemia, skin and soft tissue infection and unknown focus were the bacteraemia sources with a higher proportion of fluoroquinolone-resistant isolates (51%, 42% and 39%, respectively). The bacteraemia sources with a higher proportion of ESBL-producing strains isolated were skin

Table 1. Epidemiological and clinical characteristics of *E. coli* bacteraemia episodes, *n* = 4758

Characteristics	<i>n</i> (%)
Age in years (mean ± SD)	65 ± 18
Male gender	2205 (46)
Co-morbidity	
diabetes mellitus	852 (18)
solid-organ neoplasm	832 (17)
heart failure	533 (11)
liver cirrhosis	555 (12)
haematological neoplasm	520 (11)
uropathology	313 (7)
chronic lung disease	297 (6)
chronic renal insufficiency	281 (6)
haemodialysis	69 (1)
SOT	278 (6)
HIV infection	115 (2)
alcoholism	116 (2)
HSCT	83 (2)
Prognosis of underlying disease: ultimately or rapidly fatal	1808 (38)
Origin of bacteraemia: nosocomial-acquired	1399 (29)
Previous admission (last month)	642 (13)
Previous antibiotic therapy	1055 (22)
Previous FQ	378 (8)
Previous β-lactam	575 (12)
Corticosteroids	662 (14)
Neutropenia	358 (8)
Central venous catheterization	819 (17)
Urinary catheterization	549 (12)
Previous surgery	380 (8)
Fever	4613 (97)
Shock	650 (14)
Mechanical ventilation	60 (1)
Inappropriate empirical therapy	349 (7)
FQ-resistant strain	1300 (27)
ESBL production	211 (4)
Polymicrobial bacteraemia	429 (9)
Persistent bacteraemia	77 (2)
Mortality	440 (9)

HSCT, haematopoietic stem cell transplantation; SOT, solid-organ transplantation; FQ, fluoroquinolone; ESBL, extended-spectrum β-lactamase.

Antibiotic-resistant *E. coli* strains and bacteraemia outcome

Table 2. Most important sources of *E. coli* bacteraemia and their percentages of mortality and antibiotic resistance

	<i>n</i> (%) ^a	Community-acquired, <i>n</i> (%) ^b	Nosocomial origin, <i>n</i> (%) ^b	Mortality, <i>n</i> (%) ^b	FQ-resistant, <i>n</i> (%) ^b	ESBL-producing, <i>n</i> (%) ^b
Urinary tract infection	2598 (55)	2180 (84)	418 (16)	113 (4)	599 (23)	83 (3)
Unknown focus	686 (14)	280 (41)	406 (59)	106 (15)	269 (39)	45 (7)
Biliary infection	604 (13)	473 (78)	131 (22)	47 (8)	139 (23)	21 (3)
Intra-abdominal infection	321 (7)	212 (66)	109 (34)	82 (26)	90 (28)	17 (5)
Catheter-related bacteraemia	186 (4)	6 (3)	180 (97)	9 (5)	94 (51)	21 (11)
Pneumonia	154 (3)	90 (58)	64 (42)	57 (37)	44 (29)	9 (6)
Skin and soft tissue infection	84 (2)	32 (38)	52 (62)	15 (18)	35 (42)	11 (13)
Other	125 (3)	86 (69)	39 (31)	11 (9)	30 (24)	4 (3)
Total	4758	3359 (71)	1399 (29)	440 (9)	1300 (27)	211 (4)

FQ, fluoroquinolone; ESBL, extended-spectrum β -lactamase.

^a% of column.

^b% of row.

Table 3. Chronological evolution of susceptibility to antibiotics of *E. coli* isolations from blood cultures

Characteristic	1991–95, <i>n</i> (%)	1996–2000, <i>n</i> (%)	2001–07, <i>n</i> (%)
Total bacteraemia episodes	4192	5496	8392
<i>E. coli</i> bacteraemia episodes	940 (22)	1478 (27)	2340 (28)
FQ-resistant strain	121 (13)	367 (25)	812 (35)
community-acquired	50 (41)	193 (53)	453 (56)
nosocomial origin	71 (59)	174 (47)	359 (44)
ESBL-producing strain	3 (<1)	30 (2)	178 (8)
community-acquired	—	18 (60)	64 (36)
nosocomial origin	3 (<1)	12 (40)	114 (64)
Mortality	73 (8)	142 (10)	225 (10)

FQ, fluoroquinolone; ESBL, extended-spectrum β -lactamase.

and soft tissue infection and catheter-related bacteraemia (13% and 11%, respectively).

