Mortality and delay in effective therapy associated with extended-spectrum \( \beta \)-lactamase production in Enterobacteriaceae bacteraemia: a systematic review and meta-analysis

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**Objectives:** We performed a systematic review and meta-analysis to examine the impact of extended-spectrum \( \beta \)-lactamase (ESBL) production on mortality and delay in effective therapy in Enterobacteriaceae bacteraemia.

**Methods:** We searched the PubMed database using the terms ‘bacteremia or bloodstream’ and ‘ESBL or extended-spectrum beta-lactamase’. Included studies contained numbers of and mortality figures for patients with bacteraemia caused by ESBL producers and non-producers. Data extracted included crude relative risk (RR), adjusted odds ratio and 95% confidence intervals (CIs) for mortality and delayed effective therapy. Results were pooled using a random effects model.

**Results:** Sixteen studies met inclusion criteria. Meta-analysis of crude RRs demonstrated significantly increased mortality in ESBL-associated bacteraemia (pooled RR 1.85, 95% CI 1.39–2.47, \( P < 0.001 \)). However, only one study reported RR controlled for confounding. Ten studies reported comparative data on delay in effective therapy. Meta-analysis of crude RRs demonstrated significantly increased incidence of delay in effective therapy in ESBL-associated bacteraemia (pooled RR 5.56, 95% CI 2.94–10.51, \( P < 0.001 \)).

**Conclusions:** In Enterobacteriaceae bacteraemia, ESBL production is associated with increased mortality and delay in effective therapy. However, lack of controlled studies limits interpretation regarding causality, and further controlled studies are required.

Keywords: antimicrobial resistance, Gram-negative, outcomes, bloodstream infection

**Introduction**

Extended-spectrum \( \beta \)-lactamase (ESBL)-producing bacilli from the family Enterobacteriaceae are increasingly identified as pathogens, having become endemic in many healthcare settings, and recently reported in community-acquired infections as well.\(^1\)–\(^3\) Initially reported in outbreaks of *Escherichia coli* and *Klebsiella pneumoniae*, these enzymes have been isolated from a variety of Enterobacteriaceae\(^4\) and were found to cause \(~7\%\) of infections in hospital settings in the 1990s.\(^5\) In 2003, over 20% of pathogenic *K. pneumoniae* isolates in US intensive care units were resistant to third-generation cephalosporins.\(^5\) Moreover, ESBL presence in Enterobacteriaceae has been associated with high proportions of resistance to non-\( \beta \)-lactam classes of antibiotics as well.\(^6\)

While the impact of antimicrobial resistance on patient outcomes has been studied extensively for a variety of Gram-positive and Gram-negative pathogens,\(^7\)–\(^9\) data on the specific impact of ESBL production on outcomes in Enterobacteriaceae infection are much more scarce.\(^10\)\(^,\)\(^11\) We recently compared outcomes of ESBL-associated versus non-ESBL-associated Enterobacteriaceae bacteraemia at our institution, and found ESBL production to be an independent predictor of mortality, length of stay, delay in institution of appropriate therapy and cost.\(^12\)

In the present analysis, we have attempted to provide an accurate summary of the existing published evidence regarding the association of ESBL production, delay in effective therapy and mortality in patients with bacteraemia. We also aimed to examine the published evidence for causality, by analysing the data from controlled studies. The question of whether ESBL...
production, either directly, or indirectly by leading to inappropriate therapy, is responsible for adverse outcomes is important for a number of reasons. Confirmation of ESBL presence by the clinical microbiology laboratory remains expensive and labour-intensive and is no longer mandatory per European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines. Treatment options for ESBL-associated infection are limited and often withheld from empirical use. Extensive infection control resources are required to contain ESBL spread, which is generally plasmid-mediated. The extent of healthcare resources that should be dedicated to detection, treatment and control of ESBL-associated pathogens is therefore a particularly relevant topic to care providers and administrators alike.

The published literature on outcomes of ESBL infections is sparse, and without consistent conclusions. To summarize the outcomes associated with ESBLs in the published literature and to understand differences between study results, we conducted a systematic review of the literature and meta-analysis to determine whether ESBL production is associated with increased mortality and delay in appropriate therapy in patients with Enterobacteriaceae bacteraemia.

Methods

A literature search was performed using the PubMed database through to 30 April 2006, to identify studies comparing mortality of ESBL- and non-ESBL-associated Enterobacteriaceae bacteraemia. The search strategy used the terms ‘bacteraemia or bloodstream’ and ‘ESBL or extended-spectrum beta-lactamase’. No language restrictions were applied.

