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Role of place of acquisition and inappropriate empirical antibiotic therapy on the outcome of extended-spectrum β-lactamase-producing Enterobacteriaceae infections

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ABSTRACT

The impact of inappropriate empirical antibiotic therapy (IEAT) on the outcome of severe infections due to extended-spectrum β-lactamase-producing Enterobacteriaceae (ESBL-Ent) remains unclear. Current evidence is limited by study design and lack of confounder control. The main objective of this study was to define the outcome of severe infections due to ESBL-Ent according to clinical parameters and place of infection acquisition. Adult hospitalised patients with ESBL-Ent infections were included in a 3-year multicentre prospective study. Primary outcomes were IEAT rates and crude mortality of severe infections, adjusted by place of acquisition [community-acquired infection (CAI), healthcare-associated infection (HCAI) and hospital-acquired infection (HAI)]. Among 729 patients, 519 (71.2%) were diagnosed with HAI, 176 (24.1%) with HCAI and 34 (4.7%) with CAI. Moreover, 32.9% of patients received IEAT; higher rates of IEAT were observed in pneumonia (23%) and deep surgical site infections (19%). HCAIs were more frequently associated with IEAT than HAIs (48.3% vs. 27.9%; OR = 1.7, 95% CI 1.2–2.4). The overall mortality rate for severe infections ($n = 264$) was 12.1% and was significantly higher in HCAIs (20%) than HAIs (10%) (RR = 2.3, 95% CI 1.01–5.3). IEAT significantly increased the risk of mortality in bloodstream infections (RR = 8.3, 95% CI 2–46.3). Rates of IEAT and overall mortality of ESBL-Ent severe infections were higher in HCAIs than HAIs. Prompt diagnosis of patients with severe HCAIs due to ESBL-Ent is essential since these infections receive high rates of IEAT and significantly higher mortality than HAIs [ClinicalTrials.gov Identifier: NCT00404625].

1. Introduction

The epidemiology of infections due to extended-spectrum β-lactamase-producing Enterobacteriaceae (ESBL-Ent) has changed drastically in recent years and it is now an important healthcare burden [1]. In 2016, the European Antimicrobial Resistance Surveillance Network (EARS-Net), encompassing 30 European Union/European Economic Area (EU/EEA) countries, reported a general European-wide increase in resistance with regard to Gram-negative bacteria under surveillance (*Escherichia coli, Klebsiella pneumoniae* and *Pseudomonas aeruginosa*). The EU/EAA

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Table 1
Definitions of place of infection acquisition.

Classification	Definition
Community-acquired infection (CAI)	Diagnosed within 48 h from hospital admission in patients with no risk factors for community-onset infection
Healthcare-associated infection (HCAI)	Diagnosed within 48 h from hospital admission in patients with at least one of the following risk factors: admission from long-term care-facility or nursing home; central venous catheter or urinary catheter; dialysis; ambulatory visits; and visiting nursing assistance in the previous 30 days and/or hospitalisation in the previous 6 months
Hospital-acquired infection (HAI)	Diagnosed after 48 h of hospital admission and not incubating at the time of admission

population-weighted mean of *E. coli* isolates resistant to third-generation cephalosporins (most of which were ESBL-producers) was 12.4% in 2016, representing an increase over the previous 3 years in more than one-third of the EARS-Net reporting countries [2]. In the USA, the incidence both of ESBL-producing *Klebsiella* infections and ESBL-producing *E. coli* infections has grown equally over the past two decades, with one study even reporting 16.6 infections per 10 000 discharges [3]. In Malawi, ESBL resistance rose from 0.7% to 30.3% in *E. coli*, from 11.8% to 90.5% in *Klebsiella* spp. and from 30.4% to 71.9% in other Enterobacteriaceae [4]. Among pathogens causing bloodstream infections (BSIs), percentages of ESBL production ranged from 18.8% to 49% in *E. coli* and *Enterobacter* spp., respectively [5,6].

