Effects of Inappropriate Administration of Empirical Antibiotics on Mortality in Adults With Bacteraemia: Systematic Review and Meta-Analysis

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Introduction: Bloodstream infections are associated with high mortality rates and contribute substantially to healthcare costs, but a consensus on the prognostic benefits of appropriate empirical antimicrobial therapy (EAT) for bacteraemia is lacking.

Methods: We performed a systematic search of the PubMed, Cochrane Library, and Embase databases through July 2021. Studies comparing the mortality rates of patients receiving appropriate and inappropriate EAT were considered eligible. The quality of the included studies was assessed using Joanna Briggs Institute checklists.

Results: We ultimately assessed 198 studies of 89,962 total patients. The pooled odds ratio (OR) for the prognostic impacts of inappropriate EAT was 2.06 ($P < 0.001$), and the funnel plot was symmetrically distributed. Among subgroups without between-study heterogeneity ($I^2 = 0\%$), those of patients with severe sepsis and septic shock (OR, 2.14), Pitt bacteraemia scores of $\geq 4$ (OR, 1.88), cirrhosis (OR, 2.56), older age (OR, 1.78), and community-onset/acquired Enterobacteriaceae bacteraemia infection (OR, 2.53) indicated a significant effect of inappropriate EAT on mortality. The pooled adjusted OR of 125 studies using multivariable analyses for the effects of inappropriate EAT on mortality was 2.02 ($P < 0.001$), and the subgroups with low heterogeneity ($I^2 < 25\%$) exhibiting significant effects of inappropriate EAT were those of patients with vascular catheter infections (adjusted OR, 2.40), pneumonia (adjusted OR, 2.72), or Enterobacteriaceae bacteraemia (adjusted OR, 4.35). Notably, the pooled univariable and multivariable analyses were consistent in revealing the negligible impacts of inappropriate EAT on the subgroups of patients with urinary tract infections and Enterobacter bacteraemia.

Conclusion: Although the current evidence is insufficient to demonstrate the benefits of prompt EAT in specific bacteraemic populations, we indicated that inappropriate EAT is associated with unfavorable mortality outcomes overall and in numerous subgroups. Prospective studies designed to test these specific populations are needed to ensure reliable conclusions.
INTRODUCTION
Bacteraemia is associated with a high mortality rate and contribute substantially to healthcare costs (1). Antibiotic therapy, both empirical and definitive, is the mainstay of treatment for such systemic infections. Although studies have extensively researched the association between the appropriate administration of empirical antimicrobial therapy (EAT) and short-term mortality outcomes in sepsis (2), the potential benefits of appropriate EAT in bloodstream infections remain unknown. Numerous studies have reported EAT to have trivial effects (3–6), whereas others have reported a beneficial fatality rate reduction (7–10). We believe that these variations in results are due to differences among studies in the bacteraemia severity, host immunity status, target patient populations, causative microorganisms, and bacteraemia source. Therefore, we conducted a systematic review and meta-analysis to assess the effects of appropriate EAT on mortality in specific clinical scenarios, and such an assessment is essential for the optimal antimicrobial stewardship.

METHODS

Study Selection

Study Design
This analysis followed the updated Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (11), and our protocol was registered at the International Prospective Register of Systematic Reviews under the registration number CRD42021270274. We considered case–control studies, cohort studies, and clinical trials on adult patients with bacteraemia, without restrictions regarding onset location, causative microorganisms, antimicrobial-resistant microorganisms, sources of bacteraemia, illness severity, or comorbidities. Reviews, guideline articles, case reports, duplicate studies, studies with patient overlap, and studies on patients without bacteraemia were excluded. In the full-text assessment of eligible articles, articles were excluded if they (i) included participants aged <18 years, (ii) did not assess EAT or distinguish it from definitive treatment, (iii) did not assess the EAT–mortality association, (iv) did not define EAT, or (v) were published in a language other than English.

Patients
The patients included were adults with microbiologically documented bloodstream infections.

Intervention
The intervention was inappropriate (vs. appropriate) administration of empirical antimicrobials. An antimicrobial in vitro active against the causative microorganism was regarded as “appropriate” treatment. “Empirical” therapy was defined as that administered at initial sampling of blood cultures, within 24, 48, and 72 h, or 5 days after culture sampling, or prior to culture result.

Outcome
The primary outcomes in this meta-analysis included short-term (i.e., 7-day, 14-day, 21-day, 28- or 30-day), in-hospital, and long-term mortality.

Literature Search
The PubMed, Cochrane Library, and Embase databases were searched from their inception to July 2021 for articles on appropriate or inappropriate antimicrobial administration in adults with bacteraemia. The following terms for searches were applied: (antibiotic OR antimicrobial) AND (inappropriate OR inappropriate) AND (empirical or initial) AND (bacteraemia OR bacteraemia OR bloodstream) AND (mortality OR fatality OR death OR dead OR alive OR survival) NOT (children OR neonate OR adolescent OR infant OR pediatric). Details regarding the search strategy are presented in Supplementary Table 1. Additional studies were identified by perusing reference lists of systematic reviews.

Study Selection, Data Extraction, and Quality Assessment

Firstly, the results of the literature searches were screened based on study eligibility criteria and discrepancies were periodically resolved by consensus in the team conference. Focusing on the included studies, the extracted data included the study design, types and severity of patient comorbidities, sources of bacteraemia, causative microorganisms, the type and proportion of antibiotic-resistant isolates, inclusion and exclusion criteria, EAT definition, the percentage of patients receiving appropriate EAT, mortality, results of unadjusted and adjusted analyses, and covariates adjusted for in multivariable analyses.

Because none of randomized clinical trials or studies was recognized in our systematic review, the quality of the included studies was evaluated using the Newcastle-Ottawa Quality (NOQ) assessment for all the included cohort or case-control studies (12). This assessment includes the appropriateness of the cohort selection and comparison between case and control groups, outcome evaluation, and patient follow-up. The maximum score of the NOQ assessment is 9 (the highest quality), and the scores of 7–9, 4–6, and 0–3 were regarded as the high, moderate, and low quality of studies, respectively (12).

Two investigators (C.-C.L. and Y.-P. H.) independently screened the search results according to exclusion criteria, recorded the clinical information, and assessed study quality from each study; and a third investigator (W.-C.K.) was consulted to resolve any disagreements during periodic meetings.

Systematic Review Registration: https://www.crd.york.ac.uk/prospero/, identifier: CRD42021270274.

Keywords: empirical antibiotic, bacteraemia, mortality, systematic review, meta-analysis
**Data Synthesis and Analysis**

**Unadjusted Analysis**

We computed the numbers of assessed and fatal patients for individual studies and pooled them for the meta-analysis. We investigated heterogeneity through subgroup analyses based on the following: infection acquisition (community-onset/acquired, hospital-onset/acquired, or healthcare-associated), comorbidity types (liver cirrhosis or haemato-oncological), age (≥65 years), neutropenia status, bacteraemia sources (vascular catheter, pneumonia, or biliary tract, or urinary tract), bacteraemia severity (intensive care unit [ICU] admission, severe sepsis and septic shock, Pitt bacteraemia score of ≥4 at onset, or non-ICU admission), microbial groups (Enterobacteriaceae or glucose non-fermentative rods), specific microorganisms (Staphylococcus aureus, Escherichia coli, Klebsiella pneumoniae, Enterobacter spp., Pseudomonas spp., or Acinetobacter spp.), and antibiotic-resistant microorganisms (methicillin-resistant S. aureus, extended-spectrum beta-lactamase [ESBL]-producing Enterobacteriaceae, multidrug-resistant [MDR] Enterobacteriaceae, or carbapenem-resistant Enterobacteriaceae). Moreover, because of the different EAT cut-offs and mortality assessments of each study, the subgroup analyses included subgroups of various EAT delays (0, 24, 48, and 72 h, 5 days, or prior to culture results) and different (7-14, 21-28, or 30-day; in-hospital; or long-term) mortality measures after the initial culture sampling.

**Adjusted Analysis**

Of the 198 studies initially included, 73 did not report an adjusted analysis and were therefore excluded because we could not input adjusted odds ratios (ORs) for our analyses. Among the 125 studies that used multivariate analyses, 16 reported nonsignificant results but no numerical data; another reported a significant multivariable result but no numerical data; and the remaining 108 studies provided their multivariate results in terms of adjusted ORs and 96% confidence intervals (CIs). For these 108 studies, the adjusted ORs for mortality of inappropriate EAT were inputted for 84 studies that directly reported the effects of inappropriate EAT. For the remaining 24 studies that only demonstrated the effect of appropriate EAT on mortality, the adjusted ORs and 95% CIs were inversely inputted. Moreover, for the 16 studies that reported nonsignificant effects of inappropriate EAT without providing any numerical data, an adjusted OR of 1 and the 95% CI from the univariable analysis were inputted as a dispersion measure. For one study reporting a significant effect of inappropriate EAT but no numerical data from multivariable analysis, the OR and 95% CI were inputted from univariable analyses. Accordingly, our main adjusted analyses included all studies that assessed the effects of inappropriate EAT on mortality through multivariable regression. As in the univariable analysis, further subgroup analyses were performed to minimize the effects of between-study heterogeneity.

**Statistical Methods**

Consistent with the previously established methods (13, 14), irrespective of unadjusted and adjusted ORs, the meta-analysis was conducted to recognize the pooled effects of inappropriate ETA on patient outcomes, and adopted a random-effects model under the assumption that the considerably heterogeneity in study results is due to the diverse study populations and multivariate regression models used for adjusting for confounding factors. Between-study heterogeneity and consistency were assessed using Cochran’s Q test and I²; we aimed to eliminate this heterogeneity through the subgroup analyses. To assess the effect of small-population studies, a funnel plot of standard errors against ORs was constructed for the univariate and multivariate results of all included studies. All analyses were performed using Review Manager (version 5.3).

**RESULTS**

In total, 198 studies (3–10, 15–204), were selected from 981 potentially relevant studies on the basis of the inclusion and exclusion criteria (Figure 1). Total 89,962 patients were assessed; the majority (n = 64,008, 71.2%) received appropriate EAT, and the overall mortality rate was 21.3% (n = 19,181). The publication year, geographic location, design, acquisition sources, bacteraemia sources, target patient population, causative microorganisms, mortality rate, numbers of patients receiving appropriate EAT, ORs and adjusted ORs of inappropriate EAT, and study quality of each study are presented in Supplementary Table 2. The majority (190 studies) of the included studies were cohort studies and the remaining eight studies were case–control studies, which had a median (interquartile range [IQR]) NOQ score of 7 (6–7).