Only published articles were included. Abstracts of selected studies were reviewed based on inclusion criteria established by the authors prior to the literature search. Studies were considered for inclusion if they reported on mortality of ESBL-associated Enterobacteriaceae bloodstream infection. Studies that provided comparative mortality data for ESBL-associated and non-ESBL-associated bacteraemia were included in the meta-analysis. Both authors participated in the data extraction from each study included.

Data collected included the location and years of the study, the age range of the population studied, the number of patients with ESBL bacteraemia included and the number who died, the number of patients with non-ESBL bacteraemia included and the number who died, the adjusted odds ratio (OR) and 95% confidence intervals (CIs) for mortality associated with ESBL production in studies in which multivariable modelling was performed, and the percentage of patients in each cohort for whom there was a delay in institution of effective therapy. When mortality was recorded at more than one point in the follow-up period, the latest reported mortality figures were used.

Statistical analyses were performed using Stata software, version 7 (Stata Corporation, College Station, TX, USA). As all included studies were cohort studies, the relative risk (RR) and 95% CI for mortality associated with ESBL production in each study were calculated using the crude numbers reported. Subgroup meta-analyses were also performed comparing geographical and age variation, i.e. the pooled mortality results for the Asian studies were compared with those of the non-Asian studies, and the results of the studies in exclusively paediatric populations were compared with those of the remaining studies. Finally, an additional meta-analysis of studies reporting on delay in effective therapy was conducted to determine whether there is an association between ESBL production and delay.

Results

The search yielded 111 studies, all of which were reviewed. Sixteen studies met inclusion criteria. The crude RR for mortality was calculated for each of these studies. Of the 16 studies included in the meta-analysis, only one reported an OR for mortality after adjustment by multivariable analysis. The meta-analysis therefore assessed only the pooled unadjusted RR for mortality.

The studies were conducted during the years 1996–2003 and involved centres from 11 countries, spanning 5 continents (6 from Asia, only 1 from the US). All centres were large, acute care hospitals. Four studies included paediatric patients exclusively. The organisms studied were primarily K. pneumoniae and E. coli, though two studies included Proteus spp., one study included salmonellae and one study included a number of species of Enterobacteriaceae. Data collected from the studies are summarized in Table 1, with outcomes summarized in Table 2.

Meta-analysis of crude RRs demonstrated significantly increased mortality in ESBL-associated bacteraemia (pooled RR 1.85, 95% CI 1.39–2.47, P < 0.001). The individual and pooled crude RRs and CIs for the included studies as yielded by the random effects model are summarized in Figure 1. Significant heterogeneity was present among the study results (P = 0.001). Publication bias was not found (P = 0.45).

Comparison of the pooled crude RR in the 6 Asian studies with that of the 10 non-Asian studies revealed similar results (1.61 versus 2.00, respectively). Comparison of the pooled crude RR in the 4 studies conducted in exclusively paediatric populations with that of the 12 studies conducted in either adult or mixed populations also revealed similar results (2.19 versus 1.74, respectively).

Ten of the included studies provided comparative data on delay in effective therapy (Tables 1 and 2). Meta-analysis of the relationship between ESBL presence and delay in effective therapy for the studies reporting data on delay revealed a significant association between ESBL production and delay (pooled crude RR 5.56, 95% CI 2.94–10.51, P < 0.001). The individual and pooled crude RRs and CIs for the included studies as yielded by the random effects model are summarized in Figure 2. Here too, significant heterogeneity was present (P < 0.001).

