Effects of confounders and intermediates on the association of bacteraemia caused by extended-spectrum β-lactamase-producing Enterobacteriaceae and patient outcome: a meta-analysis

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Background and objectives: Bacteraemia caused by Enterobacteriaceae (EB) producing extended-spectrum β-lactamase (ESBL+) has been associated with higher mortality compared with non-ESBL-producing (ESBL−) EB bacteraemia in observational studies. We conducted a systematic review and meta-analysis of these studies to assess how adjusting for confounding in multivariate analyses affects the pooled estimate, and whether multivariate analyses that include intermediates in the causal pathway of outcome (sepsis severity and inadequate empirical therapy) have lower estimates of attributable mortality.

Data sources: PubMed search on 23 November 2010 followed by manually searching reference lists of included studies.

Study eligibility criteria: Cohort studies published in English with separate mortality rates for ESBL+ and ESBL− EB bacteraemia.

Synthesis methods: Random-effects pooling of unadjusted and adjusted ORs followed by subgroup analyses to explore effects of adjustment procedures on adjusted ORs.

Results: The pooled OR for the unadjusted mortality associated with ESBL production was 2.35 (95% CI 1.90–2.91, $I^2=42\%$, 32 studies). The pooled adjusted OR was 1.52 (95% CI 1.15–2.01, $I^2=32\%$, 15 studies). Adjustment for more intermediates was associated with decreasing ORs. The pooled OR for the analyses adjusting for inadequate empirical therapy was 1.37 (95% CI 1.04–1.82).

Conclusions: ESBL production in EB bacteraemia is associated with a higher mortality compared with bacteraemia with ESBL− EB, although the estimate of this association is affected by adjustment procedures. Adjustment for inadequate empirical therapy leads to a reduction in ORs, indicating that higher mortality is likely to be mediated through this phenomenon.

Keywords: empirical therapy, subgroup analysis, statistical adjustment

Introduction

Production of extended-spectrum β-lactamases (ESBLs) renders Enterobacteriaceae (EB) resistant to third-generation cephalosporins, which are the antibiotics that are deployed most often to treat infections caused by these bacteria. As *Escherichia coli*, *Klebsiella* spp. and *Enterobacter* spp. are important pathogens in community- and hospital-onset infections,[1] the increasing prevalence of ESBL-producing (ESBL+) bacteria may have serious consequences for patient outcome, especially since ESBL production is associated with co-resistance to other classes of antibiotics.[2]

A worse outcome of infections caused by antibiotic-resistant bacteria could result from: (i) a delay between onset of infection and initiation of adequate therapy; (ii) associations between resistance genes and the presence of virulence genes; and (iii) differences in effectiveness and side effects between antibiotics used for resistant and susceptible pathogens. Differences in outcome from infections caused by antibiotic-resistant pathogens can only be derived from observational studies, which are

highly susceptible to confounding. Patients with a higher severity of illness generally require longer hospitalization and more antibiotics, which is associated with higher rates of colonization and infection by resistant bacteria. This implies that the prognosis of such patients, compared with patients infected with susceptible pathogens, is already worse before the onset of the infection.[3] Therefore, adjustment for the relevant confounders is crucial when investigating the causal relationship between antibiotic resistance and patient outcome.

In many studies the presence of inadequate empirical therapy and septic shock were included as confounders.[4] Yet if antibiotic resistance increases mortality it is likely to be mediated through higher rates of inadequate empirical therapy and the development of septic shock.[4,5] Such determinants, therefore, are not confounders but intermediates, and adjustment (as if they were confounders) might obscure the true causal relationship. We aimed to quantify the effects of adjustment for true confounders and intermediates on the attributable mortality of bacteraemia caused by ESBL+ EB using a systematic review and meta-analysis approach.

Methods

Literature search and study selection

On 23 November 2010 the following search was performed in the PubMed database, applying tags for free text in titles and abstracts: (esbl* OR extended spectrum beta lactamase*) AND (blood stream infection* OR bloodstream infection* OR bacteraemia* OR bacteremia* OR septicaemia* OR septicemia*) AND (mortal* OR fatal* OR lethal* OR death* OR dead OR surviv* OR alive OR outcome*). No limits were set. Abstracts of all references identified were reviewed by W. C. R. and potentially relevant studies were reviewed in full. Reference lists were checked in an attempt to identify additional studies. Studies were included if they were observational cohorts (whether prospective or retrospective) providing separate mortality rates for patients that had developed bacteraemia caused by ESBL+ and non-ESBL-producing (ESBL−) EB. Reducing the number of cases, specifying a domain or matching ESBL− cases to ESBL+ cases was allowed, as long as no cases were omitted based on resistance properties. Studies had to be written in English. The preferred definition of mortality was day 30 all-cause mortality, but if not available, other definitions were used with preference for the one closest to day 30 all-cause mortality. Hence, all-cause mortality took preference over infection-related mortality.