**Univariate (Unadjusted) Analysis for Mortality**

For the 89,962 patients assessed in 198 studies, the pooled OR for prognostic impacts of inappropriate EAT was 2.06 (95% CI, 1.88–2.25; P < 0.001), as shown in Supplementary Figure 1A; and these studies were symmetrically distributed around the pooled OR in the funnel plot (Supplementary Figure 1B). Because considerable between-study heterogeneity was observed (P < 0.001, I² = 72%), subgroup meta-analyses based on the acquisition sources, bacteraemia sources, target patient populations, causative microorganisms, differential timeline cutoffs (after initial sampling of blood cultures) for EAT definition, and varied timeline cutoffs assessed for mortality outcomes were conducted (Table 1). The detailed forest plots for these subgroup analyses are presented in Supplementary Figure 2. The effects of inappropriate EAT remained significant in nearly all subgroups (Table 1); however, the between-study heterogeneity remained significant in most of the subgroups. Among the eight subgroups without between-study heterogeneity (I² = 0%), inappropriate EAT was significantly associated with mortality in the following: patients experiencing severe sepsis and septic shock (OR, 2.14; 95% CI, 1.81–2.53), patients with Pitt bacteraemia scores of ≥4 (OR, 1.88; 95% CI, 1.33–2.67), patients with cirrhosis (OR, 2.56; 95% CI, 2.02–3.26), patients aged ≥65 years (OR, 1.78; 95% CI, 1.38–2.31), patients with community-onset/acquired Enterobacteriaceae bacteraemia (OR, 2.53; 95% CI, 1.63–3.92), and studies with an EAT assessment period of <5 days (OR,
3.00; 95% CI, 1.92–4.69). Conversely, the effect of inappropriate EAT on mortality was negative among non–ICU patients (OR, 0.90; 95% CI, 0.59–1.36) and patients with urinary tract infection–induced bacteraemia (OR, 1.31; 95% CI, 0.86–1.98). Notably, between-study heterogeneity remained significant in each subgroup detailing the varied assessment periods for EAT or mortality, but the association of inappropriate EAT with mortality was consistently significant.

### Multivariate (Adjusted) Analysis for Mortality

Of the 125 studies reporting adjusted multivariable results for mortality risk, the pooled adjusted OR for prognostic impacts of inappropriate EAT was 2.02 (95% CI, 1.86–2.49), with an asymmetrical distribution of studies around the pooled OR in the funnel plot (Supplementary Figure 3). Because considerable heterogeneity was observed ($I^2 = 92\%$, $P < 0.001$), we conducted further subgroup analyses (Table 2). The forest plots of these subgroup analyses are presented in Supplementary Figure 4. The effects of inappropriate EAT remained significant in nearly all subgroups, and the between-study heterogeneity remained considerable in most subgroups. Among the subgroups without heterogeneity, inappropriate EAT remained significant impacts in the subgroups of patients acquiring bacteraemia from a vascular catheter (adjusted OR, 2.40; 95% CI, 1.63–3.53) or pneumonia (adjusted OR, 2.72; 95% CI, 2.07–3.57), those with mixed Enterobacteriaceae bacteraemia (adjusted OR, 4.35; 95% CI, 1.28–14.76), and those in studies measuring mortality within 7 (adjusted OR, 3.08; 95% CI, 1.98–4.79) or 14 (adjusted OR, 2.31; 95% CI, 1.72–3.09) days after the initial culture sampling. However, the prognostic impact of inappropriate EAT was nonsignificant in patients with Enterobacter bacteraemia.
| Characteristics/subgroups                  | Study No. | Patients No. | Unadjusted OR of inappropriate EAT (95% CI) | P (%) | P-value |
|-------------------------------------------|-----------|--------------|---------------------------------------------|-------|---------|
| All patients                              | 198       | 89,926       | 2.06 (1.88–2.25)                            | 78    | <0.001  |
| Location of onset                         |           |              |                                             |       |         |
| Community                                 | 18        | 12,766       | 2.49 (1.90–3.27)                            | 72    | <0.001  |
| Hospital                                  | 28        | 6,508        | 2.33 (1.76–3.07)                            | 76    | <0.001  |
| Healthcare-associated                     | 4         | 2,442        | 2.32 (1.13–4.78)                            | 92    | <0.001  |
| Bacteraemia severity                      |           |              |                                             |       |         |
| ICU patients                              | 16        | 6,356        | 2.58 (1.88–3.54)                            | 82    | <0.001  |
| Severe sepsis and septic shock            | 5         | 2,793        | 2.14 (1.81–2.53)                            | 0     | <0.001  |
| Pitt bacteraemia score ≥ 4 at onset       | 2         | 776          | 1.88 (1.33–2.67)                            | 0     | <0.001  |
| Non-ICU patients                          | 3         | 827          | 0.90 (0.59–1.36)                            | 0     | 0.61    |
| Specific population                       |           |              |                                             |       |         |
| Comorbid haemato-oncology                 | 11        | 5,822        | 3.10 (1.85–5.19)                            | 90    | <0.001  |
| Comorbid liver cirrhosis                  | 5         | 1,674        | 2.56 (2.02–3.26)                            | 0     | <0.001  |
| Older patients (≥ 65 years)               | 4         | 2,955        | 1.78 (1.38–2.31)                            | 0     | <0.001  |
| Neutropenia                               | 4         | 1,789        | 2.48 (0.85–7.30)                            | 72    | 0.10    |
| Bacteraemia source                        |           |              |                                             |       |         |
| Vascular catheter                         | 5         | 1,493        | 1.46 (0.92–2.32)                            | 61    | 0.11    |
| Pneumonia                                 | 9         | 1,987        | 2.02 (1.28–3.20)                            | 61    | 0.002   |
| Biliary tract                             | 4         | 2,675        | 1.71 (1.11–2.64)                            | 46    | 0.02    |
| Urinary tract                             | 4         | 1,763        | 1.31 (0.86–1.98)                            | 0     | 0.21    |
| Causative microorganism                   |           |              |                                             |       |         |
| Staphylococcus aureus                     |           |              |                                             |       |         |
| Overall                                   | 24        | 7,228        | 1.71 (1.36–2.15)                            | 68    | <0.001  |
| Hospital-onset/acquired                   | 4         | 792          | 1.31 (0.54–3.19)                            | 86    | 0.55    |
| Community-acquired                        | 1         | 86           | 2.85 (0.91–8.92)                            | -     | 0.07    |
| Enterobacteriaceae                        |           |              |                                             |       |         |
| Overall                                   | 45        | 13,760       | 2.01 (1.55–2.61)                            | 81    | <0.001  |
| Hospital-onset/acquired                   | 5         | 806          | 2.87 (1.62–5.05)                            | 62    | <0.001  |
| Community-onset/acquired                  | 4         | 1,077        | 2.53 (1.63–3.92)                            | 0     | <0.001  |
| Glucose non-fermentative rods             | 34        | 6,961        | 2.20 (1.73–2.79)                            | 68    | <0.001  |
| Specific species                          |           |              |                                             |       |         |
| Escherichia coli                          | 14        | 7,371        | 2.77 (1.62–4.72)                            | 80    | <0.001  |
| Klebsiella pneumonia                      | 13        | 3,557        | 2.02 (1.46–2.80)                            | 59    | <0.001  |
| Enterobacter spp.                         | 5         | 921          | 1.56 (0.93–2.62)                            | 48    | 0.09    |
| Pseudomonas spp.                          | 17        | 4,866        | 1.74 (1.45–2.10)                            | 25    | <0.001  |
| Acinetobacter spp.                        | 16        | 1,919        | 2.55 (1.53–4.27)                            | 77    | <0.001  |
| Antibiotic-resistant microorganism        |           |              |                                             |       |         |
| MRSA                                      | 9         | 2,061        | 1.70 (1.10–2.63)                            | 81    | 0.02    |
| ESBL-producing Enterobacteriaceae         | 13        | 1,795        | 1.39 (0.85–2.28)                            | 77    | 0.19    |
| MDR Enterobacteriaceae                    | 2         | 366          | 1.80 (0.62–5.21)                            | 77    | 0.28    |
| Carbapenem-resistant Enterobacteriaceae   | 8         | 845          | 2.45 (1.16–5.17)                            | 80    | 0.02    |
| EAT timeliness regard to initial culture   |           |              |                                             |       |         |
| ≤ 0 h                                     | 32        | 13,288       | 2.15 (1.63–2.85)                            | 86    | <0.001  |
| <24 h                                     | 69        | 33,554       | 1.95 (1.72–2.22)                            | 73    | <0.001  |
| <48 h                                     | 43        | 17,029       | 1.92 (1.59–2.32)                            | 76    | <0.001  |
| <72 h                                     | 9         | 909          | 2.49 (1.34–4.62)                            | 64    | 0.004   |
| <5 days                                   | 3         | 383          | 3.00 (1.92–4.69)                            | 0     | <0.001  |
| Prior to culture result                   | 49        | 28,684       | 2.02 (1.66–2.46)                            | 79    | <0.001  |
| Mortality timeline regard to initial culture |       |              |                                             |       |         |
| ≤ 7 days                                  | 10        | 3,408        | 6.83 (3.40–13.73)                           | 85    | <0.001  |
| ≤ 14 days                                 | 20        | 4,118        | 2.12 (1.63–2.77)                            | 54    | <0.001  |
| ≤ 21 days                                 | 8         | 1,049        | 4.41 (2.11–9.19)                            | 81    | <0.001  |
| ≤ 28 or 30 days                           | 114       | 59,868       | 1.79 (1.59–2.03)                            | 77    | <0.001  |
| In-hospital                               | 59        | 23,013       | 2.36 (2.01–2.78)                            | 78    | <0.001  |
| Long-term                                 | 4         | 7,426        | 1.56 (1.21–2.00)                            | 62    | <0.001  |