Discussion

It is not universally accepted that ESBL production per se is responsible for adverse outcomes in invasive infection. In fact, roughly half of the studies included in our meta-analysis did not yield a significantly increased RR for mortality associated with ESBL presence. Our study therefore provides important information, in demonstrating an almost 2-fold increase in mortality associated with ESBL production among patients with Enterobacteriaceae bloodstream infection. We could not prove...
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<td>Schwaber</td>
<td>Israel</td>
<td>2000–03</td>
<td>adult tertiary care hospital</td>
<td><em>E. coli</em>, <em>Klebsiella</em> spp., <em>Proteus</em> spp.</td>
<td>retrospective cohort</td>
<td>adults with ESBL bacteraemia</td>
<td>cases 64%; controls 47%</td>
<td>(median) cases 76; controls 78</td>
<td>comparison by individual conditions and by McCabe score</td>
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<td>17</td>
<td>Tumbarello</td>
<td>Italy</td>
<td>1999–2003</td>
<td>university hospital</td>
<td><em>K. pneumoniae</em></td>
<td>retrospective cohort</td>
<td>ESBL bacteraemia and SIRS</td>
<td>cases 64%; controls 73%</td>
<td>(mean) cases 64; controls 58</td>
<td>comparison by individual conditions and by Charlson score</td>
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<td>18</td>
<td>Marra</td>
<td>Brazil</td>
<td>1996–2001</td>
<td>tertiary care hospital</td>
<td><em>K. pneumoniae</em></td>
<td>retrospective cohort</td>
<td>hospital-acquired ESBL bacteraemia</td>
<td>cases 45%; controls 54%</td>
<td>compared by number &lt;1 year and number &gt;60 years</td>
<td>comparison by individual conditions and by McCabe score</td>
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<td>19</td>
<td>Endimiani</td>
<td>Italy</td>
<td>1997–2004</td>
<td>university hospital</td>
<td><em>P. mirabilis</em></td>
<td>retrospective cohort</td>
<td>ESBL bacteraemia</td>
<td>cases 78%; controls 50%</td>
<td>(mean) cases 71; controls 67</td>
<td>comparison by McCabe and Charlson scores</td>
</tr>
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<td>20</td>
<td>Zaoutis</td>
<td>USA</td>
<td>1999–2003</td>
<td>tertiary care children’s hospital</td>
<td><em>E. coli</em> and <em>Klebsiella</em> spp.</td>
<td>retrospective cohort</td>
<td>ESBL bacteraemia</td>
<td>cases 37%; controls 56%</td>
<td>(median) cases 2; controls 1</td>
<td>comparison by individual conditions</td>
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<td>Blomberg</td>
<td>Tanzania</td>
<td>2002–02</td>
<td>tertiary care hospital — children’s department</td>
<td><em>E. coli</em>, <em>K. pneumoniae</em>, salmonellae</td>
<td>retrospective cohort</td>
<td>ESBL bacteraemia and fever or other signs of severe infection</td>
<td>cases 56%; controls not stated</td>
<td>(range) 0–7 years</td>
<td>Paciﬁtric department</td>
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<td>22</td>
<td>Panhotra</td>
<td>Saudi Arabia</td>
<td>2001–03</td>
<td>tertiary care hospital</td>
<td><em>K. pneumoniae</em></td>
<td>retrospective cohort</td>
<td>hospital-acquired ESBL bacteraemia with clinical signs and symptoms</td>
<td>overall 58%</td>
<td>(mean) cases 54; controls 39.5</td>
<td>comparison by individual conditions</td>
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<td>23</td>
<td>Kang</td>
<td>South Korea</td>
<td>1998–2002</td>
<td>tertiary care hospital</td>
<td><em>K. pneumoniae</em></td>
<td>retrospective, matched (1:1, by age, sex, nosocomial versus community acquisition, ward) cohort</td>
<td>ESBL bacteraemia with SIRS</td>
<td>cases 62%; controls 60%</td>
<td>(mean) cases and controls 53; (median) cases and controls 54</td>
<td>comparison by individual conditions</td>
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Table 1. Studies included in the meta-analyses
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<td>Kim BN</td>
<td>South Korea</td>
<td>1999–2000</td>
<td>tertiary care hospital</td>
<td><em>K. pneumoniae</em></td>
<td>retrospective cohort</td>