Antimicrobial resistance has deleterious effects on health economics and clinical outcome as it leads to higher in-hospital mortality, high rates of clinical failure, prolonged infection-related hospital stay and increased costs [7]. Recent studies have confirmed that bacteraemia due to ESBL-producing isolates is associated with an increased risk of death [relative risk = 1.63, 95% confidence interval (CI) 1.13–2.35] as well as higher mortality compared with bacteraemia due to non-ESBL-Ent [8]. Recent data from Finland showed that urinary tract infections (UTIs) caused by ESBL-producing bacteria result in double the healthcare costs compared with ESBL-negative patients, mainly due to the increased length of stay [9]. Antimicrobial resistance clearly affects the rate of inappropriate empirical antibiotic therapy (IEAT), however the link between IEAT and worse clinical outcome is more debatable [10]. A recent retrospective study analysing 601 BSIs due to ESBL-Ent showed no association between appropriate treatment and cure/improvement. The only significant determinants of clinical outcome were infection source, infection severity and baseline co-morbidities [11].

The aim of this prospective multicentre cohort study was to determine the impact of IEAT within 48 h on the outcome of ESBL-Ent infections in hospitalised patients, with a focus on place of infection acquisition.

2. Materials and methods

A multicentre prospective cohort study was performed including all adult patients (age >16 years) with infection (i.e. bloodstream, lung, surgical site, skin and soft tissue, and urinary tract) caused by ESBL-Ent hospitalised from 1 June 2007 to 31 May 2010 in five large Italian hospitals, namely 'Careggi' University Hospital (Florence), 'Azienda Ospedaliera Provincia di Lecco' (Lecco), 'Azienda Ospedaliera Provincia di Lodi' (Lodi), 'Ospedali Riuniti di Bergamo' (Bergamo) and 'Azienda Ospedaliera Provincia di Cremona' (Cremona). The hospitals were selected for their homogeneity of hospital admission and infection control procedures. In all centres, the US Centers for Disease Control and Prevention (CDC) infection control measures were applied, including contact precaution for patients colonised or infected with ESBL-Ent [12]. Local ethical committee approval was obtained in all centres. Physicians reviewed microbiological data on a daily basis to identify patients who met the inclusion criteria. All patients with a microbiological culture yielding ESBL-Ent were prospectively reviewed by dedicated study personnel and by attending physicians in order to define infected patients according to CDC definitions. Epidemiological and clinical variables were recorded for all patients following their admission to the study and during hospitalisation according to the study design. Table 1 illustrates the definition for place of infection acquisition. Severe infections were defined as BSI, deep surgical site infection (SSI) and pneumonia. IEAT was defined as initiation of in vitro ineffective therapy against the ESBL-Ent (according to the results of the antimicrobial susceptibility pattern of the isolate) 1 day prior or 2 days after microbiological samples were taken. In the case of combination therapy, empirical treatment was considered appropriate if at least one antibiotic agent effective against the ESBL-Ent was administered. Crude mortality was defined as death occurring during hospitalisation.

Medical records of patient admissions as well as microbiology and pharmacy databases were reviewed. Data collected at study enrolment included: patient demographics; transfer from another hospital; residence in a long-term care facility or nursing home; previous hospitalisation within 6 months; chronic haemodialysis; presence of a central venous catheter (CVC) or urinary catheter; intensive care unit (ICU) stay; ambulatory visits; and surgical procedures within 30 days of study inclusion. An aggregate co-morbidity measure based upon the Chronic Disease Score (CDS), derived and validated for studies of antibiotic-resistant infections, was applied to assess the comorbidity-attributable risk [13]. Antibiotics administered during a 30-day period prior to study enrolment for ≥48 h were also recorded. In case of oral and intravenous antibiotic exposure, individual antibiotics, antibiotic classes and combination types were recorded, including penicillins, vancomycin, cephalosporins, antibiotics with predominantly anaerobic activity (metronidazole and clindamycin), aminoglycosides, quinolones and carbapenems. Dosages and duration of antibiotic therapy were noted. Hospital length of stay (LOS) after infection diagnosis, management of infection, timing and type of empirical and susceptibility-based antimicrobial therapy, and crude mortality were extracted from medical records through daily patient visits. All patients with infections caused by ESBL-Ent were followed until hospital discharge or death.