CI, confidence interval; EAT, empirical antimicrobial therapy; ESBL, extended-spectrum beta-lactamase; ICU, intensive care unit; MDR, multi-drug resistant; MRSA, Methicillin-resistant Staphylococcus aureus; OR, odds ratio.
**TABLE 2 | Adjusted analyses in overall and subgroup patients.**

| Characteristics/ subgroups                      | Study No. | Adjusted OR (95% CI) of inappropriate EAT | P (%) | P-value |
|-------------------------------------------------|-----------|-------------------------------------------|-------|---------|
| Overall                                         | 125       | 2.02 (1.86–2.20)                          | 92    | <0.001  |
| Location of onset                               |           |                                           |       |         |
| Community                                       | 12        | 1.95 (1.58–2.41)                          | 50    | <0.001  |
| Hospital                                        | 23        | 1.92 (1.55–2.39)                          | 92    | <0.001  |
| Healthcare-associated                           | 3         | 2.07 (0.97–4.46)                          | 77    | 0.06    |
| Bacteraemia severity                            |           |                                           |       |         |
| ICU patients                                    | 14        | 2.26 (1.56–3.28)                          | 91    | <0.001  |
| Severe sepsis and septic shock                  | 2         | 2.76 (1.47–6.20)                          | 90    | <0.001  |
| Pitt bacteraemia score ≥ 4                      | 2         | 2.02 (1.07–3.81)                          | 58    | <0.001  |
| Specific population                             |           |                                           |       |         |
| Comorbid haemato-oncology                       | 7         | 2.50 (1.41–4.43)                          | 57    | 0.002   |
| Comorbid liver cirrhosis                        | 5         | 3.70 (1.90–7.20)                          | 90    | <0.001  |
| Older patients (≥ 65 years)                     | 3         | 1.36 (0.86–2.15)                          | 78    | 0.20    |
| Bacteraemia source                              |           |                                           |       |         |
| Vascular catheter                               | 4         | 2.40 (1.63–3.53)                          | 0     | <0.001  |
| Pneumonia                                       | 4         | 2.72 (2.07–3.57)                          | 0     | <0.001  |
| Biliary tract                                   | 3         | 1.82 (1.17–2.83)                          | 49    | 0.007   |
| Urinary tract                                   | 3         | 1.40 (0.82–2.38)                          | 65    | 0.22    |
| Causative microorganism                         |           |                                           |       |         |
| Gram-positive cocci                             |           |                                           |       |         |
| *Staphylococcus aureus*                         | 15        | 2.12 (1.55–2.92)                          | 78    | <0.001  |
| *Enterococcus* spp.                             | 1         | 5.00 (2.50–10.00)                         | -     | <0.001  |
| *Streptococcus* spp.                            | 1         | 10.60 (1.20–93.63)                        | -     | <0.001  |
| Enterobacteriaceae                              | 20        | 1.07 (1.021.11)                           | 83    | <0.001  |
| *Escherichia coli*                              | 6         | 3.00 (2.00–4.50)                          | 73    | <0.001  |
| *Klebsiella pneumonia*                          | 9         | 1.05 (1.00–1.10)                          | 81    | 0.04    |
| *Enterobacter* spp.                             | 2         | 1.00 (0.89–1.12)                          | 8     | 1.00    |
| *Proteus* spp.                                  | 1         | 9.85 (2.67–36.34)                         | -     | <0.001  |
| Mixed                                           | 2         | 3.47 (1.74–6.93)                          | 2     | <0.001  |
| Glucose non-fermentative rod                    | 27        | 1.09 (1.04–1.14)                          | 85    | <0.001  |
| *Pseudomonas* spp.                              | 12        | 1.05 (0.99–1.10)                          | 82    | 0.08    |
| *Acinetobacter* spp.                            | 13        | 1.28 (1.15–1.43)                          | 87    | <0.001  |
| *Burkholderia* spp.                             | 1         | 23.92 (1.31–435.86)                       | -     | 0.03    |
| Mixed                                           | 1         | 4.35 (1.28–14.76)                         | -     | 0.02    |
| Antibiotic-resistant microorganism              |           |                                           |       |         |
| MRSA                                            | 6         | 2.34 (1.30–4.21)                          | 89    | 0.004   |
| ESBL-producing                                  | 6         | 2.03 (1.05–3.93)                          | 71    | 0.04    |
| Enterobacteriaceae                              |           |                                           |       |         |
| Carbapenem-resistant                            | 4         | 2.40 (1.21–4.74)                          | 77    | 0.01    |
| Enterobacteriaceae                              |           |                                           |       |         |
| EAT timeliness regard to initial culture        |           |                                           |       |         |
| 0 h                                             | 14        | 1.76 (1.35–2.30)                          | 72    | <0.001  |
| <24 h                                           | 46        | 2.08 (1.77–2.44)                          | 91    | <0.001  |
| <48 h                                           | 30        | 2.45 (1.95–3.08)                          | 75    | <0.001  |
| <72 h                                           | 6         | 1.70 (1.15–2.51)                          | 81    | 0.007   |
| <5 days                                         | 3         | 2.76 (1.27–6.09)                          | 56    | 0.01    |
| Prior to culture result                         | 29        | 1.85 (1.59–2.16)                          | 93    | <0.001  |
| Mortality timeline regard to initial culture    |           |                                           |       |         |
| ≤7 days                                         | 5         | 3.08 (1.98–4.79)                          | 11    | <0.001  |
| ≤14 days                                        | 10        | 2.31 (1.72–3.09)                          | 19    | <0.001  |
| ≤21 days                                        | 5         | 3.78 (2.06–6.96)                          | 55    | <0.001  |
| ≤28 or 30 days                                  | 69        | 2.07 (1.82–2.35)                          | 90    | <0.001  |
| In-hospital                                     | 40        | 1.81 (1.56–2.10)                          | 93    | <0.001  |
| Long-term                                       | 4         | 1.68 (1.10–2.54)                          | 74    | 0.02    |

CI, confidence interval; EAT, empirical antimicrobial therapy; ESBL, extended-spectrum beta-lactamase; ICU, intensive care unit; MRSA, methicillin-resistant *Staphylococcus aureus*; OR, odds ratio.
The predictive ability of inappropriate EAT was significant in all different assessment periods of EAT and mortality outcomes, and agent comorbidity severity. Procalcitonin 7 Laboratory data 54 53.5 (101) Patient demographics Age 63 52.1 (121) Gender 26 20.8 (125) Functional capacity 11 8.8 (125) Laboratory data Albumin 10 8.0 (125) C-reactive protein or procalcitonin 6 4.8 (125) Comorbidity Any 78 62.4 (125) Hemato-oncology 42 36.8 (114) Liver disease 29 24.2 (120) Renal disease 29 23.2 (125) Cardiovascular disease 19 15.2 (125) Diabetes mellitus 15 12.0 (125) Pulmonary disease 15 12.0 (125) Neutropenia 26 21.5 (121) Immunosuppressive agent 35 28.0 (125) Source control 11 9.2 (120) | The distribution of confounding factors adjusted for multivariate analyses. Confounding factors | The number of studies adopted for adjusting | Frequencies (the numbers of studies should be analyzed by the multivariate model) |
|---|---|---|
| Bacteraemia severity | 118 | 89.6 (125) |
| Comorbidity severity | 64 | 51.2 (125) |
| Bacteraemia source | 79 | 66.4 (119) |
| Acquisition place | 54 | 53.5 (101) |
| Patient demographics | | |
| Age | 63 | 52.1 (121) |
| Gender | 26 | 20.8 (125) |
| Functional capacity | 11 | 8.8 (125) |
| Laboratory data | | |
| Albumin | 10 | 8.0 (125) |
| C-reactive protein or procalcitonin | 6 | 4.8 (125) |
| Comorbidity | | |
| Any | 78 | 62.4 (125) |
| Hemato-oncology | 42 | 36.8 (114) |
| Liver disease | 29 | 24.2 (120) |
| Renal disease | 29 | 23.2 (125) |
| Cardiovascular disease | 19 | 15.2 (125) |
| Diabetes mellitus | 15 | 12.0 (125) |
| Pulmonary disease | 15 | 12.0 (125) |
| Neutropenia | 26 | 21.5 (121) |
| Immunosuppressive agent | 35 | 28.0 (125) |
| Source control | 11 | 9.2 (120) |

(OR, 1.00; 95% CI, 0.89–1.12). As in the univariable analyses, considerable heterogeneity was found in all subgroups with different assessment periods of EAT and mortality outcomes, and the predictive ability of inappropriate EAT was significant in all these subgroups.

Confounding factors for mortality outcomes for potential enrolment in multivariable analyses were calculated in each individual study (Table 3). Nearly all studies (89.6%) assessed bacteraemia severity, using scores such as the Acute Physiology Age and Chronic Health Evaluation; Acute Physiology Score; Sepsis-related (Sequential) Organ Failure Assessment score; and Pitt bacteraemia score. Formal scores for comorbidity severity (i.e., Charlson comorbidity index or McCabe classification) were used in approximately 50% of the studies. Other confounding factors assessed in more than half of the studies were the bacteraemia source, acquisition source, patient age, and the presence of any comorbidity. The median (IQR) number of confounding factors included in the multivariable models was 5 (4–7), and the median (IQR) of the ratio of confounding factors to deaths was 13.0 (7.6–28.8).

### Non-specific Comorbid Patients With Overall Bacteraemia

We evaluated the prognostic effect of inappropriate EAT in 14 bacteraemia studies of patients with nonspecific comorbidities and bacteraemia without the specific causative microorganism and specific acquisition source. Both the univariable (Figure 2A) and multivariable (Figure 2B) analyses revealed significant adverse effects of inappropriate EAT, with an OR of 2.31 and adjusted OR of 1.78 for mortality; the between-study heterogeneity remained considerable ($I^2 = 91\%$ and 71%, respectively).

### DISCUSSION

Bacteraemia is an common and complex disease with mortality rates widely ranged from 1.2% (122) to 90% (63), depending on host’s immune status or comorbidities, severity of illness at onset, and bacteraemia sources. Of numerous studies previously reported the prognostic effect of inappropriate EAT, the definition of “empirical” administration and mortality assessed for study outcomes were not consistent. To diminish the publication bias, the study adopted by any reasonable definition of “empirical” administration and “short- or long-term outcomes” was comprehensively enrolled in our analyses. Despite the existence of considerable between-study heterogeneity herein, the prognostic impacts of inappropriate EAT remained significant in all the subgroups categorized by different cutoff timelines of EAT or mortality. Furthermore, irrespectively of whether through univariable or multivariable analyses, the pooled effect of inappropriate EAT was significant in all included patients and its impact was nearly all evidenced in patients subgrouped by different acquisition places, bacteraemia severity, bacteraemia sources, aimed patient populations, and causative microorganisms. Accordingly, the prognostic disadvantage of delayed administration of appropriate antimicrobials was emphasized in our analyses.

