Detecting risk and predicting patient mortality in patients with extended-spectrum β -lactamase-producing *Enterobacteriaceae* bloodstream infections

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Extended-spectrum β -lactamases (ESBLs) have been increasingly described worldwide, especially among *Enterobacteriaceae* isolates, and recently not only in the nosocomial, but also in the community setting. Bloodstream infections (BSIs) caused by ESBL-producing *Enterobacteriaceae* have been associated with increased rates of treatment failure, mortality and hospital costs. Any delay in the initiation of adequate antibiotic therapy is potentially lethal for patients with BSIs caused by ESBL-producing *Enterobacteriaceae*. The awareness of changes in bacterial resistance patterns, the careful knowledge of risk factors for ESBL infection and of factors facilitating adverse outcome, giving attention to local epidemiology, can improve the efficacy of empirical treatment protocols. The aim of this review is to focus on the main characteristics of BSIs caused by ESBL-producing *Enterobacteriaceae*, with particular emphasis on risk factors for these infections and factors related to mortality.

Extended-spectrum β -lactamases (ESBLs) are plasmid-mediated β -lactamases that confer resistance to oxyimino-cephalosporins and monobactams and have been increasingly described worldwide since their first description in the early 1980s, especially among *Enterobacteriaceae* isolates, and recently not only in the nosocomial, but also in the community setting [1–3].

The rate of ESBL production among *Enterobacteriaceae* varies worldwide. According to data reported by the European Antimicrobial Resistance Surveillance Network [101], the resistance rate to third-generation cephalosporins (mostly related to ESBL production) of *Klebsiella pneumoniae* (Kp) and *Escherichia coli* (Ec) clinical isolates collected in 28 European countries were 27.5 and 8.5%, respectively, with proportions of resistant isolates in the reporting countries ranging from 2.6 to 24.8% for Ec and from 1.7 to 75.6% for Kp.

Bloodstream infections (BSIs) caused by ESBL-producing *Enterobacteriaceae* have been associated with increased rates of treatment failure, mortality and hospital costs [1,4,5]. The presence of an ESBL determinant significantly reduces the number of antibiotic drugs to which the infecting organism is susceptible and, particularly in case of nosocomial infections, ESBL genes are often associated with other resistance genes, thus generating complex multidrug-resistant

phenotypes of isolates and frequently causing a delay in initiation of adequate antimicrobial therapy [2,6,7].

The aim of this review is to focus on the main characteristics of BSIs caused by ESBL-producing *Enterobacteriaceae*, with particular emphasis on risk factors for these infections and factors related to mortality.

A literature search was performed using the PubMed database through to 25 April 2012, in order to identify studies investigating risk factors for ESBL-producing *Enterobacteriaceae* BSIs and factors associated with mortality for these infections. Searches were performed using the following search terms: '(bacteremia OR bloodstream) AND (ESBL OR extended-spectrum beta-lactamase OR extended-spectrum β -lactamase)'. Only papers published in English were considered.

Risk factors for BSIs caused by ESBL-producing *Enterobacteriaceae*

Several studies have been conducted to identify risk factors for BSIs caused by ESBL-producing *Enterobacteriaceae*; only 30 studies with multivariable regression models have been included, and principal data reported in these studies are shown in TABLE 1 [8–37].

In general, there is a large heterogeneity among these studies. Firstly, they include different

Keywords

- bloodstream infection
- *Enterobacteriaceae* ■ ESBL
- *Escherichia coli* ■ extended-spectrum β -lactamase
- *Klebsiella pneumoniae*
- prognostic indicator ■ risk factor

Table 1. Risks factors for bloodstream infections caused by extended-spectrum β -lactamase-producing *Enterobacteriaceae* in 30 different observational studies.

Study (year)	Type of study	Setting	Acquisition of infection	Period	Enterobacteria	Cases/controls (n)	Type of controls	Risk factors	OR (95% CI)	Ref.
Tumbarello <i>et al.</i> (2006)	Retrospective case–control	Tertiary care	Any	1999–2003	Kp	48/100	No Kp infection	Age Length of hospitalization Previous antibiotic therapy	1.14 (1.08–1.21) 1.10 (1.04–1.16) 11.81 (2.73–51.08)	[8]
Rodríguez-Baño <i>et al.</i> (2010)	Prospective case–control	Multicenter	Nosocomial	2004–2006	Ec	96/190	Nosocomial BSI (other than ESBL-Ec) Non-ESBL-Ec BSI	Previous oxyimino- β -lactam use Transplant Previous oxyimino- β -lactam use Unknown source of BSI Hospital stay (per day)	3.1 (1.7–5.7) 4.8 (1.4–15.7) 6.0 (3.0–11.8) 0.4 (0.2–0.9) 1.02 (1.00–1.03)	[9]
Wu <i>et al.</i> (2010)	Retrospective case–control	Tertiary care	Any	2005–2007	Ec	91/91	Non-ESBL-Ec BSI	Indwelling urinary catheter Previous antibiotic therapy Previous oxyimino-cephalosporin use Community-acquired BSI	6.21 (1.91–20.25) 2.93 (1.18–7.30) 5.16 (1.03–25.79) 0.22 (0.09–0.57)	[10]
Superti <i>et al.</i> (2009)	Retrospective case–control	Tertiary care	Nosocomial	2004–2006	Ec, Kp	51/94	Non-ESBL-Ec/-Kp BSI	Recent use of piperacillin/tazobactam Kp BSI	6.2 (1.1–34.7) 6.7 (2.3–20.2)	[11]
Skippin <i>et al.</i> (2006)	Prospective case–control	Tertiary care	Any	2003–2005	Ec, Kp	50/50	Non-ESBL-Ec/-Kp BSI	Previous β -lactam use Prior admission to ICU Length of stay >15 days	11.57 (2.27–59.07) 13.98 (2.80–69.59) 2.63 (1.01–6.89)	[12]
Rodríguez-Baño <i>et al.</i> (2010)	Prospective case–control	Multicenter	Community	2004–2006	Ec	95/190	BSI (other than ESBL-Ec)	Age >65 years Female sex Healthcare-associated BSI Cirrhosis of liver Obstructive urinary tract disease Indwelling urinary catheter Previous antibiotic therapy Admission from LTCF Recent use of fluoroquinolones Healthcare-associated BSI Chronic obstructive pulmonary disease Indwelling urinary catheter Previous antibiotic therapy Admission from LTCF Recent use of fluoroquinolones	2.3 (1.2–4.3) 1.9 (1.07–3.5) 2.1 (1.2–3.8) 4.7 (1.4–15.4) 3.5 (1.5–7.8) 2.3 (1.05–5.0) 1.9 (1.03–3.5) 8.6 (2.0–36.2) 2.8 (1.2–6.5) 2.1 (1.2–3.8) 3.1 (1.3–7.0) 3.1 (1.5–6.5) 2.7 (1.5–4.9) 5.3 (1.6–17.3) 4.7 (2.0–11.1)	[13]
						95/188	Non-ESBL-Ec BSI	Recent use of cephalosporins	10.3 (2.1–50.3)	

BSI: Bloodstream infection; CTX: Cefotaxime; CTZ: Cefazidime; Ec: *Escherichia coli*; ESBL: Extended-spectrum β -lactamase; HM: Hematological malignancy; ICU: Intensive care unit; Kp: *Klebsiella pneumoniae*; LTCF: Long-term care facility; NR: Not reported; OR: Odds ratio; Pm: *Proteus mirabilis*.