Data extraction

From the studies matching our inclusion criteria, the following data were extracted by W. C. R. with the help of structured data forms: characteristics of the study (location of study; period of study; hospital type(s) included; study design; inclusion of hospital-onset infections, community-onset infections or both, and definition thereof; ages of patients included; patient wards included; other inclusion and exclusion criteria; pathogens studied; and definitions of mortality, inadequate empirical therapy and septic shock); ESBL+ and ESBL− group sizes; ESBL+ and ESBL− mortality rates; and characteristics of the study population (ESBL prevalence; mean age; and proportions of patients with infections being nosocomial, with the urinary tract as bacteraemia source, with septic shock, treated in the intensive care unit at bacteraemia onset, in each McCabe–Jackson category, with neutropenia and with polymicrobial infections). Mean length of stay before onset of bacteraemia was also extracted where possible.

ORs for ESBL production from adjusted analyses (referred to as aORs) were also collected, including information on whether corrections were performed for inadequate empirical therapy, underlying disease severity and/or sepsis severity (by means of severe sepsis/septic shock or scoring systems used at onset of bacteraemia). Adjustments for inadequate empirical therapy and sepsis severity were classified as adjustments for intermediates. Adjustment for underlying disease was defined as adjusting for at least one of the following six variables: (i) a range of separate comorbidities; (ii) more than two comorbidities from that range; (iii) the Charlson comorbidity index; (iv) the McCabe–Jackson score; (v) a scoring system used before onset of bacteraemia; and (vi) length of stay before onset of bacteraemia.[6] In the absence of relevant data, authors were requested to provide additional information.

We developed a modified Newcastle–Ottawa scale to judge the quality of included studies (see the Supplementary data available at JAC Online).[7] The total score (ranging from 0 to 9) was split into a selection–outcome score (ranging from 0 to 7) and a comparability score reflecting adjustment, selection or matching procedures (ranging from 0 to 2). Furthermore, in the case of multivariate analyses, we collected data on the covariate to event ratio in the final model and the explicit reporting of the procedure behind the model and of the variables eligible for inclusion in the model.

Data analysis

The meta-analysis was performed using Comprehensive Meta Analysis version 2 (Biostat). A random-effects model was applied, as heterogeneity was assumed a priori to be high. Heterogeneity was reported using the Q statistic (including its significance) and the I^2 measure. A funnel plot of standard errors against log unadjusted ORs (uORs) was used to assess publication bias. Subgroup analyses were performed using a mixed-effect analysis. Mixed-effect meta-regressions were performed using the maximum likelihood method. P values <0.05 were considered significant.

The uORs and 95% CIs for mortality rates using ESBL as the independent variable were calculated and pooled. Sensitivity analysis using outliers in study size or uOR were performed. The effects of study characteristics and population characteristics on uORs for mortality were assessed by means of subgroup analyses and meta-regression.

The aORs and 95% CIs for ESBL production from studies that included a multivariate analysis of mortality were pooled. If the aOR with its 95% CI was not available, but ESBL was reported not to be significantly associated with mortality, an aOR of 1 was imputed, and the standard error of the unadjusted analysis was used as the measure of dispersion.[8] Variables were categorized as having been adjusted for if they were in the final multivariate model, but also if they had been included in a stepwise selection procedure (e.g. bivariate testing), but had not ended up in the final model. The effects of decisions to correct for particular variables were assessed using subgroup analyses.

Subgroup analyses were also performed to relate scores on the Newcastle–Ottawa scale and quality indicators of the regression analysis to either uORs or aORs.

This meta-analysis was reported according to the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guideline.[9]

Results

In the PubMed search, 139 articles were identified, of which 31 met the inclusion criteria for meta-analysis (Figure 1).[10–40] One other study was identified in reference lists of selected articles,[41] increasing the number of included studies to 32 (Table 1).