A pooled analysis of the univariable results revealed the negligible impact of inappropriate EAT on four subgroups, namely the bacteraemia source of urinary tract infections (four studies), neutropenia individuals (four), MDR-Enterobacteriaceae bacteraemia (two), and non–ICU patients (three). However, other than for studies dealing with urinary tract infections, multivariable analyses were not performed within these studies, because the majority (8/9, 88.9%) revealed similar mortality rates for patients who did not receive appropriate EAT and those who received through the univariate analyses. Currently in literature search, few studies have evaluated the prognostic effect of inappropriate EAT on these subgroups; we believe this is because the nonsignificant effects limit their publications. Although the current evidence is insufficient to highlight the prognostic disadvantage of inappropriate EAT, further studies focusing on these specific populations are warranted.

The pooled results of the univariable and multivariable analyses consistently indicated that inappropriate EAT significantly impacted the prognoses of nearly all subgroup patients. Moreover, the pooled univariable and multivariable analyses consistently revealed negligible impacts of inappropriate EAT on two subgroups: the bacteraemia source of urinary tract infections and *Enterobacter* bacteraemia. However, the pooled results of the univariable and multivariable analyses differed for the prognostic effects in several subgroups herein, including...
those of healthcare-associated acquisition, older patients, and bacteraemia caused by vascular catheter infections or ESBL-producing Enterobacteriaceae. In such the situation, we believe that the multivariable analysis is necessary to clarify the independent effectiveness of antimicrobial therapy. Taking the ESBL-producer as an example, its crucial association with vascular catheter infections (205), severe comorbid patients (205), older patients (41), or healthcare-associated bacteraemia (205) has been established. Moreover, the association of ESBL-producers and delayed EAT or unfavorable prognoses had been evidenced (19, 111, 144, 145). Consequently, to diminish the ESBL-producer, a crucial confounding factor, affecting the prognostic effects of inappropriate EAT, adjustments for the above parameters were essential. Accordingly, based on the pooled result of multivariable analyses herein, the prognostic effect of delayed EAT was trivial in patients with healthcare-associated bacteraemia or the older patients experiencing bacteraemia and significant in those with bacteraemia caused by vascular catheter infections or ESBL-producing Enterobacteriaceae.

This meta-analysis has several limitations. First, because of ethical concerns with testing the negative effects of inappropriate EAT on mortality, randomized clinical trials comparing the outcomes of appropriate and inappropriate EAT are limited in the literature. Therefore, consistent with that in previous meta-analyses of appropriate EAT administration in patients with sepsis (206–208), between-study heterogeneity might arise from nonrandomised studies herein. Second, in accordance with previous methods (206), we used reasonable assumptions to comprehensively capture the multivariate result of each study to minimize publication bias, such as the inverse input of adjusted ORs and 95% CIs for included studies reporting only the prognostic effects of appropriate EAT. However, the publication bias in the adjusted analyses remained greater than that in the unadjusted analyses. We believe that this bias was partially caused by the lack of included studies that found no significant impact.
of inappropriate EAT and those that reported their multivariate results only qualitatively, resulting in their true values of adjusted ORs being unavailable for our collection. Moreover, because of the publication bias, another leading limitation of the present study is the prognostic benefits of appropriate EAT only 293 disclosed in specific bacteraemic populations. Third, to avoid confusing the reader with a “massive” meta-analysis, only studies with mortality as the assessed outcome were included in our analyses. Therefore, information detailing the impacts of inappropriate EAT on the economic outcome, microbiological clearance rate, and hospitalization length was not presented herein.

Although current evidence cannot sufficiently support the disadvantage of inappropriate EAT in specific populations with bacteraemia, such as elderly patients, non–ICU patients, causative Enterobacter species, and the source of urinary tract infections, this review and meta-analysis of contemporaneous literature demonstrates that inappropriate EAT is associated with unfavorable mortality outcomes overall and in most patient subgroups. Our findings underscore the necessity of precision medicine for the rapid diagnosis and for “treating the right patient with the right drug at the right time.”

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

AUTHOR CONTRIBUTIONS

C-CL executed the main database searches and helped to extract data from individual studies by using prespecified methods determined by all study authors and drafted this manuscript. C-CL and Y-PH independently reviewed 416 studies and helped to capture data from individual studies by using prespecified methods determined by all authors. W-CK revised it carefully from a professional point of view. All authors contributed to the inception of the research question, study design, read, and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.869822/full#supplementary-material

REFERENCES

1. Bates DW, Pruess KE, Lee TH. How bad are bacteremia and sepsis?: Outcomes in a cohort with suspected bacteremia. Arch Intern Med. (1995) 155:593–598. doi: 10.1001/archinte.155.6.593
2. Levy MM, Evans LE, Rhodes A. The surviving sepsis campaign bundle: 2018 update. Intensive Care Med. (2018) 44:925–8. doi: 10.1007/s00134-018-5085-0
3. Endimiani A, Tamborini A, Luzzaro F, Lombardi G, Toniolo A. A two-year analysis of risk factors and outcome in patients with bloodstream infection. Jpn J Infect Dis. (2003) 56:1–7.
4. Kim SH, Park WB, Lee CS, Kang CL, Bang JW, Kim HB, et al. Outcome of inappropriate empirical antibiotic therapy in patients with Staphylococcus aureus bacteraemia: analytical strategy using propensity scores. Clin Microbiol Infect. (2006) 12:13–21. doi: 10.1111/j.1469-0691.2005.01294.x
5. Retamar P, Lopez-Prieto MD, Nátera C, de Cueto M, Nuño E, Herrero M, et al. Reappraisal of the outcome of healthcare-associated and community-acquired bacteraemia: a prospective cohort study. BMC Infect Dis. (2013) 13:1–10. doi: 10.1186/1471-2334-13-34
6. Boel J, Søgaard M, Andreasen V, Jarløv JO, Arpi M. Evaluating antibiotic stewardship programs in patients with bacteremia using administrative data: a cohort study. Eur J Clin Microbiol Infect Dis. (2015) 34:1475–84. doi: 10.1007/s10096-015-2378-x
7. Lee CC, Lee CH, Yang CY, Hsieh CC, Tang HJ, Ko WC. Beneficial effects of early empirical administration of appropriate antimicrobials on survival and defervescence in adults with community-onset bacteraemia. Crit Care. (2019) 23:1–12. doi: 10.1186/s13054-019-2632-1
8. Falcone M, Bassetti M, Tiseo G, Giordano C, Nencini E, Russo A, et al. Time to appropriate antibiotic therapy is a predictor of outcome in patients with bloodstream infection caused by KPC-producing Klebsiella pneumoniae. Crit Care. (2020) 24:1–12. doi: 10.1186/s13054-020-2742-9
9. Chen HC, Lin WL, Lin CC, Hsieh WH, Hsieh CH, Wu MH, et al. Outcome of inadequate empirical antibiotic therapy in emergency department patients with community-onset bloodstream infections. J Antimicrob Chemother. (2013) 68:947–53. doi: 10.1093/jac/dks475
10. Seo H, Lee SC, Chung H, Ra SH, Sang H, Kim MN, et al. Clinical and microbiological analysis of risk factors for mortality in patients with carbapenem-resistant enterobacteriaceae bacteremia. Int J Antimicrob Agents. (2020) 56:106126. doi: 10.1016/j.ijantimicag.2020.106126
11. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. Updating guidance for reporting systematic reviews: development of the PRISMA 2020 statement. J Clin Epidemiol. (2021) 134:103–12. doi: 10.1016/j.jclinepi.2021.02.003
12. The Newcastle–Ottawa Scale (NOS) for Assessing the Quality of Nonrandomized Studies in Meta-Analyses. Available online at: www.ohri.ca/programs/clinical_epidemiology/oxford.htm (accessed April 18, 2022).
13. Hampel H, Abraham NS, El-Serag HB. Meta-analysis: obesity and the risk for gastroesophageal reflux disease and its complications. Ann Intern Med. (2005) 143:199–211. doi: 10.7326/0003-4819-143-3-20050820-00006
14. Petrelli F, Ghidini M, Ghidini A, Perego G, Cabiddu M, Khakoo S, et al. Use of antibiotics and risk of cancer: a systematic review and meta-analysis of observational studies. Cancers. (2019) 11:1174. doi: 10.3390/cancers11081174
15. Babar ZU, Dodani SK, Nasm A. Treatment outcome and adverse effects of colistin in adult patients with carbapenem-resistant gram-negative bacteremia from Pakistan. Int J Infect Dis. (2021) 106:171–5. doi: 10.1016/j.ijid.2021.03.004
16. Martinez-Nadal G, Puerta-Alcalde P, Gudiol C, Cardozo C, Albazane-Puig A, Marco F, et al. Inappropriate empirical antibiotic treatment in high-risk neutropenic patients with bacteremia in the era of multidrug resistance. Clin Infect Dis. (2020) 70:1068–74. doi: 10.1093/cid/ciaa219
17. Álvarez-Marin R, Navarro-Amuedo D, Gasch-Blasi O, Rodriguez-Martínez JM, Calvo-Montes J, Lara-Contreras R, et al. A prospective, multicenter case control study of risk factors for acquisition and mortality in Enterobacter species bacteremia. J Infect. (2020) 80:174–81. doi: 10.1016/j.jinf.2019.09.017
18. Shargian-Alon L, Gafter-Gvili A, Ben-Zvi H, Wolach O, Yeshurun M, Raanani P, et al. Risk factors for mortality due to Acinetobacter baumannii bacteremia in patients with hematological malignancies—a retrospective study. Leuk Lymphoma. (2019) 60:2787–92. doi: 10.1080/10428194.2019.1599113

19. Lim CL, Spelman D. Mortality impact of empirical antimicrobial therapy in ESBL- and AmpC-producing Enterobacteriaceae bacteremia in an Australian tertiary hospital. Infect Dis Health. (2019) 24:124–33. doi: 10.1016/j.idh.2019.02.001

20. Chusri S, Chongsuvivatwong V, Silpapojakul K, Singkhamanan K, Hortiwakul T, Charernmak B, et al. Clinical characteristics and outcomes of community and hospital-acquired Acinetobacter baumannii bacteremia. J Microbiol Immunol Infect. (2019) 52:796–806. doi: 10.1016/j.jmii.2019.03.004

21. Yamaga S, Shime N. Association between appropriate empiric antimicrobial therapy and mortality from bloodstream infections in the intensive care unit. J Infect Chemother. (2018) 24:267–71. doi: 10.1016/j.jiac.2017.11.011

22. Saliba P, Hornero A, Cuervo G, Grau I, Jimenez E, Garcia D, et al. Mortality risk factors among non-ICU patients with nosocomial vascular catheter-related bloodstream infections: a prospective cohort study. J Hosp Infect. (2018) 99:48–54. doi: 10.1016/j.jhin.2017.11.002