The primary outcomes of the study were the rates of IEAT and crude mortality in patients with severe infection due to ESBL-Ent adjusted by co-morbidities, clinical condition and place of infection acquisition. Secondary outcomes were epidemiological and clinical variables associated with first diagnosis of ESBL-Ent infection according to the place of acquisition.

Analysis of mortality was performed by comparing deceased infected patients with survivors of infection (evaluable in patients with severe infections, i.e. BSI, deep SSI and pneumonia). To identify patients at high risk of presenting at hospital admission with healthcare-associated infection (HCAI) and those at risk of developing hospital-acquired infection (HAI) due to ESBL-Ent, patients were compared through two nested case–control studies. In order to reduce confounding, patients with HCAI or HAI (cases) were compared with controls (ratio 1:1) randomly selected among patients admitted to the same ward with no infection due to ESBL-Ent at hospital admission (HCAI) or during their hospital stay (HAI). To control for LOS, patients with HAI (cases) were matched

Table 2
Aetiology and place of acquisition of 729 extended-spectrum β-lactamase-producing Enterobacteriaceae (ESBL-Ent) infections stratified by infection site.

Site of infection [*n* (%[a])]	Aetiology [*n* (%[b])]	Place of infection acquisition [*n* (%[c])]		
		HAI (*n* = 519)	HCAI (*n* = 176)	CAI (*n* = 34)
Urinary tract (*n* = 461; 63.2%)	*Escherichia coli* (*n* = 321; 69.6%)	329 (63.4%)	111 (63.1%)	21 (61.8%)
	Klebsiella pneumoniae (*n* = 64; 13.9%)			
	Proteus mirabilis (*n* = 68; 14.8%)			
	Other (*n* = 8; 1.7%)			
Bloodstream (*n* = 130; 17.8%)	*E. coli* (*n* = 83; 63.8%)	77 (14.8%)	45 (25.6%)	8 (23.5%)
	K. pneumoniae (*n* = 35; 26.9)			
	P. mirabilis (*n* = 11; 8.5%)			
	Enterobacter cloacae (*n* = 1; 0.8%)			
Lung (*n* = 43; 5.9%)	*E. coli* (*n* = 26; 60.5%)	30 (5.8%)	13 (7.4%)	–
	K. pneumoniae (*n* = 9; 20.9%)			
	P. mirabilis (*n* = 5; 11.6%)			
	Other (*n* = 3; 7.0%)			
Skin and soft tissue (*n* = 4; 0.5%)	*E. coli* (*n* = 4; 100%)	–	3 (1.7%)	1 (2.9%)
Surgical site (*n* = 91; 12.5%)	*E. coli* (*n* = 50; 54.9%)	83 (16.0%)	4 (2.3%)	4 (11.8%)
	K. pneumoniae (*n* = 17; 18.7%)			
	P. mirabilis (*n* = 18 (19.8%)			
	Other (*n* = 6; 6.6%)			

HAI, hospital-acquired infection; HCAI, healthcare-associated infection; CAI, community-acquired infection.
[a] Percentage for each site of infection out of total number of ESBL-Ent infections.
[b] Percentage with each aetiology among number of that each infection type.
[c] Percentage of each infection type among number with each place of acquisition.

(1:1) with randomly selected controls among patients with an equal LOS. If more than one control was available per case, the patient with the date and time of admission closest to the case was chosen.

2.1. Microbiological methods

Antimicrobial susceptibility testing was performed by disk diffusion method as recommended by the Clinical and Laboratory Standards Institute (CLSI), and categorical assignment was done according to CLSI breakpoints [14]. All isolates were confirmed for ESBL production by a combination disk diffusion test according to CLSI guidelines using cefotaxime and ceftazidime as indicator molecules, alone and in combination with clavulanic acid. The presence of AmpC-type, TEM, SHV and CTX-M β-lactamase genes was investigated by PCR as described previously [15–18]. Nucleotide sequences were determined on both strands of the PCR amplification products at the Macrogen sequencing facility (Macrogen Inc., Seoul, South Korea).