Pooling of the 32 uORs yielded a pooled OR for mortality due to ESBL+ EB bacteraemia of 2.35 (95% CI 1.90–2.91), with
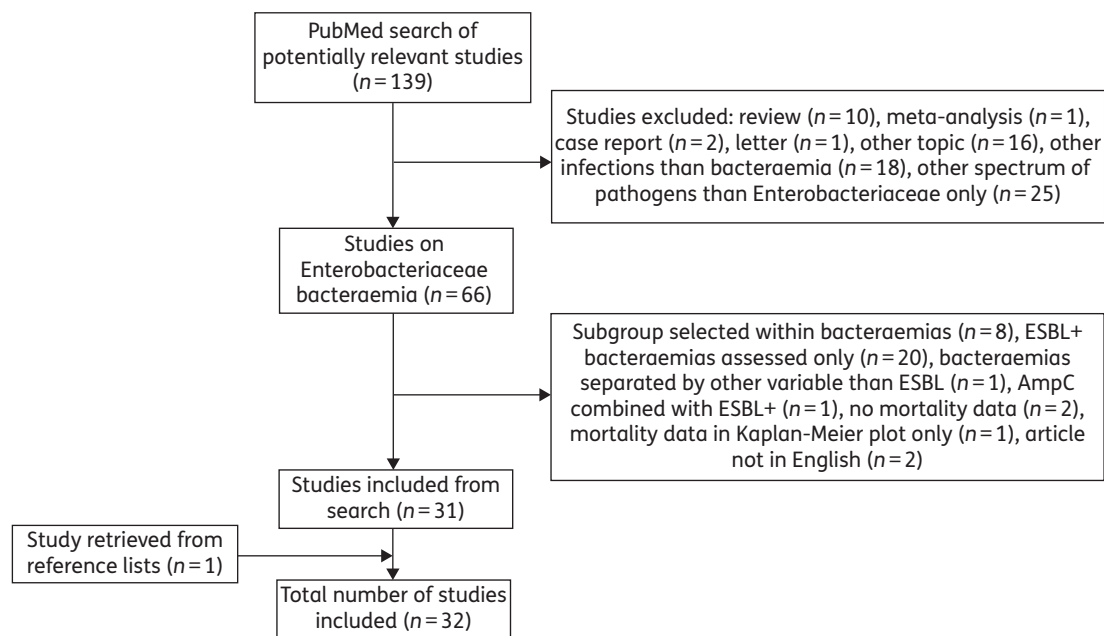
Figure 1. Flow chart of the study.

moderate heterogeneity ($Q=53.68$, $P<0.01$, $I^2=42\%$) (Figure S1, available as Supplementary data at *JAC* Online). A funnel plot revealed the possibility of publication bias, as small studies showing small effects were missing (Figure 2). Five studies in the lower right were not balanced by studies on the left side of the funnel plot, and exclusion of these changed the pooled uOR to 2.18 (95% CI 1.79–2.65; $Q=38.97$, $P=0.05$, $I^2=33\%$). Exclusion of the largest study with 4758 patients hardly changed the uOR (2.40, 95% CI 1.91–3.01).

Results of subgroup analyses and meta-regression

Subgroup analyses of unadjusted results based on study design, definitions of mortality, pathogens included, patient groups included and origin of bacteraemia did not yield statistically significant differences in pooled uORs (Table 2). Multivariate analyses were performed in 17 studies. From eight of these, aORs for mortality due to ESBL were available [either published ($n=7$) or obtained after contacting authors ($n=1$)]. For the eight studies that reported aORs, the pooled uOR for mortality was higher than for the nine studies that performed multivariate analyses without reporting aORs [3.02 (95% CI 2.21–4.13) versus 1.83 (95% CI 1.35–2.49), $P=0.03$] (Table 2).

In meta-regression, including 13 studies of adults, the uOR for mortality due to ESBL+ EB bacteraemia was associated with the mean age of the population studied, with an increase in uOR of 0.03 per year increase in mean age ($P=0.02$) [Table S1 (available as Supplementary data at *JAC* Online); patient population characteristics are shown in Table S2 (available as Supplementary data at *JAC* Online)]. Each 1% increase in patients classified as having rapidly fatal underlying disease by the McCabe–Jackson score was also significantly associated with an increase in uOR of 0.03 ($P=0.05$), although just nine studies could be included in the meta-regression. Three other characteristics tended to

be associated with the uOR for mortality: the percentage of patients with the urinary tract as source of bacteraemia (0.01 increase in OR per 1% increase, $P=0.08$), the percentage of patients suffering from neutropenia (slope 0.01, $P=0.07$) and the percentage of patients developing septic shock during bacteraemia (slope -0.09, $P=0.07$). However, data on septic shock were available from only seven studies.

Results after adjustments

The association between ESBL+ EB bacteraemia and mortality was investigated through multivariate analysis in 17 studies,[11,13–15,17,19,22–24,26,28,30–32,34–36] three of which included separate multivariate analyses with and without adjustment for inadequate empirical therapy.[22,24,31] One multivariate analysis was excluded, as only the variable 'treatment failure' was in the final model, a variable not used in any of the other multivariate analyses.[15] This resulted in 16 multivariate analyses that were analysed in more detail, and aORs for mortality were available from 8 analyses.[13,19,22,24,31,32,34,35] In seven of the eight studies that did not provide an aOR for mortality, it was reported that ESBL was not statistically significantly associated with mortality, and an aOR of 1 was imputed.[14,17,23,26,28,30,36] In the remaining study ESBL reportedly was significantly associated with mortality, but an aOR was not available.[11]

Pooling of 15 studies yielded an aOR of 1.52 (95% CI 1.15–2.01) with moderate heterogeneity ($Q=20.49$, $P=0.12$, $I^2=32\%$) (Figure 3). From the three studies that presented two aORs, the aOR closest to 1 was taken. Without the seven imputed aORs, this pooled aOR would have been 2.27 (95% CI 1.64–3.13). In the funnel plot of the uORs (Figure 2), the 15 studies had a distribution pattern similar to the entire set of studies.