23. Park SY, Lee EJ, Kim T, Yu SN, Park K-H, Lee MS, et al. Early administration of appropriate antimicrobial agents to improve the outcome of carbapenem-resistant Acinetobacter baumannii complex bacteraemia pneumonia. Int J Antimicrob Agents. (2018) 51:407–12. doi: 10.1016/j.ijantimicag.2017.10.018

24. Liu LH, Wang NY, Wu AJY, Lin CC, Lee CM, Liu CP. Citrobacter freundii bacteremia: Risk factors of mortality and prevalence of resistance genes. J Microbiol Immunol Infect. (2018) 51:565–72. doi: 10.1016/j.jmii.2016.08.016

25. Kuo SH, Lin WR, Lin JY, Huang CH, Jao YT, Yang PW, et al. The epidemiology, antibiograms and predictors of mortality among critically-ill patients with central line-associated bloodstream infections. J Microbiol Immunol Infect. (2018) 51:401–10. doi: 10.1016/j.jmii.2017.08.016

26. Kleinheider F, Cohen MJ, Moses AE, Patlial O, Strahilevitz J, Cahan A. Empiric antibiotic protocols for cancer patients with neutropenia: a single–center study of treatment efficacy and mortality in patients with bacteremia. Int J Antimicrob Agents. (2018) 51:71–6. doi: 10.1016/j.ijantimicag.2017.06.016

27. Haruki Y, Hagiya H, Haruki M, Sugiyama T. Clinical characteristics and outcome of critically ill patients with bacteremia caused by extended-spectrum β-lactamase-producing and non-producing E. coli. J Infect Chemother. (2018) 24:944–7. doi: 10.1016/j.jiac.2018.04.016

28. Bassetti M, Righi E, Del Giacomo P, Sartor A, Ansaldi F, Trucchì C, et al. Predictors of mortality with Staphylococcus aureus bacteremia in elderly adults. J Am Geriatr Soc. (2018) 66:1284–9. doi: 10.1111/jgs.15391

29. Bartoletti M, Giannella M, Lewis R, Caraceni P, Tedeschi S, Paul M, et al. Multicenter clinical and molecular epidemiological analysis of bacteremia due to carbapenem-resistant Enterobacteriaceae (CRE) in the CRE epicenter of the United States. Antimicrob Agents Chemother. (2017) 61:e02349–02316. doi: 10.1128/AAC.02349-16

30. Royo-Cebreiros C, Gudiol C, Garcia J, Tubau F, Laporte J, Ardanuy C, et al. Characteristics, etiology, antimicrobial resistance and outcomes of bacteraemic cholangitis in patients with solid tumours: a prospective cohort study. J Infect. (2017) 74:172–8. doi: 10.1016/j.jinf.2016.10.008

31. Man MY, Shum HP, Chan YH, Chan K, Yan WW, Lee R, et al. Clinical predictors and outcomes of Klebsiella pneumoniae bacteremia in a regional hospital in Hong Kong. J Hosp Infect. (2017) 97:35–41. doi: 10.1016/j.jhin.2017.06.007

32. Ma J, Li N, Liu Y, Wang C, Liu X, Chen S, et al. Antimicrobial resistance patterns, clinical features, and risk factors for septic shock and death of nosocomial E. coli bacteraemia in adult patients with hematological disease: a monocenter retrospective study in China. Medicine. (2017) 96:e6959. doi: 10.1097/MD.0000000000006959

33. Li L, Huang H. Risk factors of mortality in bloodstream infections caused by Klebsiella pneumoniae: a single-center retrospective study in China. Medicine. (2017) 96:e7924. doi: 10.1097/MD.0000000000007924

34. Lee CC, Wang JL, Lee CH, Hung YP, Hong MY, Chang CM, et al. Age-related trends in adults with community-onset bacteremia. Antimicrob Agents Chemother. (2017) 61:e01030–01017. doi: 10.1128/AAC.01050-17

35. Gradel KO, Jensen US, Schønheyder HC, Østergaard C, Knudsen JD, Wehberg S, et al. Impact of appropriate empirical antibiotic treatment on recurrence and mortality in patients with bacteremia: a population-based cohort study. BMC Infect Dis. (2017) 17:1–9. doi: 10.1186/s12879-017-2233-2

36. Adrie C, Garrant C, Beche L, Essaied WI, Schwebel C, Ramon M, Mournier R, et al. Attributable mortality of ICU-acquired bloodstream infections: impact of the source, causative microorganism, resistance profile and antimicrobial therapy. J Infect. (2017) 74:131–41. doi: 10.1016/j.jinf.2016.11.001

37. Yoon YK, Park DW, Sohn JW, Kim HY, Kim YS, Lee CS, et al. Effects of inappropriate empirical antibiotic therapy on mortality in patients with healthcare-associated methicillin-resistant Staphylococcus aureus bacteraemia: a propensity-matched analysis. BMC Infect Dis. (2016) 16:1–12. doi: 10.1186/s12879-016-1650-8

38. Ukimaz M, Elaldi N, Balkan I, Arslan F, Batirol AA, Bakici MZ, et al. Mortality predictors of Staphylococcus aureus bacteremia: a prospective multicenter study. Ann Clin Microbiol Antimicrob. (2016) 15:1–10. doi: 10.1186/s12941-016-0122-8

39. Trecarichi EM, Pagano L, Martino B, Candoni A, Di Blasi R, Nadali G, et al. Bloodstream infections caused by Klebsiella pneumoniae in onco-hematological patients: clinical impact of carbapenem resistance in a multicentre prospective study. Am J Hematol. (2016) 91:1076–81. doi: 10.1002/ajh.24489

40. Savage RD, Fowler RA, Rishu AH, Bagshaw SM, Cook D, Dodek P, et al. The effect of inadequate initial empiric antimicrobial treatment on mortality in critically ill patients with bloodstream infections: a multi-centre retrospective cohort study. PLoS ONE. (2016) 11:e0154944. doi: 10.1371/journal.pone.0154944

41. Migiyama Y, Yanagihara K, Nagaoka K, Harada Y, Yamada K, et al. Multicenter clinical and molecular epidemiological analysis of bacteremia in patients with hematological malignancy: a multicentre retrospective study from the Infection Working Party of Jiangsu Society of Hematology. Eur J Clin Microbiol Infect Dis. (2017) 36:1073–81. doi: 10.1007/s10096-016-2895-2

42. Wang W, Jiang T, Zhang W, Li C, Chen J, Xiang D, et al. Predictors of mortality in bloodstream infections caused by multidrug-resistant gram-negative bacteria: 4 years of experience. Am J Infect Control. (2017) 45:59–64. doi: 10.1016/j.ajic.2016.08.008

43. Tagashira Y, Sakamoto N, Isogai T, Hikone M, Kosaka A, Chino R, et al. Impact of inadequate initial antimicrobial therapy on mortality in patients with bacteraemic cholangitis: a retrospective cohort study. Clin Microbiol Infect. (2017) 23:740–7. doi: 10.1016/j.cmi.2017.02.027

44. Yoon YK, Park DW, Sohn JW, Kim HY, Kim YS, Lee CS, et al. Predictors of mortality in bloodstream infections caused by multidrug-resistant gram-negative bacteria: a 4-year retrospective study. Am J Infect Control. (2017) 45:59–64. doi: 10.1016/j.ajic.2016.08.008
50. Gudiol C, Royo-Cebrecos C, Laporte J, Ardanuy C, García-Vidal C, Antonio M, et al. Clinical features, aetiology and outcome of bacteraemic pneumonia in neutropenic cancer patients. Respir. (2016) 21:1411–8. doi: 10.1111/resp.12488

51. De la Calle C, Morata L, Cobos-Trigueros N, Martinez J, Cardozo C, Mensa J, et al. Staphylococcus aureus bacteremia. J Clin Microbiol Infect Dis. (2015) 35:497–502. doi: 10.1016/j.sico.2015.2666-8

52. Cheng WL, Hsueh PR, Lee CC, Li MJ, Chang CM, et al. Bacteremia pneumonia caused by extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella pneumoniae: appropriateness of empirical treatment matters. J Microbiol Infect. (2016) 49:208–15. doi: 10.15620/jmij.2015.10.025

53. Abraham K, Dolman HS, Zimmerman LH, Faris J, Edelman DA, Cheng WL, Hsueh PR, Lee CC, Li CW, Li MJ, Chang CM, et al. Clinical features and impact of empirical therapy in cirrhotic patients with bacteremia. J Hepatol. (2015) 81:405–18. doi: 10.1016/j.jhep.2015.03.004

54. Wu JN, Gan TE, Zhu YX, Cao JM, Ji CH, Wu YH, et al. Epidemiology and microbiology of nosocomial bloodstream infections: analysis of 482 cases from a retrospective surveillance study. J Zhonghai Univ Sci B. (2015) 16760–7. doi: 10.1631/jzua.B1400108

55. Picot-Guéraud R, Batailler P, Caspar Y, Hennebique A, Mallaret M-R, Dabbagh T, et al. Impact of prompt catheter withdrawal and adequate antimicrobial therapy on the outcome of critically ill surgical patients with bacteremia. Am J Surg. (2015) 209:692–7. doi: 10.1016/j.amjsurg.2015.10.025

56. Rodriguez-Pardo D, Almirante B, Fernández-Hidalgo N, Piguera C, Ferrer C, Planes A, et al. Impact of prompt catheter withdrawal and adequate antimicrobial therapy on the prognosis of hospital-acquired parenteral nutrition catheter-related bacteraemia. Clin Microbiol Infect. (2014) 20:1205–10. doi: 10.1111/1469-0691.12703

57. Marin M, Gudiol C, García-Vidal C, Ardanuy C, Carratalá J. Bloodstream infections in patients with solid tumors: epidemiology, antibiotic therapy, and outcomes in 528 episodes in a single cancer center. Medicine. (2014) 93:143–9. doi: 10.1097/MD.0000000000000226

58. Lee HY, Chen CL, Wu SR, Huang CW, Chiu CH. Risk factors and outcome analysis of Acinetobacter baumannii complex bacteremia in critical patients. Crit Care Med. (2014) 42:1081–8. doi: 10.1097/CCM.0000000000001215

59. Kim YJ, Jun YH, Kim YR, Park KG, Park YJ, Kang JY, et al. Risk factors for mortality in patients with Pseudomonas aeruginosa bacteremia: retrospective study of impact of combination antimicrobial therapy. BMC Infect Dis. (2014) 14:1–7. doi: 10.1186/1756-3305-14-161