Table 1. Risks factors for bloodstream infections caused by extended-spectrum β -lactamase-producing *Enterobacteriaceae* in 30 different observational studies (cont.).

Study (year)	Type of study	Setting	Acquisition of infection	Period	Enterobacteria	Cases/controls (n)	Type of controls	Risk factors	OR (95% CI)	Ref.
Qureshi et al. (2011)	Retrospective case-control	Multicenter	Any	2005–2008	<i>Enterobacter cloacae</i>	16/106	Non-ESBL- <i>E. cloacae</i> BSI	Admission from nursing home Indwelling gastrostomy tube	15.66 (3.81–64.32) 21.33 (3.12–145.82)	[14]
Ortega et al. (2009)	Prospective case-control	Tertiary care	Any	1991–2007	Ec	211/4547	Non-ESBL-Ec BSI	Nosocomial acquisition Previous hospitalization Indwelling urinary catheter Previous β -lactam use	1.68 (1.04–2.71) 1.93 (1.37–2.70) 1.88 (1.28–2.76) 2.81 (1.95–4.04)	[15]
Mosqueda-Gómez et al. (2008)	Retrospective case-control	Tertiary care	Any	1993–2002	Kp	17/104	Non-ESBL-Kp BSI	Recent use of cephalosporins ICU stay	7.6 (1.1–53.5) 5.6 (1.1–27.9)	[16]
Kim et al. (2002)	Retrospective case-control	Tertiary care (pediatric)	Any	1993–1998	Ec, Kp	49/93	Non-ESBL-Ec/-Kp BSI	Previous hospitalization Recent use of cephalosporins Prior admission to ICU	4.52 (1.6–13.1) 5.56 (1.9–16.0) 35.7 (6.0–214.1)	[17]
Kim et al. (2002)	Retrospective case-control	Tertiary care	Any	1999–2000	Kp	44/118	Non-ESBL-Kp BSI	Biliary drainage catheter Previous antibiotic therapy Nosocomial acquisition	4.76 (1.16–21.77) 4.37 (1.28–4.91) 3.50 (1.14–11.80)	[18]
Kang et al. (2004)	Retrospective case-control	Tertiary care	Any	1998–2002	Kp	60/60	Non-ESBL-Kp BSI	Indwelling urinary catheter Recent invasive procedures Number of antibiotics previously administered	5.23 (1.29–21.25) 9.34 (2.76–31.65) 1.55 for an increment of 1 in the number of antibiotics used (1.01–2.40)	[19]
Du et al. (2002)	Retrospective case-control	Tertiary care	Nosocomial	1997–1999	Ec, Kp	23/62	Non-ESBL-Ec/-Kp BSI	Recent use of cephalosporins	4.14 (1.44–11.87)	[20]
Ben-Ami et al. (2006)	Prospective case-control	Tertiary care	Community	2003	Ec, Kp, Pm	28/72	Non-ESBL-Ec/-Kp/-Pm BSI	Male sex Admission from LTCF	2.57 (1.08–6.12) 4.76 (1.82–12.40)	[21]

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Table 1. Risks factors for bloodstream infections caused by extended-spectrum β -lactamase-producing *Enterobacteriaceae* in 30 different observational studies (cont.).

Study (year)	Type of study	Setting	Acquisition of infection	Period	Enterobacteria	Cases/controls (n)	Type of controls	Risk factors	OR (95% CI)	Ref.
Ariffin <i>et al.</i> (2000)	Prospective case-control	Tertiary care (children with febrile neutropenia)	Nosocomial	1996–1997	Kp	15/16	CTZ-sensitive Kp BSI	Hospital stay >2 weeks Recent use of cephalosporins	14.9 (2.3–99.6) 11.1 (1.3–95.2)	[22]
Zaoutis <i>et al.</i> (2005)	Retrospective case-control	Tertiary care (pediatric)	Any	1999–2003	Ec, Kp	35/105	Non-ESBL-Ec/-Kp BSI	Recent use of cephalosporins Female sex Kp BSI Recent use of steroids	5.82 (1.92–17.68) 4.49 (1.49–13.51) 3.48 (1.07–11.32) 4.04 (1.30–12.50)	[23]
Paterson <i>et al.</i> (2004)	Prospective case-control	Multicenter	Nosocomial	1996–1997	Kp	78/175	Non-ESBL-Kp BSI	Previous oxyimino- β -lactam use	3.8 (1.1–13.8)	[24]
Behar <i>et al.</i> (2008)	Prospective case-control	Tertiary care	Nosocomial	1999	Kp	114/72 114/114	Non-ESBL-Kp BSI No Kp infection	Time at risk Time at risk Recent use of cephalosporins Central venous catheter	3.52 (1.47–8.43) 5.74 (2.26–14.59) 5.64 (1.90–16.72) 5.31 (1.67–16.82)	[25]
Menashe <i>et al.</i> (2001)	Prospective case-control	Tertiary care	Nosocomial	1997	Ec, Kp	26/29	Non-ESBL <i>Enterobacteriaceae</i> BSIs	Previous antibiotic therapy Central venous catheter	NR NR	[26]
Ho <i>et al.</i> (2001)	Retrospective case-control	Tertiary care	Any	1996–1998	Ec	50/100	Non-ESBL-Ec BSI	Nosocomial acquisition Severe underlying diseases Urinary source of BSI	16.5 (5.6–49) 31.2 (6.7–144) 7.8 (2.6–23.8)	[27]
Tumbarello <i>et al.</i> (2012)	Retrospective case-control	Tertiary care	Any	1999–2009	Pm	36/100	No Pm infection	Admission from LTCF Recent use of fluoroquinolones Recent use of cephalosporins Indwelling urinary catheter Previous hospitalization	9.78 (1.94–49.16) 5.52 (1.30–23.43) 4.72 (1.31–16.99) 3.89 (1.50–10.09) 2.68 (1.04–6.89)	[28]

BSI: Bloodstream infection; CTX: Cefotaxime; CTZ: Ceftriaxime; Ec: *Escherichia coli*; ESBL: Extended-spectrum β -lactamase; HM: Hematological malignancy; ICU: intensive care unit; Kp: *Klebsiella pneumoniae*; LTCF: Long-term care facility; NR: Not reported; OR: Odds ratio; Pm: *Proteus mirabilis*.