Table 1. Study characteristics

Reference	First author	Year	Country	Study period	Study design	Study population	Pathogens	Mortality definition	ESBL+ group size[a]	ESBL− group size[a]	ESBL+ mortality	ESBL− mortality
10	Ariffin	2000	Malaysia	01/1996–12/1997	prospective	≤12 years, on paediatric oncology unit with neutropenia	*Klebsiella pneumoniae*	related	16	15	8 (50%)	2 (13%)
11	Blomberg	2005	Tanzania	08/2001–08/2002	retro- or prospective	≤7 years	*Escherichia coli, Klebsiella* spp., *Salmonella* spp.	in hospital	19/14	106/85	10 (71%)	33 (39%)
12	Borer	2002	Israel	01/1997–08/1997	retrospective	>18 years, CO only	EB	?	6	113	5 (83%)	16 (14%)
13	Cordery	2008	UK	03/2004–03/2006	retrospective, incomplete cohort[b]	adults on ICU[c]	*Escherichia coli, Klebsiella* spp.	in ICU	16	39	11 (69%)	14 (36%)
14	Daikos	2007	Greece	11/2003–06/2005	prospective	not restricted	EB	14 day	23[d]	210[d]	4 (17%)	24 (11%)
15	Du	2002	China	01/1997–12/1999	retrospective	HO only	*Escherichia coli, Klebsiella pneumoniae*	in hospital	23	62	3 (13%)	18 (29%)
16	Endimiani	2005	Italy	01/1997–06/2004	retrospective	not restricted	*Proteus mirabilis*	1 month? (related)	11/9	14	3 (33%)	2 (14%)
17	Gudiol	2010	Spain	01/2006–10/2008	prospective	adult cancer patients and HSC transplant recipients	*Escherichia coli*	(7 day) 30 day	17	118	6 (35%)	23 (19%)
18	Ho	2002	China	01/1996–12/1998	retrospective, incomplete cohort[e]	not restricted	*Escherichia coli*	30 day	50	100	9 (18%)	7 (7%)
19	Kang	2010	South Korea	10/2006–09/2007, 09/2008–04/2009	multicentre, retrospective	CO only	*Escherichia coli*	30 day	82/40	783/516	6 (15%)	39 (8%)
20	Kim BN	2002	South Korea	07/1999–06/2000	retrospective	≥15 years	*Klebsiella pneumoniae*	related	44/43	118/115	10 (23%)	23 (20%)
21	Kim YK	2002	South Korea	11/1993–12/1998	retrospective	≤17 years	*Escherichia coli, Klebsiella pneumoniae*	related	49/45	93/87	12 (27%)	5 (6%)
22	Marchaim	2010	Israel	11/2006–02/2008	multicentre, prospective, incomplete cohort[f]	>18 years, CO only	EB	in hospital (related)	205/185	242/216	55 (30%)	23 (11%)
23	Marra	2006	Brazil	01/1996–05/2001	retrospective	HO only	*Klebsiella pneumoniae*	15 day	56	52	18 (32%)	8 (15%)
24	Melzer	2007	UK	06/2003–11/2005	prospective	≥16 years	*Escherichia coli*	30 day	46	308	28 (61%)	73 (24%)
25	Memon	2009	Saudi Arabia	01/2006–12/2007	retro- or prospective	adults	*Escherichia coli, Klebsiella pneumoniae*	30 day (related)	29	80	6 (21%)	18 (23%)
26	Menashe	2001	Israel	01/1997–08/1997	retro- or prospective	>18 years, HO only	EB	in hospital + 28 day after discharge	26	29	13 (50%)	11 (38%)
27	Mosqueda-Gómez	2008	Mexico	01/1993–12/2002	retrospective	adults	*Klebsiella pneumoniae*	all-cause	17	104	6 (35%)	28 (27%)
28	Ortega	2009	Spain	01/1999–12/2007	prospective	not restricted	*Escherichia coli*	30 day	211	4547	33 (16%)	413 (9%)
29	Panhotra	2004	Saudi Arabia	07/2001–07/2003	retrospective	HO only	*Klebsiella pneumoniae*	related	10	16	6 (60%)	1 (6%)
41	Paterson	2004	international	01/1996–12/1997	multicentre, prospective	>16 years, HO only	*Klebsiella pneumoniae*	14 day	78	175	21 (27%)	40 (23%)
30	Peña	2001	Spain	05/1993–06/1995	prospective	adults, HO only	*Klebsiella pneumoniae*	in hospital (related)	49	43	16 (33%)	12 (28%)
31	Rodríguez-Baño	2010	Spain	10/2004–01/2006	multicentre, prospective, incomplete cohort[g]	>14 years, CO only	*Escherichia coli*	14 day	95	188/187	16 (17%)	15 (8%)
32	Schwaber	2006	Israel	01/2000–12/2003	retrospective, incomplete cohort[h]	adults	*Escherichia coli, Klebsiella* spp., *Proteus* spp.	in hospital (related)	99	99	35 (35%)	18 (18%)