The chronological evolution of incidence and antibiotic susceptibility of *E. coli* isolates is shown in Table 3. The fluoroquinolone resistance increased during the period of the study (13% in 1991–95, 25% in 1996–2000 and 35% in 2001–07). There was also an increase in ESBL-producing strains during the 2001–07 period (8% compared with 2% in the previous period). Mortality accounted for 10% during the last 12 years.

Risk factors for mortality

The independent risk factors for mortality are shown in Table 4. The two main independent risk factors for mortality were shock at presentation (OR: 10.28, 95% CI: 7.80–13.56, $P < 0.001$), followed by inappropriate empirical therapy (OR: 4.83, 95% CI: 3.48–6.71, $P < 0.001$). The isolation of an antibiotic-resistant strain was not an independent risk factor for mortality. Inappropriate empirical therapy was significantly more frequent for infections caused by fluoroquinolone-resistant strains ($n = 203$, 16%, $P < 0.001$) and ESBL-producing strains ($n = 110$, 52%, $P < 0.001$) (Table 5).

Table 4. Multivariate analysis of risk factors associated with mortality in *E. coli* bacteraemia

Characteristics	OR	95% CI	<i>P</i> value
Shock	10.28	7.80–13.56	<0.001
Inappropriate empirical therapy	4.83	3.48–6.71	<0.001
Pneumonia	4.23	2.52–7.09	<0.001
Liver cirrhosis	2.57	1.82–3.62	<0.001
Intra-abdominal infection	2.41	1.61–3.60	<0.001
Solid-organ cancer	1.83	1.35–2.48	<0.001
Neutropenia	1.75	1.14–2.69	0.01
Chronic renal insufficiency	1.69	1.08–2.66	0.03
Corticosteroids	1.61	1.17–2.22	0.004

Risk factors for the isolation of an antibiotic-resistant strain

Independent risk factors associated with the isolation of a fluoroquinolone-resistant strain (Table 6) were: nosocomial origin (OR: 1.61, $P < 0.001$); urinary catheterization (OR: 2.44,

Table 5. Proportion of inappropriate empirical therapy according to antibiotic susceptibility pattern

Antibiotic susceptibility pattern	<i>n</i>	Inappropriate empirical therapy, <i>n</i> (%) ^a	<i>P</i> value
FQ-susceptible	3458	146 (4)	<0.001
FQ-resistant	1300	203 (16)	
No ESBL production	4547	239 (5)	<0.001
ESBL-producing strain	211	110 (52)	

FQ, fluoroquinolone; ESBL, extended-spectrum β -lactamase.
^a% of row.

Table 6. Multivariate analysis of risk factors associated with the isolation of a fluoroquinolone-resistant *E. coli* strain

Characteristics	OR	95% CI	<i>P</i> value
Nosocomial origin	1.61	1.25–2.08	<0.001
Unknown focus	1.55	1.23–1.95	<0.001
Catheter-related bacteraemia	1.51	1.00–2.28	0.05
Urinary catheterization	2.44	1.92–3.11	<0.001
Previous admission	1.73	1.42–2.10	<0.001
Previous therapy with FQ	7.41	5.10–10.78	<0.001

FQ, fluoroquinolone.

Table 7. Multivariate analysis of risk factors associated with the isolation of an ESBL-producing *E. coli* strain in bacteraemia

Characteristics	OR	95% CI	<i>P</i> value
Nosocomial origin	1.68	1.04–2.71	0.03
Previous admission	1.93	1.37–2.70	<0.001
Urinary catheterization	1.88	1.28–2.76	0.001
Previous therapy with β -lactam	2.81	1.95–4.04	<0.001

$P < 0.001$); and previous antibiotic therapy with a fluoroquinolone (OR: 7.41, $P < 0.001$). The independent risk factors associated with the isolation of an ESBL-producing strain (Table 7) were: nosocomial origin (OR: 1.68, $P = 0.03$); urinary catheterization (OR: 1.88, $P = 0.001$); and previous therapy with a β -lactam antibiotic (OR: 2.81, $P < 0.001$).

For data regarding univariate analysis for mortality, fluoroquinolone susceptibility and ESBL production, please see Tables S1–S3 [available as Supplementary data at JAC Online (<http://jac.oxfordjournals.org/>)].