Table 1. Risks factors for bloodstream infections caused by extended-spectrum β -lactamase-producing *Enterobacteriaceae* in 30 different observational studies (cont.).

Study (year)	Type of study	Setting	Acquisition of infection	Period	Enterobacteria	Cases/controls (n)	Type of controls	Risk factors	OR (95% CI)	Ref.
Park <i>et al.</i> (2011)	Retrospective case-control	Secondary care	Community	2005–2010	Ec	50/100	Non-ESBL-Ec BSI	Healthcare-associated BSI Recent use of antibiotics Recent use of antibiotics Female gender Obstructive urinary tract disease	4.2 (1.7–10.2) 4.3 (1.5–12.3) 3.9 (1.3–11.5) 10.8 (3.2–36.8) 4.5 (1.4–14.8)	[29]
Marchaim <i>et al.</i> (2010)	Prospective case-control	Multicenter	Community	2006–2008	Ec, Kp, Pm	205/242	Non-ESBL-Ec BSI	Older age >2 comorbidities Dependent functional status Admission from LTCF Previous hospitalization (3 months) Recent use of antibiotics Recent use of β -lactams Recent use of fluoroquinolones Previous invasive procedures or surgery (1 year) Shock or multiorgan failure or emergency room admission	1.8 (1.1–3.1) 1.5 (1.2–1.8) 2.04 (1.43–2.94) 3.0 (1.6–5.6) 1.5 (1.3–1.8) 2.4 (1.4–4.4) 2.7 (NR) 2.6 (NR) 1.4 (1.2–1.6) 3.1 (1.6–5.7)	[30]
Kang <i>et al.</i> (2012)	Retrospective case-control	Multicenter (adults with HMs)	Any	2006–2009	Ec, Kp	37/119	Non-ESBL-Ec/-Kp BSI	ICU stay Nosocomial acquisition	7.03 (1.79–27.6) 5.66 (1.60–20.23)	[31]
Cornejo-Juárez <i>et al.</i> (2012)	Retrospective case-control	Tertiary care (adults with HMs)	Any	2004–2009	Ec	100/100	Non-ESBL-Ec BSI	Previous hospitalization (3 months) Recent use of cephalosporins	3.6 (1.3–9.9) 1.8 (0.9–3.4)	[32]
Kang <i>et al.</i> (2010)	Retrospective case-control	Multicenter	Community	2006–2009	Ec	82/783	Non-ESBL-Ec BSI	Unknown source of BSI Underlying liver disease Healthcare-associated BSI Neutropenia	2.99 (1.84–4.88) 2.03 (1.12–3.86) 1.86 (1.44–2.39) 0.11 (0.02–0.88)	[33]
Lee <i>et al.</i> (2010)	Retrospective case-control	Tertiary care	Any	2001–2008	<i>E. cloacae</i>	121/85	Non-ESBL CTX-resistant <i>E. cloacae</i> BSI	Polymicrobial BSI Vascular catheter-related BSI BSI onset in ICU ≥ 3 comorbidities Recent use of fluoroquinolones	2.70 (1.06–6.87) 2.43 (1.15–5.15) 2.25 (1.03–4.88) 4.18 (1.88–9.28) 4.18 (1.28–13.6)	[34]

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Table 1. Risks factors for bloodstream infections caused by extended-spectrum β -lactamase-producing *Enterobacteriaceae* in 30 different observational studies (cont.).

Study (year)	Type of study	Setting	Acquisition of infection	Period	Enterobacteria	Cases/controls (n)	Type of controls	Risk factors	OR (95% CI)	Ref.
Freeman et al. (2012)	Retrospective case-control	Tertiary care	Any	2003–2007	<i>Enterobacteriaceae</i>	44/44	Non-ESBL <i>Enterobacteriaceae</i>	Previous colonization with an ESBL organism Previous exposure to first-generation cephalosporins Previous exposure to fluoroquinolones Previous total in-patients days Previous total in-patients days under general surgery	46.2 (3.45–619) 12.3 (1.01–148) 6.56 (1.79–24) 1.03 (1.01–1.06) 0.95 (0.9–0.99)	[35]
Quirante et al. (2011)	Retrospective case-control	Tertiary care	Any	2000–2006	Ec, Kp	53/159	Non-ESBL-Ec BSI	Recent use of >2 classes of antimicrobials	12.50 (2.50–62.42)	[36]
Tuon et al. (2011)	Retrospective case-control	Tertiary care	Any	2006–2009	Kp	63/41	Non-ESBL-Kp BSI	Mechanical ventilation Central venous line	NR NR	[37]

BSI: Bloodstream infection; CTX: Cefotaxime; CTZ: Cefazidime; Ec: *Escherichia coli*; ESBL: Extended-spectrum β -lactamase; HM: Hematological malignancy; ICU: Intensive care unit; Kp: *Klebsiella pneumoniae*; LTCF: Long-term care facility; NR: Not reported; OR: Odds ratio; Pm: *Proteus mirabilis*.

species of *Enterobacteriaceae*: eight studies have been conducted on Kp BSIs [8,16,18,19,22,24,25,37], eight on Ec BSIs [9,10,13,15,27,29,32,33], one on *Proteus mirabilis* (Pm) BSIs [28], seven on Ec and Kp BSIs [11,12,17,20,23,31,36], two on Ec, Kp and Pm BSIs [21,30], two on all species of *Enterobacteriaceae* [26,35] and two on *Enterobacter cloacae* BSIs [14,34]. Secondly, acquisition of BSI (i.e., community-acquired, healthcare-associated and nosocomial) was different among the studies: 18 studies included cases with any type of BSI acquisition [8,10,12,14–19,23,27,28,31,32,34–37], whereas seven included only nosocomial BSIs [9,11,20,22,24–26] and five only community-acquired BSIs [13,21,29,30,33]. Thirdly, only ten [9,12,13,15,21,22,24–26,30] out of the 30 studies included have been conducted prospectively. These differences could be important because of the different epidemiology of the populations studied or the accuracy of data included. In this regard, the spread in the past decade of ESBL-producing Ec strains encoding CTX-M enzymes has been reported, particularly in nonhospitalized patients [13,21], with frequencies of ESBL enzymes belonging to this family of up to 87% in a cohort of patients with community-acquired ESBL-producing Ec BSIs [13], thus suggesting that the epidemiology of *Enterobacteriaceae* isolates encoding CTX-M enzymes could be different from those encoding the other ESBLs. Recently, Wu and colleagues have analyzed patients with Ec BSIs caused by strains that produce CTX-M or non-CTX-M ESBLs and found that chronic renal failure and intensive care unit (ICU) stay were independent predictors of CTX-M ESBL-producing Ec BSIs [38].