2.2. Statistical analysis

Quantitative variables were tested for normal distribution and were compared by two-tailed *t*-test. Differences between groups were assessed by χ^2 test and Fisher's exact test. The precision of the relative risk (RR) was determined by calculating a 95% CI. A *P*-value of <0.05 was considered statistically significant. Variables from the univariate analysis were considered for inclusion in the regression analysis if the *P*-value was <0.05. Backward stepwise logistic regression was performed and the model that was considered biologically plausible and had the lowest −2 log likelihood ratio was chosen as the final model. All study results were adjusted for the main epidemiological variables (age, sex and comorbidities), type of empirical antibiotic therapy (inappropriate versus appropriate) and place of infection acquisition [community-acquired infection (CAI) versus HCAI versus HAI]. The results are presented as multivariate (adjusted) RRs. The Hosmer–Lemeshow goodness-of-fit test was used to assess the model fit. Statistical analysis was performed using the software program Inter-cooled Stata (Stata Statistical Software: Release 9.0; StataCorp LP, College Station, TX).

Sample size determination was performed for the mortality analysis and was based on data extracted from previous retrospective studies [19,20]. The decrease in the overall mortality rate among patients with appropriate empirical antibiotic therapy (p1) versus patients with IEAT (p2) was set to 20%. The required sample size with a power of 0.08 was therefore 407 patients with infections caused by ESBL-Ent, of which 45% were severe infections (i.e. bacteraemia, deep SSI and pneumonia).

3. Results

3.1. Cohort study

A total of 729 patients were enrolled in the study with the following infections due to ESBL-Ent: UTI (461; 63.2%); BSI (130; 17.8%), deep SSI (91; 12.5%); pulmonary infection (43; 5.9%); and skin and soft-tissue infection (4; 0.5%). A total of 519 infections were classified as HAI (71.2%), 176 as HCAI (24.1%) and 34 as CAI (4.7%). Thirty patients (4.1%) had septic shock at infection onset and 25 (3.4%) required ICU admission. *Escherichia coli* was the most commonly isolated micro-organism (ranging from 69.9% in UTIs to 54.9% in deep SSIs), followed by *K. pneumoniae* and *Proteus mirabilis*. The majority of CAIs were UTIs (61.8%), followed by BSIs (23.5%). Table 2 describes the distribution of infections according to infection site, place of acquisition and aetiology.

3.2. Microbiological results

Among β-lactam/β-lactamase inhibitor combinations, piperacillin/tazobactam (TZP) was more active than amoxicillin/clavulanic acid (AMC) (74% and 23%, respectively). The susceptibility rate to gentamicin was low (58%), whereas 93% of isolates were susceptible to amikacin. The rate of resistance to fluoroquinolones was very high, with 87% and 97% of isolates resistant to ciprofloxacin and levofloxacin, respectively. *Klebsiella pneumoniae* showed high levels of resistance to β-lactam/β-lactamase inhibitor combinations (only 12% and 35% of isolates susceptible to AMC and TZP, respectively). A significant percentage (22%) of isolates, mostly *E. coli*, exhibited a multidrug-resistant phenotype that, in addition to expanded-spectrum cephalosporins (third- and fourth-generation), also included fluoroquinolones (both ciprofloxacin and levofloxacin) and gentamicin.

Table 3
Rate of inappropriate empirical antibiotic therapy (IEAT) and outcome in 729 patients with infection due to extended-spectrum β-lactamase-producing Enterobacteriaceae (ESBL-Ent).