33	Superti	2009	Brazil	06/2004–03/2006	retrospective	≥19 years, HO only	*Escherichia coli, Klebsiella pneumoniae*	60 day	51	94	26 (51%)	28 (30%)
34	Szilágyi	2009	Hungary	01/2005–12/2008	multicentre, retrospective, incomplete cohort[b]	HO only	*Klebsiella pneumoniae*	in hospital (related)	100	100	36 (36%)	23 (23%)
35	Trecarichi	2009	Italy	01/2000–12/2007	retrospective	≥15 years, on haematology ward	*Escherichia coli*	30 day	26	36	11 (42%)	2 (6%)
36	Tsai	2010	Taiwan	01/2005–12/2006	retrospective	DM patients	*Klebsiella pneumoniae*	in hospital[i]	27[j]	166[j]	11 (41%)	35 (21%)
37	Tumbarello	2006	Italy	01/1999–12/2003	retrospective	not restricted	*Klebsiella pneumoniae*	(7 day) 21 day	48	99	25 (52%)	29 (29%)
38	Tumbarello	2010	Italy	01/2006–12/2006	retrospective	≥18 years	*Escherichia coli*	21 day in hospital	37	97	11 (30%)	6 (6%)
39	Tuon	2010	Brazil	01/2006–01/2009	retrospective	>12 years	*Enterobacter* spp.	30 day	28	30	14 (50%)	14 (47%)
40	Zaoutis	2005	USA	05/1999–09/2003	retrospective, incomplete cohort[b]	children	*Escherichia coli, Klebsiella* spp.	in hospital	35	105	8 (23%)	14 (13%)

HO, hospital onset; CO, community onset; ICU, intensive care unit; HSC, haematopoietic stem cell; DM, diabetes mellitus.

The table shows characteristics of the 32 studies that were retrieved in the PubMed search and by checking reference lists of included studies. Mortality definitions in brackets are not used in the analyses presented.

[a]The number before a forward slash indicates the total number of episodes included and the number after a forward slash indicates the number taken into account in the univariate analysis of mortality.

[b]Random selection from all ESBL− cases.

[c]Including patients 72 h post-ICU discharge, excluding neurosurgical and cardiothoracic patients.

[d]Designed as integron+ versus integron−.

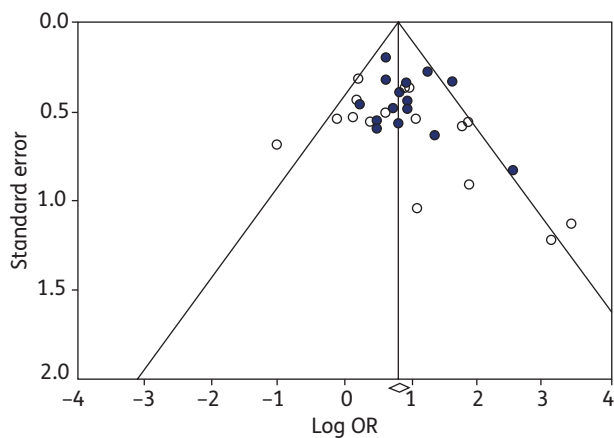[e]ESBL− cases matched on specialty, sex, age and isolation date.

[f]ESBL− cases matched on date in the same hospital.

[g]Random selection from all ESBL− cases the month following the ESBL+ case in the same hospital.

[h]Matched on pathogen.

[i]Including critical discharge against medical advice.

[j]Designed as community-acquired versus nosocomial.

Figure 2. Funnel plot for uORs. The 15 studies from which the aOR was pooled are indicated by filled circles.