Finally, patients with BSIs caused by non-ESBL-producing *Enterobacteriaceae* have been used as control groups in all except two studies, both by Tumbarello *et al.*, in which patients with no evidence of *Enterobacteriaceae* (i.e., Kp and Pm, respectively) infection were used in a double case-control study design [8,28], whereas in the other four studies with a case-double control design, patients with BSIs caused by bacteria other than *Enterobacteriaceae* [30] or other than ESBL-producing *Enterobacteriaceae* [9,13] and patients without cultures positive for *Enterobacteriaceae* [25] were also used as control groups. The importance of the selection of an appropriate control group for studies investigating risk factors for antibiotic-resistant bacteria infections has been previously outlined, and differences in types and magnitude of identified risk factors could depend on the different control groups used. In this regard, Harris

et al. highlighted that in studies investigating risk factors for infections caused by antibiotic-resistant bacteria, a control group consisting of patients with the susceptible form of the same organism (as in most of the studies included in the present review) might lead to an overestimation of the importance of previous antimicrobial use [39]. More generally, a distinction could be made between a prognostic approach (when the question to be answered is: ‘Which patients with suspected BSIs are infected with an ESBL-producing organism?’) and an etiologic approach (when the questions to be answered are: ‘What drives the spread of ESBLs in clinical patients?’ or ‘What are the risk factors for acquiring ESBL-producing bacteria in different settings [e.g., hospital or community]?’); the source population for the first question would be patients with a BSI caused by the susceptible form of the same organism or by a different pathogen, and for the latter questions, it would be patients belonging to the same setting (i.e., hospitalized or community patients) [25,39].

Given the above, seven studies identified recent antibiotic therapy as a risk factor for ESBL-producing *Enterobacteriaceae* BSIs, with odds ratios (ORs) ranging from 1.9 to 11.81 [8,10,13,18,26,29,30]. In a study by Kang *et al.*, the number of antibiotics previously administered was independently associated with BSIs caused by ESBL-producing Kp, with an OR of 1.55 for an increment of 1 in the number of antibiotics used [19]. Similarly, in a study by Quirante *et al.*, recent use of more than two classes of antimicrobials was found to increase the risk of ESBL-producing Ec or Kp BSIs by approximately 12 times [36]. In the case double-control study of Park *et al.*, comparison with both control groups revealed that the recent use of antibiotics was the only independent risk factor for ESBL acquisition [29].

When single antibiotic classes were analyzed, recent use of β -lactams was identified as a risk factor for ESBL-producing *Enterobacteriaceae* BSIs, with ORs ranging from 1.8 to 12.3, in 17 studies [9–13,15–17,20,22–25,28,30,32,35]; in particular, in 11 of these studies, the oxyimino-cephalosporins were the previous β -lactams used [10,13,16,17,20,22,23,25,28,32,35]. In a survey of 13 different hospitals conducted by Rodríguez-Baño *et al.*, previous fluoroquinolones use was associated with community-acquired ESBL-producing Ec BSIs in two case-control studies involving as controls patients with community-acquired BSIs caused by bacteria other than ESBL-producing Ec and by non-ESBL-producing Ec,

respectively [13]. Previous use of fluoroquinolones has also been reported as an independent risk factor for ESBL-producing *Enterobacteriaceae* BSIs in four other studies [28,30,34,35].

Factors related to previous hospitalization have been found to be independently associated with ESBL-producing *Enterobacteriaceae* BSIs in several studies [8–10,12–18,21,22,25,28–35]. In particular, a prolonged length of hospital stay has been reported to increase the risk of ESBL-producing *Enterobacteriaceae* compared with controls, with ORs ranging from 1.03 to 14.9 [8,12,15,17,22,25,35]; an increment of OR for ESBL-producing Ec BSIs of 1.02 per day of hospital stay was found in a study by Rodríguez-Baño *et al.* [9], and previous stay in an ICU was found to increase the risk up to 35.7 times [12,16,17]. In other studies, nosocomial acquisition and healthcare-associated acquisition of BSIs have been recognized as more likely to occur in ESBL-producing *Enterobacteriaceae* BSIs [13,15,18,27,29,31,33], and, conversely, community-acquired infection has been reported to be a negative predictor for ESBL production [10].

The third important group of risk factors that have been associated with ESBL-producing *Enterobacteriaceae* BSIs includes previous invasive procedures and/or presence of devices [10,13–15,18,19,25,26,28,30,34,37]. In particular, urinary catheterization has been found to be an independent risk factor in four studies, increasing the risk of BSIs caused by ESBL-producing *Enterobacteriaceae* by 1.88–6.21 times [10,13,15,19]; other devices identified in individual studies were gastrostomy tubes [14], biliary drainage catheters [18], mechanical ventilators [37] and central venous catheters [25,26,34,37].

Factors related to the patient’s clinical status and underlying diseases, such as old age, transplant, liver cirrhosis and chronic obstructive pulmonary disease, have also been reported to increase the likelihood of ESBL-producing *Enterobacteriaceae* BSIs [8,9,13,27,29,30,33,34].

In recent years, ESBL-producing *Enterobacteriaceae* have been increasingly reported to be pathogens in community-acquired infections [1,3,13,21,29,30,33,40], and this has important implications for the management of these infections, particularly concerning the choice of efficacious empirical treatment for those that are serious. Risk factors for non-nosocomial ESBL-producing *Enterobacteriaceae* BSIs have been specifically investigated in five studies [13,21,29,30,33]. In the case-control-control study of Rodríguez-Baño *et al.*, a number of risk factors were identified, which were slightly different depending on the