Variable	HAIs ($n = 519$)	HCAIs ($n = 176$)	CAIs ($n = 34$)	*P*-value
Rate of IEAT [*n* (%)]	145 (27.9)	85 (48.3)	10 (29.4)	<0.001
Hospital LOS post study inclusion (days) (mean ± S.D.)	20 ± 26	16 ± 20	9 ± 8	0.01
Bloodstream infection	20 ± 26	14 ± 16	11 ± 11	0.03
Deep surgical site infection	17 ± 17	11 ± 14	–	0.80
Lung infection	24 ± 23	15 ± 11	–	0.33
Urinary tract infection	20 ± 24	23 ± 23	9 ±11	0.30
Mortality (%)	10	20	–	0.03

HAI, hospital-acquired infection; HCAI, healthcare-associated infection; CAI, community-acquired infection; LOS, length of stay; S.D., standard deviation.

CTX-M-type enzymes were overall more prevalent than TEM- and SHV-type ESBLs (73% vs. 10% and 4%, respectively) and were present in 92% and 90% of *E. coli* and *K. pneumoniae* isolates, respectively. In *P. mirabilis*, TEM-type enzymes and AmpC production were most prevalent (36% and 57%, respectively). CTX-M-type genes were frequently associated with TEM-type determinants in *E. coli* (57%). $bla_{\text{SHV-12}}$ was the most prevalent (86%) among isolates with SHV-type ESBL genes, and $bla_{\text{TEM-92}}$ was the most prevalent (85%) among those with TEM-type ESBL genes. The most prevalent CTX-M variants were CTX-M-15, followed by CTX-M-1. CTX-M belonged mostly to group 1 (96%), group 9 (3%) and group 2 (1%). Among CTX-M group 1, the most common were CTX-M-15 (67%) and CTX-M-1 (32%).

3.3. Inappropriate empirical antibiotic therapy and mortality

Overall, 32.9% of patients (240/729) received IEAT, which increased the risk of mortality in severe infections (RR = 8.3, 95% CI 1.01–13.3; $P < 0.01$). After stratifying by type of infection, IEAT increased the risk of mortality of BSI infection by 8 times (95% CI 2.0–46.3). Patients with HCAI more frequently received IEAT than those with HAI and CAI ($P < 0.001$). Hospital LOS of <5 days was associated with a significantly higher risk for IEAT [odds ratio (OR) = 2.2, 95% CI 1.2–4.5]. Table 3 details IEAT according to the type of infection and place of acquisition. Higher rates of IEAT were observed in pulmonary infections and deep SSIs.

Analysis of mortality was restricted to 264 severe infections. The overall mortality rate was 12.1% (32/264) and was significantly higher in HCAIs (20%) compared with HAIs (10%) (RR = 2.3, 95% CI 1.01–5.3; $P = 0.03$). No death was observed in patients with CAI. When stratified by clinical condition, mortality was 13% among patients with BSIs, 12% in patients with pneumonia and 11% in deep SSIs. Among patients with BSIs, septic shock was reported in 41% of patients who died.

Hospital LOS was not significantly prolonged compared with controls (19.1 ± 24.4 days vs. 18.6 ± 24.6 days). Table 3 illustrates the mean LOS for different places of acquisition and source of infection. Significantly longer LOS was observed in HAIs, in particular in hospitalised patients with BSI. IEAT therapy significantly prolonged LOS (21.6 ± 24.1 days vs. 10.1 ± 15.4 days; $P < 0.001$).

3.4. Risk factors for extended-spectrum β-lactamase-producing Enterobacteriaceae infection

Multivariate regression analysis adjusted to place of infection acquisition was performed to identify patients at high risk of presenting at hospital admission with HCAI and patients at risk of developing HAI due to ESBL-Ent. Quinolone use for ≥7 days was likely to predict an infection due to ESBL-Ent in patients with HCAI (RR = 3.9, 95% CI 1.9–17,7; $P = 0.02$; Hosmer–Lemeshow goodness-of-fit test, 0.71). To reduce the inclusion bias related to the LOS of patients with HAI, a second model including only patients with ≥6 days of hospitalisation prior to infection diagnosis was tested. Presence of a CVC (RR = 2.9, 95% CI 2.1–3.9; $P < 0.01$) and combination therapy with cephalosporins and quinolones for ≥1 day (RR = 3.2, 95% CI 2.4–4.5; $P < 0.01$) were associated with a high risk of HAI due to ESBL-Ent (Hosmer–Lemeshow goodness-of-fit test, 0.82). In patients with CAI, no specific predictive pattern was found.