<td>adults (≥15 years) with ESBL bacteraemia</td>
<td>adults (≥15 years) without ESBL bacteraemia</td>
<td>cases 59%; controls 68%</td>
<td>&gt;65: cases 16%, controls 23%</td>
<td>all wards with patients ≥15 years old</td>
<td>comparison by McCabe score</td>
<td>in vitro susceptibility; standard dosing and administration; ESBL status considered</td>
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<td>25</td>
<td>Du</td>
<td>China</td>
<td>1997–99</td>
<td>tertiary care hospital</td>
<td><em>E. coli and K. pneumoniae</em></td>
<td>retrospective cohort</td>
<td>nosocomial ESBL bacteraemia</td>
<td>nonnosocomial non-ESBL bacteraemia</td>
<td>cases 56%; controls 44%</td>
<td>(mean) cases 50; controls 48</td>
<td>all</td>
<td>comparison by individual conditions</td>
<td>in vitro susceptibility; intravenous administration</td>
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<td>Kim YK</td>
<td>South Korea</td>
<td>1993–98</td>
<td>University Hospital–paediatric wards</td>
<td><em>E. coli and K. pneumoniae</em></td>
<td>retrospective cohort</td>
<td>ESBL bacteraemia in children aged 0–17 years</td>
<td>non-ESBL bacteraemia in children aged 0–17 years</td>
<td>cases 55%; controls 58%</td>
<td>(mean) cases 4.6; controls 7.2</td>
<td>wards with children in age group of study</td>
<td>comparison by individual conditions</td>
<td>in vitro susceptibility</td>
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<td>27</td>
<td>Borer</td>
<td>Israel</td>
<td>1997</td>
<td>tertiary care hospital</td>
<td>Entrobacteriaceae</td>
<td>retrospective cohort</td>
<td>adults with community-acquired ESBL bacteraemia</td>
<td>adults with community-acquired non-ESBL bacteraemia</td>
<td>cases 83%; controls 50%</td>
<td>(mean) cases 80; controls 64</td>
<td>adult wards</td>
<td>not specified</td>
<td>in vitro susceptibility</td>
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<td>Ho</td>
<td>Hong Kong</td>
<td>1996–98</td>
<td>University medical centre</td>
<td><em>E. coli</em></td>
<td>Retrospective, matched (1:2, by specialty, age, sex, date of culture) cohort</td>
<td>ESBL bacteraemia</td>
<td>non-ESBL bacteraemia</td>
<td>cases 40%; controls 40%</td>
<td>(mean) cases 78; controls 76</td>
<td>all</td>
<td>comparison by individual conditions and by McCabe score</td>
<td>in vitro susceptibility</td>
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<td>Menashe</td>
<td>Israel</td>
<td>1997</td>
<td>tertiary care hospital</td>
<td>Entrobacteriaceae</td>
<td>retrospective cohort</td>
<td>adults with nosocomial ESBL bacteraemia</td>
<td>adults with nosocomial non-ESBL bacteraemia</td>
<td>overall 53%</td>
<td>(median) overall 65</td>
<td>adult wards</td>
<td>comparison by individual conditions</td>
<td>according to diagnosis + in vitro susceptibility; ESBL status considered</td>
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<td>Pena</td>
<td>Spain</td>
<td>1993–95</td>
<td>teaching hospital</td>
<td><em>K. pneumoniae</em></td>
<td>prospective cohort (analysis by BSI episode, not patient unique)</td>
<td>hospital-acquired ESBL bacteremia + clinical setting of infection</td>
<td>hospital-acquired non-ESBL bacteremia + clinical setting of infection</td>
<td>cases 71%; controls 70%</td>
<td>(mean) cases 61; controls 59</td>
<td>all</td>
<td>comparison by McCabe score</td>
<td>in vitro susceptibility</td>
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<td>Malaysia</td>
<td>1996–97</td>
<td>university hospital — paediatric oncology unit</td>
<td><em>K. pneumoniae</em></td>
<td>prospective cohort (analysis by BSI episode, not patient unique)</td>
<td>children with febrile neutropenia and carbapenem-resistant bacteremia</td>
<td>children with febrile neutropenia and carbapenem-susceptible bacteremia</td>
<td>overall 55%</td>
<td>(mean) overall 76.9 months; range 7–156 months</td>
<td>paediatric oncology unit</td>
<td>comparison by individual conditions</td>
<td>in vitro susceptibility</td>
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ESBL, extended-spectrum β-lactamase; SIRS, systemic inflammatory response syndrome.