Adjustment procedures applied were considerably distinct among the studies (Table S3, available as Supplementary data at *JAC* Online). Of the 18 multivariate analyses (including three studies with two multivariate analyses each), 2 did not adjust for intermediates (i.e. sepsis severity and inadequate empirical therapy), 6 adjusted for one of these two variables and 10 adjusted for both variables. Pooled aORs were 2.87 (95% CI 1.57–5.26), 2.11 (95% CI 1.41–3.16) and 1.39 (95% CI 1.01–1.92), respectively, and this decrease was nearly statistically significant ($P = 0.07$) (Table 3). Adjustment for inadequate empirical therapy, performed in 12 studies, was associated with lower aORs [1.37 (95% CI 1.04–1.82) versus 2.77 (95% CI 2.13–3.60), $P < 0.001$].

In two analyses, adjustment for underlying disease was incorporated without adjustment for any intermediate variables. The pooled aOR for these studies was 2.87 (95% CI 1.57–5.26). The pooled aOR for the five studies that adjusted for one intermediate in addition to adjusting for underlying disease was 1.90 (95% CI 1.20–3.02), still significantly higher than 1.

Study quality assessment

uORs were not affected by the selection–outcome score calculated from our modified Newcastle–Ottawa scale or the completeness of follow-up (Table S4, available as Supplementary data at *JAC* Online). However, studies including several episodes per patient reported significantly lower ORs than studies not explicitly doing so [1.60 (95% CI 1.09–2.35) versus 2.53 (95% CI 2.00–3.21), $P = 0.05$]. Relating the comparability score to aORs did not lead to significant results. Explicit reporting of the procedure of the multivariate analysis and the variables eligible for inclusion did not influence the aORs found, and studies with a covariate to event ratio >10 did not have different aORs when compared with studies having lower ratios.

Discussion

This meta-analysis provides evidence that ESBL+ EB bacteraemia is associated with increased mortality, even after adjustment for some obvious confounders. The finding that lower ORs for mortality are derived from studies that adjust for inappropriateness of initial antibiotic therapy supports the concept that this contributes to mortality. Furthermore, many investigators have adjusted for parameters that act as intermediates rather than confounders, which may well underestimate true associations between ESBL+ EB bacteraemia and outcome. Moreover, there was evidence for publication bias, but there was no evidence that this markedly affected our study results. Finally, there is considerable heterogeneity among unadjusted study results, which can be explained partly by the association between, on the one hand, the outcome of ESBL+ EB bacteraemia and, on the other hand, the mean age of the study population and the proportion of the study population qualified as rapidly fatal with the McCabe–Jackson score. This suggests that bacteraemia with an ESBL+ pathogen has more severe consequences in elderly patients and in patients with severe comorbidities.

Our estimate of ESBL-associated mortality [pooled uOR 2.35 (95% CI 1.90–2.91)] based on uORs from 32 studies is comparable to the relative risk of 1.85 (which can be converted into an OR of 2.33)[42] obtained in a previous meta-analysis that included 16 studies.[43]

The primary outcome of our study, the aOR including as many data as possible [pooled aOR 1.52 (95% CI 1.15–2.01)], was intentionally biased towards 1, as we used imputation of non-significant aORs in multivariate analyses and included the lowest aOR if studies presented multiple adjusted aORs. Nevertheless, even with these intentional biases and the fact that underlying disease was not adjusted in some studies, whereas other investigators adjusted for intermediates, the pooled aOR remained above 1. We consider this a strong indication that ESBL+ EB bacteraemia is associated with a worse outcome than episodes with ESBL− EB. This is further supported by the finding that five studies adjusting for underlying disease still had a pooled aOR significantly higher than 1, although adjustment for one intermediate was simultaneously incorporated.

Adjustment for inadequate empirical therapy greatly reduces the association between ESBL production and higher mortality, and this finding supports the hypothesis that higher mortality in infections with highly resistant microorganisms is mediated through this phenomenon. In a large meta-analysis of studies on septic patients, inadequate empirical therapy was shown to increase mortality rates significantly.[8] This has also been reported for methicillin-resistant *Staphylococcus aureus* ('MRSA') bacteraemia,[44] although reported findings are inconclusive. For instance, two recent studies failed to identify either methicillin resistance or inappropriate empirical therapy to be associated with mortality.[45,46]

Our study also identified important inconsistencies and omissions in published papers. ESBL production is often not forced into the multivariate model, even when its association with outcome is the primary aim of the study. Furthermore, occurrence of polymicrobial bacteraemia and multiple episodes in individual patients are frequently not described, as is true for details of the timing of assessment of variables (see also McGregor *et al.*[4]). For instance, the McCabe–Jackson score can be used as a measure of underlying disease, but also as a measure of sepsis severity when determined at the onset of bacteraemia. Furthermore, there is a large amount of heterogeneity between