control group used and included the patients' recent use of antibiotics or not (i.e., fluoroquinolones and/or cephalosporins), presence of urinary catheter and presence of comorbidities (i.e., chronic obstructive pulmonary disease and/or liver cirrhosis) [13]. Interestingly, in this study, for both of the control groups used and in those of Ben-Ami *et al.* [21] and Marchaim *et al.* [30], admission from long-term care facilities (LTCFs) was among the strongest risk factors. In the study of Qureshi *et al.* involving 122 cases of *E. cloacae* BSI of which 46 (37.7%) were non-nosocomial, admission from a nursing home remained the most important risk factor for ESBL-producing isolate infection (OR: 15.66) [14]. Similarly, admission from LTCFs was found to increase the likelihood of ESBL-producing Pm BSIs by approximately ten times in a study by Tumbarello *et al.*, including 99 ESBL-producing Pm BSIs, of which 17 (seven ESBL-producing Pm BSIs and ten non-ESBL-producing Pm BSIs) were detected <48 h postadmission [28]. LTCFs have frequently been singled out as important reservoirs of ESBL-producing *Enterobacteriaceae* in different countries [2,41], and cases of serious infections acquired outside hospitals that might be caused by *Enterobacteriaceae* (e.g., complicated urinary tract infections and intra-abdominal infections) in patients admitted from LTCFs should be highly suspected as being caused by ESBL-producing isolates. In addition, Tumbarello *et al.* have recently published a scoring system for identifying patients harboring ESBL-producing *Enterobacteriaceae* at hospital admission; in the case group, 21.4% of patients had a BSI, and admission from another healthcare facility (including LTCFs) had the highest score point [40]. The complex dynamics behind ESBL-producing *Enterobacteriaceae* colonization in the community must also be highlighted, which involves reservoirs not only related to contact with healthcare facilities, but also with foreign travels, contact with animals and meat consumption, all of which being aided by antibiotic use in individuals [1–3].

Predictors for mortality in patients with BSIs caused by ESBL-producing *Enterobacteriaceae*

Only cohort studies in which multivariable regression models have been conducted in order to identify risk factors for mortality in patients suffering from BSIs caused by *Enterobacteriaceae* have been included in this review. However, the outcome of ESBL-producing *Enterobacteriaceae* BSIs might generally be the result of a complex interaction of multiple determinants, which

might be considered both confounders and/or intermediates, and adjustment in both cases might affect the true causal relationship, even in multivariable models [42].

The mortality rate for patients with BSIs caused by *Enterobacteriaceae* ranged from 8.1 to 43.6% in the 28 studies included. The principal data found in these studies are reported in TABLE 2 [9,13,15,18–20,26,28–31,33,34,43–57].

The first important inhomogeneity among these studies is that among a total of 28 cohort studies, eight had been conducted on patients with BSIs caused only by ESBL-producing *Enterobacteriaceae* [9,18,43,46–50], whereas the remaining 20 were conducted on patients with BSIs caused by both ESBL- and non-ESBL-producing *Enterobacteriaceae* [13,15,19,20,26,28–31,33,34,44,45,51–57]; of course, the ESBL production by bacterial isolates could be included as a variable in the statistical analysis for prognostic factors only in the latter studies.

In addition, the species of *Enterobacteriaceae* included are different between the studies: ten studies had been conducted on patients with Ec BSIs [9,13,15,29,33,47,51,53,56,57], six on patients with Kp BSIs [18,19,32,36,37,39], ten on patients with different species of *Enterobacteriaceae* [20,26,30,31,43,45,48,50,51,55], one on patients with *E. cloacae* BSIs [34] and one with Pm BSIs [28]. Only eight of the 28 studies were prospective [9,13,15,26,30,49,52,53] and seven were multicenter studies [9,13,30,31,43,45,49], whereas the others were retrospective and conducted in single centers. Lastly, five studies included nosocomial BSIs only [9,20,26,49,52] and six included community-acquired BSIs only [13,29,30,33,55,56], whereas the other 12 studies included cases with any type of BSI acquisition. Finally, two studies were conducted specifically in patients suffering from hematological malignancies [31,57].

Several studies have investigated the impact of ESBL production by *Enterobacteriaceae* isolates on outcome of infections caused by these bacteria, and discordant results have been reported. Schwaber *et al.* have conducted a systematic review and meta-analysis of studies published through to April 2006 in order to examine the impact of ESBL production on mortality and delay in effective therapy in patients with *Enterobacteriaceae* BSIs, demonstrating a significantly increased rate of mortality (pooled relative risk: 1.85; 95% CI: 1.39–2.47) in the ESBL group [7]. Among the 20 studies conducted on patients with BSIs caused by both ESBL- and non-ESBL-producing *Enterobacteriaceae* included in the

Table 2. Prognostic factors of bloodstream infections caused by extended-spectrum β -lactamase-producing *Enterobacteriaceae* in 28 different observational studies.

Study (year)	Type of cohort study	Setting	Acquisition of infection	Period	Enterobacteria	Type of outcome	Number died/total (%)	Risk factors for mortality	OR (95% CI)	Ref.
Anderson et al. (2006)	Retrospective	Tertiary care	Any	1995–2003	CTZ-resistant Kp	In-hospital mortality	26/60 (43.3)	Delay >72 h in adequate initial antimicrobial therapy	3.32 (1.07–10.3)	[46]
Tumbarello et al. (2008)	Retrospective	Tertiary care	Any	1999–2005	ESBL-Ec	21-day mortality	38/129 (29.4)	Inadequate initial antimicrobial therapy Unknown source of infection Septic shock	6.22 (2.33–16.61) 4.28 (1.71–10.69) 5.88 (1.26–27.45)	[47]
Tumbarello et al. (2007)	Retrospective	Tertiary care	Any	1999–2004	ESBL-Ec/Kp/Pm	21-day mortality	71/186 (38.2)	Inadequate initial antimicrobial therapy Unknown source of infection	6.28 (3.18–12.42) 2.69 (1.38–5.27)	[48]
Schwaber et al. (2006)	Retrospective	Tertiary care	Any	2000–2003	Ec, Kp, Pm	In-hospital mortality	53/198 (26.7)	ESBL production by bacterial isolates >2 comorbidities CNS disease High dichotomized McCabe score High-risk source of bacteremia	3.6 (1.4–9.5) 4.0 (1.6–10.1) 5.4 (1.5–19.9) 23.9 (7.9–72.3) 4.3 (1.7–11.3)	[51]
Rodríguez-Baño et al. (2010)	Prospective	Multicenter	Nosocomial	2004–2006	ESBL-Ec	30-day mortality	24/96 (25)	Pitt score >1 High-risk source of bacteremia Severe sepsis or shock Resistance to >3 antibiotics	5.5 (1.9–21.3) 5.8 (1.5–21.7) 3.5 (1.1–11.6) 4.9 (1.0–23.0)	[9]
Rodríguez-Baño et al. (2010)	Prospective	Multicenter	Community	2004–2006	Ec	14-day mortality	31/282 (10.9)	Urinary source of bacteremia Pitt score >1 Inadequate initial antimicrobial therapy	0.3 (0.1–0.8) 5.3 (2.3–12.2) 3.0 (1.3–12.2)	[13]
Peña et al. (2001)	Prospective	Tertiary care	Nosocomial	1993–1995	Kp	In-hospital mortality	14/78 (17.9)	Septic shock	91.7 (8.9–946.0)	[52]
Paterson et al. (2004)	Prospective	Multicenter	Nosocomial	1996–1997	ESBL-Kp	28-day mortality	10/71 (14.1)	Admission to ICU Length of hospital stay before bacteremia Carbapenem treatment	6.90 (1.78–26.69) 0.97 (0.94–0.99) 0.28 (0.08–1.00)	[49]