60. Fernandez C, Cobos-Trigueros N, Feher C, Morata L, De la Calle C, Marco F, et al. Community-onset bacteremia of unknown origin: clinical characteristics, epidemiology and outcome. J Clin Microbiol Infect Dis. (2014) 33:1973–80. doi: 10.1016/j.simo.2014.07.2146

61. Girometti N, Lewis RE, Giannella M, Ambretti L, Bartoletti M, Tedeschi S, et al. Klebsiella pneumoniae bloodstream infection: epidemiology and impact of inappropriate empirical therapy. Medicine. (2014) 93:298–309. doi: 10.1097/MD.0000000000011111

62. Falcone M, Vena A, Mezzatesta M, Gona F, Caio C, Goldoni P, et al. Role of empirical and targeted therapy in hospitalized patients with bloodstream infections caused by ESBL. Ann Ig. (2014) 26:293–304. doi: 10.7416/ai.2014.1989

63. Davis JS, McMillan M, Swaminathan A, Kelly JA, Pieira KE, Baird RW, et al. A 16-year prospective study of community-onset bacteremic Acinetobacter pneumonia: low mortality with appropriate initial empirical antibiotic protocols. Chest. (2014) 146:1038–45. doi: 10.1378/chest.13-3065

64. Bodro M, Gudiol C, Garcia-Vidal C, Tubau F, Contra A, Boix L, et al. Epidemiology, antibiotic therapy and outcomes of bacteremia caused by drug-resistant ESKEAPe pathogens in cancer patients. Support Care Cancer. (2014) 22:603–10. doi: 10.1007/s00520-012-2013-2

65. Bartoletti M, Giannella M, Caraceni P, Domenicali M, Ambretti S, Tedeschi S, et al. Epidemiology and outcomes of bloodstream infection in patients with cirrhosis. J Hepatol. (2014) 61:51–8. doi: 10.1016/j.jhep.2014.03.021

66. Yang CJ, Chung YC, Chen TC, Chang HL, Tsai YM, Huang MS, et al. The impact of inappropriate antibiotics on bacteremia patients in a community hospital in Taiwan: an emphasis on the impact of referral information for cases from a hospital affiliated nursing home. BMC Infect Dis. (2013) 13:1–8. doi: 10.1186/1471-2334-13-500

67. Ruiz-Giardin JM, Jimenez BC, Martín RM, Ortiz J, Arenas MHC, SanMartin JV, et al. Clinical diagnostic accuracy of suspected sources of bloodstream infections and its effect on mortality. J Infect Chemother. (2013) 19:843–9. doi: 10.1007/s10156-013-0571-3

68. Peña C, Suarez C, Ocampo-Sosa A, Murillas J, Almirante B, Pomar V, et al. Drug-resistant ESKAPE pathogens in cancer patients. J Infect Chemother. (2013) 19:634–9. doi: 10.1016/j.jiac.2012.09.003

69. Al-Dorzi HM, Zimmerman LH, Faris J, Edelman DA, Cheng WL, Hsueh PR, Lee CC, Li CW, Li MJ, Chang CM, et al. Clinical characteristics and outcome of elderly patients with community-onset bacteremia. J Infect. (2015) 70:135–43. doi: 10.1016/j.jinf.2014.09.002

70. Dabdoub G, Koulenti D, Tahat A, Poulakou G, Vesin A, Arvanitakis N, et al. Bloodstream infections in ICU with increased resistance: epidemiology and outcomes. Minerva Anestesiol. (2015) 81:405–18.

71. Cain SE, Kohn J, Bookstaver PB, Albrecht H, Al-Hasan MN. Stratification of the impact of inappropriate empirical antimicrobial therapy for Gram-negative bloodstream infections by predicted prognosis. Antimicrob Agents Chemother. (2015) 59:245–50. doi: 10.1128/AAC.03935-14

72. Al-Dorzi HM, Asiri AM, Shimemri A, Tanam HM, Al Johani SM, Al Dabbagh T, et al. Impact of empirical antimicrobial therapy on the outcome of critically ill patients with Acinetobacter bacteremia. Ann Thorac Med. (2015) 10:256. doi: 10.4103/1817-1737.164302

73. Zilberberg MD, Shorr AF, Micek ST, Vazquez-Guillame C, Kollef M. Multi-drug resistance, inappropriate initial antibiotic therapy and mortality in Gram-negative severe sepsis and septic shock: a retrospective cohort study. Crit care. (2014) 18:1–13. doi: 10.1186/s13054-014-0596-8

74. Shorr AF, Zilberberg MD, Micek ST, Kollef M. Predictors of hospital mortality among septic ICU patients with Acinetobacter spp. bacteremia: a cohort study. BMC Infect Dis. (2014) 14:1–7. doi: 10.1186/1471-2334-14-0572-6

75. Rodriguez-Pardo D, Almirante B, Fernández-Hidalgo N, Piguera C, Ferrer C, Planes A, et al. Impact of prompt catheter withdrawal and adequate antimicrobial therapy on the prognosis of hospital-acquired parenteral nutrition catheter-related bacteraemia. Clin Microbiol Infect. (2014) 20:1205–10. doi: 10.1111/1469-0691.12703
Hung et al. Inappropriate Empirical Antibiotics in Bacteraemia Adults

84. Kang CI, Wi YM, Ko KS, Chung DR, Peck KR, Lee NY, et al. Outcomes and risk factors for mortality in community-onset bacteraemia caused by extended-spectrum beta-lactamase-producing Escherichia coli, with a special emphasis on antimicrobial therapy. Scand J Infect Dis. (2013) 45:319–25. doi: 10.3109/03636548.2013.775749

85. Kang CI, Sung YK, Lee KH, Lee KT, Lee JK. Clinical impact of inappropriate initial antimicrobial therapy on outcome in bacteraemic biliary tract infections. Scand J Infect Dis. (2013) 45:227–34. doi: 10.3109/03636548.2012.730151

86. Horcajada J, Shaw E, Padilla B, Pintado V, Calbo E, Benito N, et al. Healthcare-associated, community-acquired and hospital-acquired bacteraemic urinary tract infections in hospitalized patients: a prospective multicentre cohort study in the era of antimicrobial resistance. Clin Microbiol Infect. (2013) 19:962–8. doi: 10.1111/1469-0691.12089

87. Gudiol C, Ayats J, Camoet M, Dominguez MÁ, García-Vidal C, Bodro M, et al. Increase in bloodstream infection due to vancomycin-susceptible Enterococcus faecium in cancer patients: risk factors, molecular epidemiology and outcomes. PLoS ONE. (2013) 8:e74734. doi: 10.1371/journal.pone.0074734

88. Gasch O, Camoet M, Dominguez M, Padilla B, Pintado V, Almirante B, et al. Predictive factors for early mortality among patients with meticillin-resistant Staphylococcus aureus bacteraemia. J Antimicrob Chemother. (2013) 68:1423–30. doi: 10.1093/jac/dkt016

89. Garnacho-Montero J, Díaz-Martín A, García-Cabrera E, Ruiz Pérez de, Pipsón M, Hernández-Caballero C, Lepe-Jiménez JÁ. Impact on hospital mortality of catheter removal and adequate antimicrobial therapy in Candida spp bloodstream infections. J Antimicrob Chemother. (2013) 68:206–13. doi: 10.1093/jac/dks347

90. Frakking FN, Rottier WC, Dorigo-Zetsma JW, van Hattem JM, Van Hees BC, Kluymans JA, et al. Appropriateness of empirical treatment and outcome in bacteraemia caused by extended-spectrum beta-lactamase-producing bacteria. Antimicrob Agents Chemother. (2013) 57:3092–9. doi: 10.1128/AAC.01523-12

91. Bang JH, Jung Y, Cheon S, Kim CJ, Song KH, Choe PG, et al. Pseudomonas aeruginosa bacteremia in patients with liver cirrhosis: a comparison with bacteremia caused by Enterobacteriaceae. BMC Infect Dis. (2013) 13:1–6. doi: 10.1186/1471-2334-13-332

92. Wu UI, Chen WC, Yang CS, Wang L, Hu FC, Chang SC, et al. Ertapenem in the treatment of bacteraemia caused by extended-spectrum beta-lactamase-producing Escherichia coli: a propensity score analysis. Int J Infect Dis. (2012) 16:e47–52. doi: 10.1016/j.ijid.2011.09.019

93. Tumbarello M, Viale P, Viscoli C, Trecarichi EM, Tumietto F, Marchese A, et al. Predictors of mortality in bloodstream infections caused by Klebsiella pneumoniae carbapenemase-producing K. pneumoniae: implications of combination therapy. Clin Infect Dis. (2012) 55:943–50. doi: 10.1093/cid/cis588

94. Tumbarello M, Trecarichi EM, Fiori B, Losito AR, D’Inzeo T, Campana F, et al. Risk factors and mortality of bloodstream infections due to antibiotic-sensitive pathogens in immunocompetent patients. Clin Microbiol Infect. (2013) 19:1791–8. doi: 10.1111/1469-0691.12089

95. Sancho S, Artero A, Zaragoza R, Camarena J, González R, Nogueira J. Tumbarello M, Artero A, Zaragoza R, Camarena J, González R, Nogueira J. The determinants of hospital mortality among patients with septic shock receiving appropriate initial antibiotic treatment. Crit Care Med. (2012) 40:2016–17. doi: 10.1097/CCM.0b013e318250a972

96. Yang Y, Lee MI, Sin HY, Kim NH, Hwang JH, Park J, et al. Differences in characteristics between healthcare-associated and community-acquired infection in community-onset Klebsiella pneumoniae bloodstream infection in Korea. BMC Infect Dis. (2012) 12:1–9. doi: 10.1186/1471-2334-12-239

97. Horino T, Chiba A, Kawano S, Kato T, Sato F, Maruyama Y, et al. Clinical characteristics and risk factors for mortality in patients with bacteraemia caused by Pseudomonas aeruginosa. Intern Med. (2012) 51:59–64. doi: 10.2169/internalmedicine.51.5698

98. Bassetti M, Trecarichi EM, Mesini A, Spanu T, Giacobbe D, Rossi M, et al. Risk factors and mortality of healthcare-associated and community-acquired Staphylococcus aureus bacteraemia. Clin Microbiol Infect. (2012) 18:862–9. doi: 10.1111/j.1469-0691.2011.03679.x