4. Discussion

A global rise both in healthcare- and community-acquired ESBL-producing *E. coli* infections has been reported [21], causing progressively more outbreaks and severe infections both in healthcare [22] and community settings [1,23]. Community reservoirs are now considered a significant point of ESBL-Ent emergence and spread, and previous studies have reported a prevalence of ESBLs at hospital admission ranging from 12.8% to 26.4% [24,25]. The current study included a prospective cohort of 729 ESBL-Ent infections, with 29% of patients being diagnosed within 48 h from hospital admission and 71% acquiring the infection in the hospital setting. The main findings of this prospective observational study were as follows: (i) mortality is significantly higher in patients with severe HCAI than in those with HAI; (ii) IEAT is associated with increased crude mortality and longer duration of hospital stay in patients with severe infections; (iii) in patients hospitalised for ≥6 days, the presence of an invasive medical device and previous combination therapy, including third-generation cephalosporins and quinolones, triples the risk of developing an infection due to ESBL-Ent; and (iv) 7 days of quinolone therapy is likely associated with the risk of presenting with ESBL-Ent at hospital admission in patients with HCAIs.

Moreover, IEAT has been shown to result in an eight times higher risk of mortality in patients with severe infections. This is particularly relevant in HCAI patients since they are most likely to receive IEAT. IEAT further significantly prolonged LOS. Significantly longer LOS post study inclusion was observed in HCAIs, in particular in hospitalised patients with BSI and pneumonia.

Previous studies have confirmed the association between prior antibiotic therapy and infection due to ESBL-Ent [26,27]. The current study demonstrated that exposure to quinolones and third-generation cephalosporins among patients hospitalised for >5 days as well as 7 days of quinolones therapy are both independently associated with ESBL infection in healthcare settings. This also suggests that the phenomenon might be dose-related. In patients with <7 days of exposure, there was no significant increase in the risk of ESBL-Ent (data not shown). This supports the hypothesis that antibiotic therapy may facilitate the selection and outgrowth of antibiotic-resistant strains since patients carrying Enterobacteriaceae become colonised by ESBL-producing strains upon antibiotic exposure and develop subsequent infections [28].

These estimates have certain limitations. First, crude in-hospital mortality rather that attributable mortality was determined. However, it is possible that the ESBL-Ent infection did not contribute to some of the deaths. Severe infections were selected to reduce the

risk of overestimation related to co-morbidities. The significantly higher rate of IEAT also supports this selection choice. It is also important to note that a specific score developed for antibiotic-resistant infections was used in this study to evaluate the impact of patient co-morbidities. Second, nested case–control studies have the potential for selection bias. However, the same protocol was applied to cases included in the prospective cohort, and all strains were re-tested in a central laboratory. None the less, recall bias regarding previous exposure to antibiotics or ambulatory clinic visits might have occurred. To counterbalance these risks, controls were selected independently of their exposure status and from the source population.

There is an urgent need to improve rapid identification of patients at risk for HCAI due to ESBL-Ent and thus increase the rate of appropriate empirical therapy of severe infections in this population. Despite growing scientific evidence on the risk of IEAT and mortality in patients with HAI, still one-third of therapies are inappropriate. According to the current results, the most important variable when evaluating a patient at hospital admission is the history of previous antibiotic exposure. The patient's antibiotic history, together with the presence of risk factors for HCAI, should immediately alert treating physicians. These results further underline the imminent need for an antimicrobial stewardship programme that not only focuses on hospitalised patients but also incorporates healthcare facilities and general practitioners.

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Competing interests

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Ethical approval

Local ethical committee approval was obtained from all participating centres.

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