APACHE: Acute Physiology and Chronic Health Evaluation; BL/BLI: β -lactam/ β -lactamase inhibitor; BSI: Bloodstream infection; CTZ: Ceftazidime; Ec: *Escherichia coli*; ESBL: Extended-spectrum β -lactamase; HM: Hematological malignancy; ICU: Intensive care unit; Kp: *Klebsiella pneumoniae*; LTCF: Long-term care facility; NR: Not reported; OR: Odds ratio; Pm: *Proteus mirabilis*.

Table 2. Prognostic factors of bloodstream infections caused by extended-spectrum β -lactamase-producing *Enterobacteriaceae* in 28 different observational studies (cont.).

Study (year)	Type of cohort study	Setting	Acquisition of infection	Period	Enterobacteria	Type of outcome	Number died/total (%)	Risk factors for mortality	OR (95% CI)	Ref.
Ortega <i>et al.</i> (2009)	Prospective	Tertiary care	Any	1991–2007	Ec	In-hospital mortality	440/4758 (9.2)	Shock Inadequate initial antimicrobial therapy Pneumonia Liver cirrhosis Intra-abdominal infection Solid-organ cancer Neutropenia Chronic renal insufficiency Steroid use	10.28 (7.80–13.56) 4.83 (3.48–6.71) 4.23 (2.52–7.09) 2.57 (1.82–3.62) 2.41 (1.61–3.60) 1.83 (1.35–2.48) 1.75 (1.14–2.69) 1.69 (1.08–2.66) 1.61 (1.17–2.22)	[15]
Melzer and Petersen (2007)	Prospective	Tertiary care	Any	2003–2005	Ec	30-day mortality	101/354 (28.5)	ESBL production by bacterial isolates Age Hypotension Not defined source of bacteremia	3.57 (1.48–8.60) – 7.01 (3.69–13.35) 4.16 (1.88–9.21)	[53]
Marra <i>et al.</i> (2006)	Retrospective	Tertiary care	Any	1996–2001	Kp	15-day mortality	26/108 (24.1)	Mechanical ventilation ≥2 comorbidities >2 antibiotics used before bacteremia Presence of rapidly fatal disease	5.27 (1.9–14.6) 2.39 (1.3–4.2) 2.30 (1.2–4.3) 2.14 (1.1–4.2)	[54]
Kim <i>et al.</i> (2002)	Retrospective	Tertiary care	Any	1999–2000	ESBL-Kp	In-hospital mortality	10/43 (23.3)	Nosocomial acquisition of bacteremia Deteriorated mental status	15.3 (1.39–212.0) 76.7 (8.25–999.0)	[18]
Kang <i>et al.</i> (2004)	Retrospective	Tertiary care	Any	1998–2002	Kp	30-day mortality	35/120 (29.2)	Increasing APACHE II score Septic shock	1.52 (1.16–1.99) 205.99 (20.57–2062.55)	[19]
Huang <i>et al.</i> (2006)	Retrospective	Tertiary care	Any	2001–2003	ESBL- <i>Enterobacteriaceae</i> other than Ec and Kp	In-hospital mortality	17/54 (31.5)	Steroid use APACHE II score ≥16 Septic shock	38.16 (2.25–647.09) 3.74 (0.74–18.88) 10.25 (1.51–69.38)	[50]
Du <i>et al.</i> (2002)	Retrospective	Tertiary care	Nosocomial	1997–1999	Ec, Kp	In-hospital mortality	21/85 (24.7)	Treatment failure	16.4 (3.59–75.78)	[20]
Apisarnthanarak <i>et al.</i> (2008)	Retrospective	Tertiary care	Community	2003–2007	Ec, Kp	In-hospital mortality	29/144 (20.1)	ESBL production by bacterial isolates Empirical treatment other than carbapenems or BL/BLU	2.5 (1.14–15.5) 2.1 (1.09–17.1)	[55]

APACHE: Acute Physiology and Chronic Health Evaluation; BL/BLU: β -lactam/ β -lactamase inhibitor; BSI: Bloodstream infection; CTZ: Ceftazidime; Ec: *Escherichia coli*; ESBL: Extended-spectrum β -lactamase; HM: Hematological malignancy; ICU: Intensive care unit; Kp: *Klebsiella pneumoniae*; LTCF: Long-term care facility; NR: Not reported; OR: Odds ratio; Pm: *Proteus mirabilis*.

Table 2. Prognostic factors of bloodstream infections caused by extended-spectrum β -lactamase-producing *Enterobacteriaceae* in 28 different observational studies (cont.).

Study (year)	Type of cohort study	Setting	Acquisition of infection	Period	Enterobacteria	Type of outcome	Number died/total (%)	Risk factors for mortality	OR (95% CI)	Ref.
Apisarnthanarak et al. (2008)	Retrospective	Tertiary care	Community	2003–2004	Ec	In-hospital mortality	14/184 (12.5)	ESBL production by bacterial isolates	41.3 (4.3–69.4)	[56]
Trecarichi et al. (2009)	Retrospective	Tertiary care (adults with HMs)	Any	2000–2007	Ec	30-day mortality	13/62 (20.9)	Inadequate initial antimicrobial therapy ESBL production by bacterial isolates Prolonged neutropenia (≥ 10 days)	14.96 (1.95–114.51) 8.84 (1.48–52.91) 8.10 (1.29–50.57)	[57]
Menashe et al. (2001)	Prospective	Tertiary care	Nosocomial	1997	<i>Enterobacteriaceae</i>	In-hospital mortality	24/55 (43.6)	Heart failure Malignancy Hospital stay >3 weeks	NR NR NR	[26]
Tumbarello et al. (2012)	Retrospective	Tertiary care	Any	1999–2009	Pm	21-day mortality	30/99 (30.3)	Septic shock Inadequate initial antimicrobial therapy ESBL production by bacterial isolates	12.97 (3.22–52.23) 9.85 (2.67–36.25) 6.62 (1.64–26.68)	[28]
Park et al. (2011)	Retrospective	Secondary care	Community	2005–2010	Ec	30-day mortality	17/150 (11.3)	Severe sepsis or septic shock Malignancy APACHE II score (per 1-point increment)	26.2 (1.5–470.7) 11.9 (1.1–134.8) 1.5 (1.1–2.0)	[29]
Marchaim et al. (2010)	Prospective	Multicenter	Community	2006–2008	Ec, Kp, Pm	In-hospital mortality	NR/401 (NR)	ESBL production by bacterial isolates Inadequate initial antimicrobial therapy Low McCabe score Dependent functional status Admission from LTCF Reduced consciousness at emergency room Shock or multiorgan failure or emergency room admission	2.3 (1.07–4.8) 9.1 (2.44–33.3) 2.5 (1.67–5.0) 2.9 (1.1–8.3) 2.5 (1.05–5.0) 3.1 (1.5–6.8) 2.5 (1.1–5.6)	[30]
Kang et al. (2012)	Retrospective	Multicenter (adults with HMs)	Any	2006–2009	Ec, Kp	30-day mortality	29/142 (20.4)	ESBL production by bacterial isolates Admission to ICU Higher Pitt score	5.64 (1.91–16.67) 4.35 (1.16–16.26) 1.50 (1.18–1.92)	[31]