Discussion

E. coli is the main causal agent of community-acquired bacteraemia and the third most frequent pathogen causing nosocomial bloodstream infection, and its incidence remained stable during the study period. According to our data, the main source of

E. coli bacteraemia was urinary tract infection (55%) followed by unknown focus and biliary infection (14% and 13%, respectively). Mortality was noted in 440 cases (9%) in our series, but it was higher in cases where pneumonia and intra-abdominal infection were the bacteraemia sources (37% and 26%, respectively). Similar to previously reported data, we observed a higher proportion of fluoroquinolone-resistant and ESBL-producing isolates in the last years of the study (2001–07, 35% and 8%, respectively).²⁷ Furthermore, the proportion of strains resistant to antibiotics was higher in bloodstream infections that were catheter-related (51% and 11%, respectively), skin and soft tissue infections (42% and 13%, respectively) and unknown focus (39% and 7%, respectively). In our series, the independent risk factors for mortality were: shock, co-morbidity (liver cirrhosis, chronic renal insufficiency, solid-organ cancer, neutropenia and simultaneous treatment with corticosteroids); the presence of pneumonia or intra-abdominal infection; and inappropriate empirical therapy. From these variables, empirical antibiotic therapy is the only one we could modify to decrease the mortality rate. When factors associated with inappropriate empirical treatment were studied, we found that they were more frequent in cases of antibiotic-resistant *E. coli* strains. Peralta *et al.*¹⁸ reported similar results in their study with 663 episodes of *E. coli* bacteraemia, of which 525 (79%) cases were of nosocomial origin.¹⁸

During the previous years of this decade, most investigations were performed regarding the clinical significance of infections caused by antibiotic-resistant *E. coli* strains. A number of studies found no significant association between ESBL production or fluoroquinolone resistance and crude mortality.^{11–12,28} In contrast, several other studies observed that patients with infection due to antibiotic-resistant bacilli tended to have poorer outcomes.^{29–31} Probably, inappropriate empirical treatment, which is more frequent in cases of antibiotic-resistant *E. coli*, is the main factor that determines mortality. This could explain the controversy that exists in the literature about the impact of infections caused by antibiotic-resistant isolates on outcome.³²

Therefore, it would be interesting to know the factors predictive of the isolation of an antibiotic-resistant *E. coli* with the objective of adequate empirical therapy. Numerous studies have assessed the variables associated with ESBL-producing enterobacteria colonization or infection.²⁷ According to our data, nosocomial acquisition and urinary catheterization were clinical predictive factors for an antibiotic-resistant isolation. Furthermore, previous antibiotic therapy with a fluoroquinolone or β -lactam was a predictive factor for the isolation of a fluoroquinolone-resistant or ESBL-producing *E. coli* strain, respectively.

There are several potential limitations to our study. First, we have reported the results of a retrospective analysis of a database prospectively collected for more than 15 years. Consequently, it is very difficult to review charts and in several cases there were several lost values. Second, we considered related and unrelated mortality together. This is an analysis option used almost always in bloodstream infection outcome studies, but the factors associated with mortality in the first week after the bacteraemia diagnosis could be different from those associated with a fatal outcome during the 30 posterior days. And third, MIC values were not available in the database. We reported susceptibility as a categorical variable, and this was a limitation to study the relation between MIC value, empirical or definitive treatment and outcome.

Finally, in hospital settings similar to ours, when *E. coli* bacteraemia is suspected to be associated with severe sepsis or septic shock, a high-risk mortality source (peritonitis or pneumonia) with risk factors for a fluoroquinolone-resistant or ESBL-producing isolation or focus with a higher proportion of resistant strains (catheter-related bacteraemia, skin and soft tissue infection or unknown focus), the initial empirical treatment should include an antibiotic with activity against cephalosporin-resistant isolates such as a carbapenem or tigecycline.

Acknowledgements

This study was partially presented at the Forty-eighth Annual Interscience Conference on Antimicrobial Agents and Chemotherapy and the Infectious Diseases Society of America Forty-sixth Annual Meeting, Washington, DC, USA, 2008.

Funding

This work was supported by grants from the *Fundación Máximo Soriano Jiménez* of Barcelona.

Transparency declarations

Conflict of interest: none to declare.

Supplementary data

Tables S1, S2 and S3 are available as Supplementary data at JAC Online (<http://jac.oxfordjournals.org/>).

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