*a*All ceftazidime-resistant isolates inferred to be ESBL producers based on clavulanic acid effect.

*b*Patients with bacteraemia who did not receive any antibiotics also considered to have delay in effective therapy.
that this increased mortality is directly attributable to ESBL production, as almost all existing studies do not provide adjusted results. Nevertheless, our finding of a >5-fold increase in the proportion of patients with delayed institution of effective therapy in the ESBL group does support a causal association between ESBL production and mortality. The lack of consensus regarding the effect of ESBLs on mortality in the literature to date is likely due in large part to small

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<th>Delay in effective therapy (%)</th>
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BSI, bloodstream infection.

*1’ used in place of ‘0’ in order to calculate relative risk and 95% CI.

*Sepsis-related mortality reported.

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Table 2. Outcomes of studies included in the meta-analyses

Figure 1. Meta-analysis of mortality in ESBL-producing versus non-ESBL-producing Enterobacteriaceae bacteraemia. Forest plot summary of the unadjusted results of the 16 studies included in the meta-analysis. The relative risk (RR) and 95% confidence intervals (CIs) are shown for each study. The pooled RR, represented by the diamond at the bottom of the figure, is 1.85 (95% CI 1.39–2.47, P < 0.001). There was significant heterogeneity among the study results (P = 0.001).
sample sizes and a resultant lack of sufficient statistical power to demonstrate an effect. Enterobacteriaceae bacteraemia in hospitalized patients, even with susceptible pathogens, is not benign, as demonstrated by the pooled crude mortality of 20% among the non-ESBL patients in the studies we included. If we take this proportion as the expected mortality among patients with non-ESBL bacteraemia and 34% as the expected mortality among those with ESBL bacteraemia (as we found), the sample size required to detect a significant association in a single study would be 342 (171 ESBL patients and 171 non-ESBL patients), assuming 80% power, an \( \alpha \) level of 5% and a ratio of 1:1 between patient groups. As many of the included studies had much smaller sample sizes, it is therefore not surprising that while only about half of the studies showed a significant association between ESBL presence and mortality, combining the results by meta-analysis showed this association to be statistically significant.

There are a number of plausible explanations for the increased mortality observed with ESBL bacteraemia. Delay in institution of effective therapy may play a role in mortality. Our meta-analysis demonstrates a strong association between ESBL production and such a delay. Delay in appropriate therapy has been demonstrated to be a risk factor for mortality in serious infections.\(^{32,33}\) Moreover, not all apparently appropriate therapies are equally effective versus ESBL producers, and variability in outcomes has been noted even according to the class of agent used, with carbapenems the most reliable class for treatment of ESBL infections.\(^{34,35}\)

An additional factor that may influence outcome in ESBL bacteraemia is enhanced virulence among ESBL-producing pathogens compared with non-ESBL producers. One virulence mechanism shown to be present preferentially in ESBL producers is serum resistance.\(^{36,37}\) This, as well as other not-yet-elucidated virulence factors, may play a part in the deleterious outcomes associated with ESBL bloodstream infection.

Our study is limited by the fact that the available literature does not permit a meta-analysis of adjusted mortality associated with ESBL infection, as only 1 of the 16 included studies reported results of a multivariable analysis of this outcome.\(^{12}\) Thus, we can draw conclusions only on crude mortality and not on attributable mortality, or causality. In addition, other adverse outcomes not explored in our analysis have been linked with ESBL infection, including increased length of hospital stay and increased costs.\(^{12}\) Our meta-analysis highlights the deficiencies of the existing literature, i.e. lack of adjusted outcomes analyses calculating the fraction of adverse outcomes attributable to ESBL production. Additional published studies regarding these outcomes, as well as further multivariable analyses of mortality and delayed effective therapy, will permit future meta-analyses to provide a more complete picture regarding the extent of the effect of ESBLs on patient outcomes. Moreover, additional studies will be required in order to distinguish differences in outcome generated by heterogeneity in such factors as study population, type of infection, ICU stay, treatment regimens, and species and type of ESBL causing infection.

The dearth of these studies, however, should provide no grounds for complacency regarding the seriousness of ESBL infection. The picture that is emerging from the small but growing body of literature regarding ESBL outcomes is one of adverse consequences associated with ESBL infection. The present study reinforces this picture by demonstrating that the pooled data currently available in the world literature is consistent with an increased risk of death and of delay in effective therapy associated with ESBL bacteraemia. As we await further studies to expand our knowledge in this area, we would be well advised to invest the resources necessary to control and reduce the burden of ESBLs in the hospital setting, as well as to develop diagnostic and therapeutic strategies to ensure timely and effective treatment for infections caused by ESBL-producing pathogens.

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![Figure 2](image_url)

**Figure 2.** Meta-analysis of delay in effective therapy in ESBL-associated versus non-ESBL-associated Enterobacteriaceae bacteraemia. Forest plot summary of the unadjusted results of the 10 studies included in the meta-analysis. The relative risk (RR) and 95% confidence intervals (CIs) are shown for each study. The pooled RR, represented by the diamond at the bottom of the figure, is 5.56 (95% CI 2.94–10.51, \( P < 0.001 \)). There was significant heterogeneity among the study results (\( P < 0.001 \)).
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Transparency declarations

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References