Table 2. Subgroup analyses of uORs

	No. of studies	No. of patients	uOR (95% CI)	I^2 (%)	P value[a]
All studies	32	9612	2.35 (1.90–2.91)	42	
Direction of design					
prospective	9	6539	2.29 (1.61–3.27)	51	0.66
retrospective	20	2810	2.51 (1.87–3.39)	42	
unknown	3	263	1.70 (0.75–3.84)	38	
Design					
incomplete cohort	7	1426	2.59 (1.96–3.43)	0	0.67
prospective complete cohort	7	5856	2.10 (1.35–3.26)	54	
retrospective complete cohort	15	2067	2.66 (1.74–4.05)	55	
unspecified complete cohort	3	263	1.70 (0.75–3.84)	38	
Definition of mortality					
all-cause fixed <28 days	6	1157	2.26 (1.48–3.45)	35	0.79
all-cause fixed 28–31 days	8	6096	2.64 (1.70–4.09)	46	
all-cause in hospital	8	1408	2.08 (1.41–3.09)	46	
other	6	604	2.21 (1.17–4.19)	50	
related	4	347	4.41 (1.3–14.94)	68	
Included pathogens					
E. coli/Klebsiella spp.	24	8426	2.29 (1.79–2.94)	46	0.36
E. coli/Klebsiella spp. and others	6	1105	2.90 (1.82–4.63)	32	
species other than *E. coli/Klebsiella* spp.	2	81	1.39 (0.55–3.49)	0	
Ages included					
adults	17	2731	2.36 (1.71–3.25)	55	0.27
all	11	6479	2.08 (1.56–2.78)	19	
children	4	402	3.58 (1.97–6.48)	0	
Origins included					
both	20	7290	2.53 (1.95–3.28)	33	0.16
community-onset only	4	1358	3.18 (1.76–5.76)	45	
hospital-onset only	8	964	1.68 (1.09–2.59)	46	
Multivariate analysis					
not performed	15	1746	2.41 (1.64–3.56)	50	0.95
performed	17	7866	2.38 (1.85–3.06)	36	
OR available	8	2108	3.02 (2.21–4.13)	25	0.03
OR not available	9	5758	1.83 (1.35–2.49)	12	

The table shows a subgroup analysis of study characteristics that may have had an effect on the outcome reported, i.e. the uOR for the association between ESBL production and mortality.
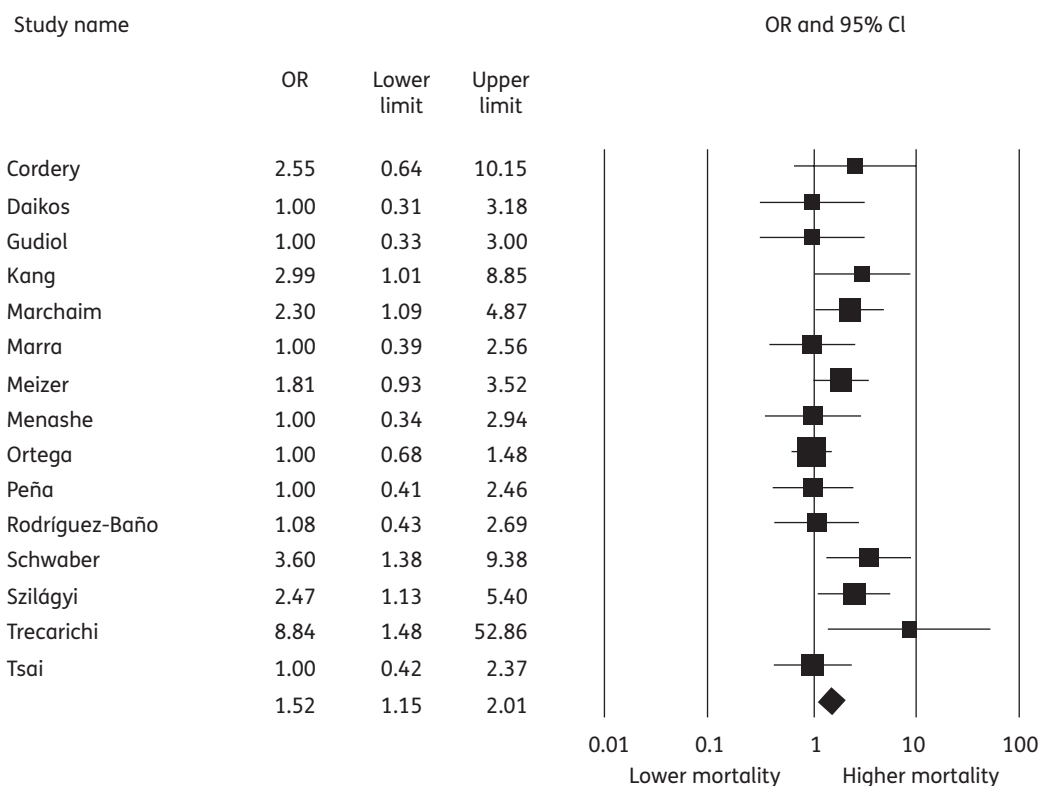[a]P value of mixed-effect analysis.

definitions for nosocomial infections, adequacy of therapy, septic shock and mortality.