99. Zarkotou O, Pournaras S, Tselioti P, Dragoumanos V, Pirtitiga V, Ranelou K, et al. Predictors of mortality in patients with bloodstream infections caused by KPC-producing Klebsiella pneumoniae and impact of appropriate antimicrobial treatment. Clin Microbiol Infect. (2011) 17:1798–803. doi: 10.1111/j.1469-0691.2011.03514.x

100. Wang SS, Lee NY, Huang WH, Tsui KC, Lee HC, et al. Clinical manifestations and prognostic factors in cancer patients with bacteraemia due to extended-spectrum beta-lactamase-producing Escherichia coli or Klebsiella pneumoniae. J Microbiol Immunol Infect. (2011) 44:282–8. doi: 10.1016/j.jmi.2011.08.004

101. Tuon FF, Kruger M, Terreri M, Pentadeo-Filho SR, Gortz L. Klebsiella ESBL bacteremia-mortality and risk factors. Braz J Infect Dis. (2011) 15:594–8. doi: 10.1590/S1413-86702011000600016

102. Tumbarello M, Repetto E, Trecarichi EM, Bernardini C, De Pascale G, Parisini A, et al. Multidrug-resistant Pseudomonas aeruginosa bloodstream infections: risk factors and mortality. Epidemiol Infect. (2011) 139:1740–9. doi: 10.1017/S0950261110003055

103. Takesue Y, Nakajima K, Takahashi Y, Ichiki K, Wada Y, Tsuchida T, et al. Clinical characteristics of vancomycin minimum inhibitory concentration of 2 µg/ml methicillin-resistant Staphylococcus aureus strains isolated from patients with bacteraemia. J Infect Chemother. (2011) 17:52–7. doi: 10.3109/1015610-011-0086-0

104. Song YJ, Cheong HJ, Choi WS, Heo JY, Noh JY, Kim WJ. Clinical and microbiological characterization of carbapenem-resistant Acinetobacter baumannii bloodstream infections. J Med Microbiol. (2011) 60:605–11. doi: 10.1099/jmm.0.029439-0

105. Shimé N, Satake S, Fujita N. De-escalation of antimicrobials in the treatment of bacteraemia due to antibiotic-sensitive pathogens in immunocompetent patients. Infection. (2011) 39:319–25. doi: 10.1007/s11576-011-0116-6
Inappropriate Empirical Antibiotics in Bacteremia Adults

116. Schechner V, Gottesman T, Schwartz O, Korem M, Maor Y, Rahav G, et al. *Pseudomonas aeruginosa* bacteremia upon hospital admission: risk factors for mortality and influence of inadequate empirical antimicrobial therapy. *Diagn Microbiol Infect Dis.* (2011) 71:38–45. doi: 10.1016/j.diagmicrobio.2011.05.010

117. Reisfeld S, Paul M, Gottesman B, Shitrit P, Leibovici L, Chowers M. The effect of empiric antibiotic therapy on mortality in delirium patients with dementia. *Eur J Clin Microbiol Infect Dis.* (2011) 30:813–8. doi: 10.1007/s10096-011-1161-x

118. Rebelo M, Pereira B, Lima J, Decq-Mota J, Vieira JD, Costa JN. Predictors of in-hospital mortality in elderly patients with bacteremia admitted to an Internal Medicine ward. *Int Arch Med.* (2011) 4:1–9. doi: 10.1186/1755-7682-4-33

119. Park SH, Choi SM, Lee DG, Kim J, Choi HJ, Kim SH, et al. Emergence of extended-spectrum β-lactamase-producing *Escherichia coli* as a cause of community-onset bacteremia in South Korea: risk factors and clinical outcomes. *Microb Drug Resist.* (2011) 17:537–44. doi: 10.1089/mdr.2011.0072

120. Ortega M, Marco F, Soriano A, Almela M, Martínez J, López J, et al. Cefotaxime resistance and outcome of *Klebsiella* spp bloodstream infection. *Eur J Clin Microbiol Infect Dis.* (2011) 30:1599–605. doi: 10.1007/s10096-011-1266-2

121. Lewis T, Chauhdry N, Nightingale P, Lambert P, Das I. Methicillin-resistant *Staphylococcus aureus* bacteremia: risk factors and clinical outcomes. *Clin Infect Dis.* (2011) 54:4085–91. doi: 10.1128/AC.00143-10

122. Shen S, Song JH, Ko KS, Yeom JS, Ki HK, Kim SW, et al. Bloodstream infections and clinical significance of healthcare-associated bacteremia: a multicenter surveillance study in Korean hospitals. *J Korean Med Sci.* (2010) 25:992–8. doi: 10.3346/kjem.2010.25.7.792

123. Schweizer ML, Furuno JP, Harris AD, Johnson JK, Sheddell MD, McGregor JC, et al. Empiric antibiotic therapy for *Staphylococcus aureus* bacteremia may not reduce in-hospital mortality: a retrospective cohort study. *PLoS ONE.* (2010) 5:e11432. doi: 10.1371/journal.pone.0011432

124. Asgeirsson H, Kristjansson M, Kristinsson KG, Gudlaugsson KNftSoI. Risk factors for mortality and impact of broad-spectrum β-lactamase-producing *Escherichia coli*: risk factors and prognosis. *Clin Infect Dis.* (2010) 50:40–8. doi: 10.1086/649537

125. Rodríguez-Baño J, Picón E, Gijón P, Hernández JR, Ruiz M, Peña C, et al. Community-onset bacteremia due to extended-spectrum β-lactamase-producing *Escherichia coli*: risk factors and prognosis. *Clin Infect Dis.* (2010) 50:40–8. doi: 10.1086/649537

126. Feodoroff B, Lauhio A, Ellström P, Rautelin H. A nationwide study of infections caused by Gram-negative pathogens. *J Infect.* (2011) 62:159–64. doi: 10.1016/j.jinf.2010.10.009

127. Martinez J, Cobos-Trigueros N, Soriano A, Almela M, Ortega M, Marco F, et al. Influence of empiric therapy with a β-lactam alone or combined with an aminoglycoside on prognosis of bacteremia due to gram-negative microorganisms. *Antimicrob Agents Chemother.* (2010) 54:3590–6. doi: 10.1128/AAC.00115–10

128. Lin PY, Chen HL, Huang CT, Su LH, Chiu CH. Biofilm production, use of intravascular indwelling catheters and inappropriate antimicrobial therapy as predictors of mortality in *Chryseobacterium meningosepticum* bacteremia. *Int J Antimicrob Agents.* (2010) 36:436–40. doi: 10.1016/j.ijantimicag.2010.06.033

129. Khan FY, Elshafee SS, Almaslamani M, Abu-Khattab M, El Hiday AH, Errayes M, et al. Epidemiology of bacteremia in Hamad general hospital, Qatar: a one year hospital-based study. *Travel Med Infect Dis.* (2010) 8:377–87. doi: 10.1016/j.trmed.2010.10.004

130. Corona A, Bertolini G, Lipman J, Wilson AP, Singer M. Antibiotic use and impact on outcome from bacteremic critical illness: the BActeraemia Study in Intensive Care (BASIC). *J Antimicrob Chemother.* (2010) 65:1276–85. doi: 10.1093/jac/dkq500

131. Abhilash K, Veeraraghavan B, Abraham O. Epidemiology and outcome of bacteremia caused by extended spectrum beta-lactamase (ESBL)-producing *Escherichia coli* and *Klebsiella* spp. in a tertiary care teaching hospital in south India. *J Assoc Physicians India.* (2010) 58(Suppl):13–7.

132. Tumbarello M, Spanu T, Di Bidino R, Marchetti M, Ruggeri M, Trecarichi EM, et al. Costs of bloodstream infections caused by *Escherichia coli* and influence of extended-spectrum β-lactamase production and inadequate initial antibiotic therapy. *Antimicrob Agents Chemother.* (2010) 54:4085–91. doi: 10.1128/AAC.00143-10

133. Tam VH, Rogers CA, Chang KT, Weston JS, Caeiro JP, Garey KW. Impact of multidrug-resistant *Pseudomonas aeruginosa* bacteremia on patient outcomes. *Antimicrob Agents Chemother.* (2010) 54:3717–22. doi: 10.1128/AAC.00207-10

134. Son JS, Song JH, Ko KS, Yeom JS, Ki HK, Kim SW, et al. Bloodstream infections and clinical significance of healthcare-associated bacteremia: a multicenter surveillance study in Korean hospitals. *J Korean Med Sci.* (2010) 25:992–8. doi: 10.3346/kjem.2010.25.7.792

135. Guirao P, de Almeida JG, Silva EP, Freitas-Correia L, Alves RL, da Costa Barata T, et al. Inadequate empirical antibiotic therapy for *Acinetobacter baumannii* bacteremia: predictive factors for isolation of an antibiotic-resistant strain and their impact on the outcome. *J Antimicrob Chemother.* (2009) 63:568–74. doi: 10.1093/jac/dkn514

136. Metan G, Sariguzel F, Sumerkan B. Factors influencing survival in patients with multi-drug-resistant *Acinetobacter baumannii* bacteremia. *Eur J Intern Med.* (2009) 20:540–4. doi: 10.1016/ejim.2009.05.005

Frontiers in Medicine | www.frontiersin.org 13 May 2022 | Volume 9 | Article 869822

Hung et al.
149. Klevay MJ, Horn DL, Neofytos D, Pfaller MA, Diekema DJ. Initial treatment and outcome of Candida glabrata versus Candida albicans bloodstream infection. Diagn Microbiol Infect Dis. (2009) 64:152–7. doi: 10.1016/j.diagmicrobio.2009.03.007.

150. Evans CT, Burns SP, Chin A, Weaver FM, Hershov RC. Predictors and outcomes of antibiotic adequacy for bloodstream infections in veterans with spinal cord injury. Arch Phys Med Rehabil. (2009) 90:1364–70. doi: 10.1016/j.apmr.2009.02.012.

151. Erbay A, Idol A, Gözel MG, Mumcuoglu I, Balaban N. Impact of early appropriate antimicrobial therapy on survival in Acinetobacter baumannii bloodstream infections. Int J Antimicrob Agents. (2009) 34:575–9. doi: 10.1016/j.ijantimicag.2009.07.006.

152. Daikos GL, Petrikkos P, Kosmidis C, Vryonis E, Skoutelis A, et al. Prospective observational study of the impact of VIM-1 metallo–β-lactamase on the outcome of patients with Klebsiella pneumoniae bloodstream infections. Antimicrob Agents Chemother. (2009) 53:1868–73. doi: 10.1128/AAC.00782-08.