APACHE: Acute Physiology and Chronic Health Evaluation; BL/BLI: β -lactam/ β -lactamase inhibitor; BSI: Bloodstream infection; CTZ: Ceftazidime; Ec: *Escherichia coli*; ESBL: Extended-spectrum β -lactamase; HM: Hematological malignancy; ICU: Intensive care unit; Kp: *Klebsiella pneumoniae*; LTCF: Long-term care facility; NR: Not reported; OR: Odds ratio; Pm: *Proteus mirabilis*.

Table 2. Prognostic factors of bloodstream infections caused by extended-spectrum β -lactamase-producing *Enterobacteriaceae* in 28 different observational studies (cont.).

Study (year)	Type of cohort study	Setting	Acquisition of infection	Enterobacteria	Type of outcome	Number died/total (%)	Risk factors for mortality	OR (95% CI)	Ref.
Kang <i>et al.</i> (2010)	Retrospective	Multicenter	Community	Ec	30-day mortality	45/556 (8.1)	ESBL production by bacterial isolates Severe sepsis Higher Pitt score Unknown source of BSI Pneumonia Underlying liver disease	2.99 (1.01–8.84) NR NR NR NR	[33]
Lee <i>et al.</i> (2010)	Retrospective	Tertiary care	Any	<i>Enterobacter cloacae</i>	In-hospital mortality	37/206 (17.9)	Pitt score ≥ 4 High serum C-reactive protein level	3.69 (1.67–8.13) 3.44 (1.32–9.01)	[34]
Lee <i>et al.</i> (2012)	Retrospective	Multicenter	Any	ESBL-Ec/Kp	In-hospital mortality	33/251 (13.1)	Severe sepsis Nosocomial acquisition of bacteremia Ertapenem resistance by bacterial isolates	9.70 (3.15–29.86) 5.61 (1.64–19.13) 5.17 (2.03–13.13)	[43]
Alvarez <i>et al.</i> (2012)	Retrospective	Tertiary care	Any	Ec	In-hospital mortality	32/226 (14.1)	Charlson score ≥ 2 Pitt score > 1.5 Urinary tract source Time to positivity of cultures ≤ 8 h	2.62 (1.10–6.23) 13.46 (5.62–32.24) 0.19 (0.06–0.63) 2.35 (1.06–5.67)	[44]
Wang <i>et al.</i> (2011)	Retrospective	Multicenter	Any	Ec, Kp	14-day mortality	27/113 (23.9)	Severe sepsis Pneumonia Inappropriate definitive antimicrobial therapy	24.29 (5.62–104.98) 5.20 (1.29–20.95) 11.3 (1.7–72.8)	[45]
APACHE: Acute Physiology and Chronic Health Evaluation; BL/BLI: β -lactam/ β -lactamase inhibitor; BSI: Bloodstream infection; CTZ: Ceftazidime; Ec: <i>Escherichia coli</i> ; ESBL: Extended-spectrum β -lactamase; HM: Hematological malignancy; ICU: Intensive care unit; Kp: <i>Klebsiella pneumoniae</i> ; LTCF: Long-term care facility; NR: Not reported; OR: Odds ratio; Pm: <i>Proteus mirabilis</i> .									

present review [13,15,19,20,26,28–31,33,34,44,45,51–57], ESBL production by bacterial isolates was independently associated with mortality in logistic regression analysis in only nine studies [28,30,31,33,51,53,55–57], with ORs ranging from 2.3 to 41.3. **These data might appear in contradiction** with the findings reported in the meta-analysis of Schwaber *et al.* [7]; however, these authors also found that only approximately half of the studies showed a significant association between ESBL production by the isolates and mortality, and attributed this finding to small sample sizes and, subsequently, to a lack of sufficient statistical power in the majority of the studies analyzed [7]. In addition, they calculated that to detect a significant association between ESBL production and mortality in a single study would require a sample size of 342 patients; among the studies published after the meta-analysis, four had a sample size greater than 342 cases: the study of Ortega and colleagues [15] included a cohort of 4758 (26%) patients, that of Marchaim *et al.* [30] 401 patients, that of Kang *et al.* had 556 patients [33] and that of Melzer and Petersen had 354 patients [53]. It is of note that in all these studies except that of Ortega *et al.* [15], ESBL production by the isolates was independently associated with mortality.

One of the most frequently reported risk factors for mortality in patients with *Enterobacteriaceae* BSIs is the delay in effective antimicrobial therapy, which was found in the meta-analysis of Schwaber *et al.* [7] to be increased by approximately fivefold (pooled relative risk: 5.36; 95% CI: 2.73–10.53) in the ESBL group.

Among the 28 studies on prognostic factors selected for this review, the inadequacy of initial antimicrobial therapy has been assessed (and included in logistic models) in 23 of them [9,13,15,18,20,28–31,33,34,43–50,52,54,55,57]; among these, this factor was independently associated with mortality in nine studies, with ORs ranging from 2.1 to 14.9 [13,15,28,30,46–48,55,57]. Conversely, use of a carbapenem (i.e., an appropriate antibiotic treatment) during the 5-day period after onset of bacteremia due to an ESBL-producing organism was independently associated with lower mortality in the study of Paterson *et al.* [49]; in the study of Apisarnthanarak *et al.* [56], the logistic regression model was adjusted for the inadequate initial antibiotic therapy, thus excluding this variable from the analysis; and in the studies of Du *et al.* [20] and Melzer and Petersen [53], the mortality rate was significantly higher in the group of patients that was inadequately treated compared

with the adequately treated group; however, when the variable of inadequate initial antibiotic therapy was included in the logistic model for prognostic factors, it was not significant in the study of Du *et al.*, whereas it was apparently not included in the logistic model in the study of Melzer *et al.* In the other 12 studies, inappropriate initial antimicrobial treatment was included in the analysis and no association with mortality was found [9,18,29,31,33,34,43–45,50,52,54]; however, the relatively small sample sizes of most of these studies could explain in large part these results. Obviously, ESBL production and inadequate empirical therapy are greatly correlated; for this reason, it is very likely that by including both of these variables in multivariable models, one can exclude the other from the model. In **FIGURE 1**, all of the studies including these variables in multivariable models have been reported in a tree diagram, according to inclusion of one or both of these variables, and the results of the statistical analyses for these variables are shown.