We recommend that new studies force ESBL production into the final multivariate model. Moreover, we advise, in agreement with Schwaber and Carmeli's proposal,[5] to present the results of multivariate analyses with and without inadequate therapy. Thereby, both the full effect of ESBL production on mortality and a possible effect apart from inadequate therapy, e.g. due to increased virulence, can be judged. In analyses including inadequate therapy it is imperative to adjust for sepsis severity as well, as it is a confounder in that case.[47] However, the severity should be assessed immediately before the administration of empirical therapy, and not afterwards, as it will represent an intermediate variable in these cases. Unfortunately, only 7 of 17 studies in our meta-analysis referring to hypotension, severe sepsis or septic shock mentioned when sepsis severity was assessed.

Our study has several limitations. The included studies were very heterogeneous in their designs and patient populations, although the heterogeneity in outcome (as measured as I^2) was moderate in most analyses. We also focused on only three variables for adjustment, and other potential confounders, such as the source of the bacteraemia, the presence of immune suppression, where the infection developed (community or nosocomial)

Study name	OR	Lower limit	Upper limit	OR and 95% CI
Cordery	2.55	0.64	10.15	
Daikos	1.00	0.31	3.18	
Gudiol	1.00	0.33	3.00	
Kang	2.99	1.01	8.85	
Marchaim	2.30	1.09	4.87	
Marra	1.00	0.39	2.56	
Meizer	1.81	0.93	3.52	
Menashe	1.00	0.34	2.94	
Ortega	1.00	0.68	1.48	
Peña	1.00	0.41	2.46	
Rodríguez-Baño	1.08	0.43	2.69	
Schwaber	3.60	1.38	9.38	
Szilágyi	2.47	1.13	5.40	
Trecarichi	8.84	1.48	52.86	
Tsai	1.00	0.42	2.37	
	1.52	1.15	2.01	

0.01   0.1   1   10   100

Lower mortality   Higher mortality

Figure 3. Meta-analysis of aORs. The aORs for the effect of ESBL production on mortality reported in each study were pooled. For studies reporting ESBL as not significantly associated with mortality on multivariate analysis, and not presenting an OR, an OR of 1 was imputed with the standard error copied from the unadjusted analysis. ORs >1 indicate a higher mortality in the ESBL+ group.

Table 3. Effects of method of adjustment on ORs

	No. of analyses	No. of patients	aOR (95% CI)	I^2 (%)	P value[a]
All studies[b]	15	7682	1.52 (1.15–2.01)	32	
Adjustments for intermediates					
none	2	398	2.87 (1.57–5.26)	0	0.07
inadequate empirical therapy or sepsis severity	6	1340	2.11 (1.41–3.16)	37	
inadequate empirical therapy and sepsis severity	10	6981	1.39 (1.01–1.92)	30	
Adjustment for inadequate empirical therapy[c]					
no	5	1435	2.77 (2.13–3.60)	0	<0.001
yes	12	7229	1.37 (1.04–1.82)	22	

Subgroup analysis of adjustment procedures that may have had an effect on the reported or imputed aOR for the association between ESBL production and mortality.
[a]P value of mixed-effect analysis.
[b]Three studies presented two multivariate analyses, one with inclusion of inadequate empirical therapy and one without. The aOR of the multivariate analysis with inclusion of inadequate empirical therapy was incorporated into this pooled aOR.
[c]One analysis was excluded, as it was unclear whether correction for inadequate empirical therapy occurred.

and functional capacity at baseline, were not analysed thoroughly, although some were addressed in the Newcastle–Ottawa scale.

Because of these limitations, our aOR for mortality associated with ESBL+ EB bacteraemia should not be interpreted as a precise estimate. We have used the meta-analytical approach to investigate and demonstrate that this estimate is susceptible to adjustment. The finding that even the most conservative adjusted estimate indicates a statistically significant association between ESBL+ EB bacteraemia and mortality, and that adjustment for

inappropriate empirical therapy reduces the association, supports the hypothesis that this infection indeed increases mortality and that this is mediated through inappropriate empirical therapy.

Supplementary data

The modified Newcastle–Ottawa scale, Figure S1 and Tables S1, S2, S3 and S4 are available as Supplementary data at *JAC* Online (http://jac.oxfordjournals.org/).

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