With regard to the adequacy of antibiotic treatment, carbapenems are generally considered to be the drug of choice for the treatment of BSIs caused by ESBL-producing *Enterobacteriaceae*. Interestingly, Rodríguez-Baño and colleagues conducted a *post hoc* analysis of patients with ESBL-producing *Ec* BSIs from six published prospective cohorts, demonstrating no significant differences in terms of mortality and length of hospital stay between patients treated, either empirically or definitively, with an active β -lactam/ β -lactam inhibitor (i.e., amoxicillin–clavulanic acid and piperacillin–tazobactam) and carbapenems, thus suggesting that β -lactam/ β -lactam inhibitors would be useful alternatives to carbapenems for these patients, in particular for definitive therapy [58].

Two studies evaluated risk factors for delay in appropriate initial antimicrobial therapy in patients with BSIs caused by *Enterobacteriaceae* [47,51]. Schwaber *et al.* found that ESBL production was the unique significant predictor of delay in appropriate therapy (OR: 25.1) in their cohort of patients with *Enterobacteriaceae* BSIs [51], and Tumbarello *et al.* determined that unknown BSI source (OR: 4.86), isolate coresistance to more than three antimicrobials (OR: 3.73), hospitalization during the 12 months preceding BSI onset (OR: 3.33) and antimicrobial therapy during the 3 months preceding BSI onset (OR: 2.65) were independent risk factors for inadequate initial antimicrobial therapy in a cohort of patients with BSIs caused by ESBL-producing *Ec* [47].

Figure 1. Tree diagram categorizing all of the studies on risk factors for mortality in patients with extended-spectrum β -lactamase-producing *Enterobacteriaceae*, according to inclusion in multivariable models of the variables ‘inadequate initial antimicrobial therapy’ and/or ‘extended-spectrum β -lactamase production by bacterial isolates’, as well as according to results of statistical analyses for these variables.

ESBL: Extended-spectrum β -lactamase; IIAT: Inadequate initial antimicrobial therapy.

Factors related to the clinical severity of the BSIs, which may sometimes be intermediates (reducing the effect of ESBL production or other factors on mortality) [42], were among the factors most frequently associated with mortality: septic shock, severe sepsis or hypotension have been found to be independently associated with mortality in 12 studies [9,19,28–30,33,43,45,47,50,52,53]; admission to an ICU or mechanical ventilation were independently associated with mortality in three studies [31,49,54]; and deteriorating mental status was independently associated with mortality in two studies [18,30]. In addition, the overall severity of the patient’s illness, expressed

as the Acute Physiology and Chronic Health Evaluation (APACHE) II score or the Pitt bacteremia score, was reported and associated with mortality in nine studies [9,13,19,29,31,33,34,44,50], with a reported threshold of ≥ 16 and >1 points for APACHE II and Pitt scores, respectively, identifying patients with a high risk for mortality [9,13,50].

A number of underlying diseases or factors related to the patient’s clinical status have been reported as being independently associated with mortality, such as age, CNS disease, pneumonia, liver cirrhosis, malignancy, neutropenia, chronic renal insufficiency and heart

failure [15,26,28,29,33,43,45,53,57]. The presence of more than two comorbidities or a rapidly fatal disease as classified by McCabe and Jackson criteria or a Charlson Comorbidity Index >2 were found to be associated with mortality in four studies [30,44,51,54], as well as corticosteroid therapy in two other studies [15,50].

In eight studies, the role of the source of BSI on mortality has been highlighted; in particular, unknown source of BSI or abdominal or respiratory tract infection (in some studies defined as 'high-risk source of BSI') have been related to adverse outcome [9,33,47,48,51,53]; conversely, a urinary source of BSI has been associated with a high probability of survival [13,44].

Finally, Alvarez *et al.* analyzed the effect of time to positivity of blood cultures on outcomes in patients with Ec BSIs and demonstrated that a lower time to positivity (<8 h) is an independent risk factor for septic shock and poor outcome [44].

Future perspective

Medical doctors and researchers should be aware of the increasing prevalence of ESBL-producing

organisms and, in particular, of the changing epidemiology with the recent emergence of community-onset severe infections caused by these bacteria, which make these infections an important public health problem.

Any delay in the initiation of adequate antibiotic therapy is potentially lethal for patients with BSIs caused by ESBL-producing *Enterobacteriaceae*. The awareness of changes in bacterial resistance patterns, the considered knowledge of risk factors for ESBL infection and of factors facilitating adverse outcome, and attention to the local epidemiology can improve the efficacy of empirical treatment protocols.

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Executive summary

Background

- Extended-spectrum β -lactamases (ESBLs) are plasmid-mediated β -lactamases that confer resistance to oxyimino-cephalosporins and monobactams and have been increasingly described worldwide, especially among *Enterobacteriaceae* isolates.
- Recently, ESBL-producing *Enterobacteriaceae* have been found to cause infections with increasing frequency in the community setting.

Risk factors for bloodstream infections caused by ESBL-producing *Enterobacteriaceae*

- Recent antibiotic therapy, particularly with β -lactams, has been reported as one of the most important risk factors for ESBL-producing *Enterobacteriaceae* bloodstream infections (BSIs).
- Presence of comorbidities and previous invasive procedures and/or presence of devices have been recognized as predicting BSIs caused by ESBL-producing *Enterobacteriaceae*, for both community- and nosocomial-acquired infections.
- Admission from long-term care facilities has been found to be strongly associated with non-nosocomial ESBL-producing *Enterobacteriaceae* BSIs.

Predictors of mortality in patients with BSIs caused by ESBL-producing *Enterobacteriaceae*

- The delay in effective antimicrobial therapy is one of the most frequently reported risk factors for mortality in patients with ESBL-producing *Enterobacteriaceae* BSIs, together with factors related to severity of comorbidities and of a patient's clinical status.

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