153. Chang EP, Chiang DH, Lin ML, Chen TL, Wang FD, Liu CY. Clinical characteristics and predictors of mortality in patients with Enterobacter aerogenes bacteremia. J Microbiol Immunol Infect. (2009) 42:329–35.

154. Ammerlaan H, Seifert H, Barhart S, Brun-Buisson C, Torres A, Martínez-Martínez L, et al. Impact of antibiotic resistance and of multi-drug resistance. Clin Infect Dis. (2008) 46:193–200. doi: 10.1086/524667.

155. Marschall J, Agniel D, Fraser VJ, Warren DK. Gram-negative bloodstream infection due to Enterobacter spp: epidemiology, risk factors and impact of multi-drug resistance. Eur J Clin Microbiol Infect Dis. (2008) 27:607–12. doi: 10.1007/s10096-008-0473-y.

156. Tumbarello M, Sali M, Trecarichi EM, Leone F, Rossini M, Fiori B, et al. Bloodstream infections caused by extended-spectrum–β-lactamase-producing Escherichia coli: risk factors for inadequate initial antimicrobial therapy. Antimicrob Agents Chemother. (2008) 52:3244–52. doi: 10.1128/AAC.00603-08.

157. Soriano A, Marco E, Martínez JA, Pisos E, Almela M, Dimova VP, et al. Influence of vancomycin minimum inhibitory concentration on the treatment of methicillin-resistant Staphylococcus aureus bacteremia. Clin Infect Dis. (2008) 46:193–200. doi: 10.1128/JCM.00782-08.

158. Ye Y, Li J, Ye D, Ji Z. Enterobacter bacteremia: Clinical features, risk factors for multiresistance and mortality in a Chinese University Hospital. Infection. (2006) 34:252–7. doi: 10.1007/s15010-006-0583-8.

159. Marchar JL, Turchi M, Martelli C, Primo M. Staphylococcus aureus bacteremia: incidence, risk factors and predictors for attributable mortality. Antimicrob Agents Chemother. (2008) 52:386–90. doi: 10.1128/AAC.00891-07.

160. Lin YC, Chen TL, Hu HL, Chen HS, Wang FD, Yu KW, et al. Clinical characteristics and risk factors for attributable mortality in Enterobacter cloacae bacteremia. J Antimicrob Chemother. (2006) 58:967–72.

161. Kang CI, Kim SH, Park WB, Lee KD, Kim HB, Kim EC, et al. Impact of initial antibiotic choice and delayed appropriate treatment on the outcome of Staphylococcus aureus bacteremia. Eur J Clin Microbiol Infect Dis. (2006) 25:181–5. doi: 10.1007/s10096-006-0096-0.

162. Schulman D, Bean DC, Khanna P, Hennessy E, Krahe D, Ely A, et al. Time to initiation of fluconazole therapy impacts mortality in patients with candidemia: a multi-institutional study. Clin Infect Dis. (2006) 43:25–31. doi: 10.1086/504810.

163. Fang CT, Shau WY, Hsuhe PR, Chen YC, Wang JT, Hung CC, et al. Early empirical glycoprotein therapy for patients with methicillin-resistant Staphylococcus aureus bacteremia: impact on the outcome. J Antimicrob Chemother. (2006) 57:511–9. doi: 10.1093/jac/dkl006.

164. Falagas ME, Kasiakou SK, Ralafidlis PI, Zouglikis G, Morfou P. Comparison of mortality of patients with Acinetobacter baumannii bacteremia receiving appropriate and inappropriate empirical therapy. J Antimicrob Chemother. (2006) 57:1251–4. doi: 10.1093/jac/dkl110.

165. Wang FD, Lin ML, Liu CY. Bacteremia in patients with hematological malignancies. Chemotherapy. (2005) 51:147–53. doi: 10.1159/000085623.

166. Shih HL, Lee HC, Lee NY, Chang CM, Wu CJ, Wang IR, et al. Seratia marcescens bacteremia at a medical center in southern Taiwan: high prevalence of cefotaxime resistance. J Microbiol Infect Dis. (2005) 38:350–7.

167. Micek ST, Lloyd AE, Ritchie DJ, Reichley RM, Fraser VJ, Kollef MH. Pseudomonas aeruginosa bloodstream infection: importance of appropriate initial antimicrobial therapy. Antimicrob Agents Chemother. (2005) 49:1306–11. doi: 10.1128/AAC.49.4.1306-1311.2005.

168. Metan G, Zarakolu P, Çakır B, Haselci G, Üzun O. Clinical outcomes and therapeutic options of bloodstream infections caused by extended-spectrum β-lactamase–producing Escherichia coli. Int J Antimicrob Agents. (2005) 26:254–7. doi: 10.1016/j.ijantimicag.2005.06.012.

169. Kang CI, Kim SH, Park WB, Lee KD, Kim HB, Kim EC, et al. Bloodstream infections caused by antibiotic-resistant gram-negative bacilli: risk factors for mortality and impact of inappropriate initial antimicrobial therapy on outcome. Antimicrob Agents Chemother. (2005) 49:7960–5. doi: 10.1128/AAC.49.11.7960-7965.2005.

170. Hung MN, Chen SY, Wang JL, Chang SC, Hsueh PR, Liao CH, et al. Community-acquired anaerobic bacteremia in adults: one-year experience in a medical center. J Microbiol Infect Dis. (2005) 38:436–43.
183. Bouza E, Pintado V, Rivera S, Blázquez R, Muñoz P, Cercenado E, et al. Nosocomial bloodstream infections caused by *Streptococcus pneumoniae*. *Clin Microbiol Infect.* (2005) 11:919–24. doi: 10.1111/j.1469-0691.2005.01260.x

184. Lin JC, Yeh KM, Peng MY, Chang FY. Community-acquired methicillin-resistant *Staphylococcus aureus* bacteremia in Taiwan: risk factors for acquisition, clinical features and outcome. *J Microbiol Immunol Infect.* (2004) 37:24–8.

185. Bouza E, Sousa D, Munoz P, Rodríguez-Creixems M, Fron C, Lechuz JG. Bloodstream infections: a trial of the impact of different methods of reporting positive blood culture results. *Clin Infect Dis.* (2004) 39:1161–9. doi: 10.1086/424520

186. Anatóliotaki M, Valatas V, Mantadakis E, Apostolakou H, Movridou D, Georgoulia V, et al. Bloodstream infections in patients with solid tumors: associated factors, microbial spectrum and outcome. *Infection.* (2004) 32:65–71. doi: 10.1007/s00108-004-0349-5

187. Zaragoza R, Arteo A, Camarena J, Sancho S, Gonzalez R, Nogueira J. The influence of inadequate empirical antimicrobial treatment on patients with bloodstream infections in an intensive care unit. *Clin Microbiol Infect.* (2003) 9:412–8. doi: 10.1046/j.1469-0691.2003.00656.x

188. Vallez J, Rello J, Ochagaiva A, Garnacho J, Alcalá MA. Community-acquired bloodstream infection in critically ill adult patients: impact of shock and inappropriate antibiotic therapy on survival. *Chest.* (2003) 123:1615–24. doi: 10.1378/chest.123.5.1615

189. MacKenzie A, Robertson L, Jappy B, Laing R, Gould IM. Audit of an *Pseudomonas* bacteremia in a large teaching hospital. *Scand J Infect Dis.* (2002) 34:520–5. doi: 10.1080/03035930110080827

190. Kragh AL, van den Bosch CH, van der Linden AB, Vennema H. The survival of patients with bloodstream infection: a systematic review and meta-analysis of the efficacy of appropriate empirical antimicrobial therapy for bacteremia. *Antimicrob Agents Chemother.* (2013) 57:4148–54. doi: 10.1128/AAC.00565-13

191. Langstaff SJ, Keefer JS, Mermel LA, Moon RE. The effect of initial antimicrobial therapy on the outcome of patients with bloodstream infections. *Arch Intern Med.* (1998) 158:868–72. doi: 10.1001/archinte.158.8.868

192. Hong et al. Inappropriate Empirical Antibiotics in Bacteraemia Adults: The benefit of appropriate empirical antibiotic treatment for *Staphylococcus aureus* bacteremia. *Clin Infect Dis.* (1998) 26:1413–7. doi: 10.1086/516355

193. Leibovici L, Shraga I, Drucker M, Konigsberger H, Samra Z, Pitlik S. The benefit of appropriate empirical antibiotic treatment in patients with bloodstream infection. *J Intern Med.* (1998) 244:379–86. doi: 10.1046/j.1365-2796.1998.00379.x

194. Carratalá J, Rosón B, Fernández-Sevilla A, Alcaide F, Gudiol F. Bacterial pneumonia in neutropenic patients with cancer: causes, empirical antibiotic therapy, and outcome. *Arch Intern Med.* (1998) 158:68–72. doi: 10.1001/archinte.158.6.686

195. Elhannan G, Sarhat M, Raz R. Empiric antibiotic treatment and the misuse of culture results and antibiotic sensitivities in patients with community-acquired bacteraemia due to urinary tract infection. *J Infect.* (1997) 35:283–8. doi: 10.1016/S0163-4453(97)93149-7

196. Phillips I, King A, Gransden WR, Eykyn SJ. The antibiotic sensitivity of bacteria isolated from the blood of patients in St Thomas' Hospital, 1969–1988. *J Antimicrob Chemother.* (1990) 25(suppl_C):59–80. doi: 10.1093/jac/25.suppl_C.59

197. Feldman C, Smith C, Levy H, Ginsburg P, Miller S, Koornhof H. *Klebsiella pneumoniae* bacteremia at an urban general hospital. *J Infect.* (1990) 20:21–31. doi: 10.1016/S0163-4530(90)92258-M

198. Meyers BR, Sherman E, Mendelson MH, Velasques G, Srulevitch-Chin E, Hubbard M, et al. Bloodstream infections in the elderly. *Am J Med.* (1989) 86:379–84. doi: 10.1016/0002-9343(89)90333-1

199. Bodey GP, Elting L, Kassamali H, Lim BP. *Escherichia coli* bacteremia in cancer patients. *Am J Med.* (1986) 81:85–95. doi: 10.1016/0002-9343(86)90518-8

200. Saraas A, Sundsfjord A, Sandven I, Brunborg C, Jenum PA. Risk factors for community-acquired urinary tract infections caused by ESBL-producing enterobacteriaceae—a case–control study in a low prevalence country. *PLoS ONE.* (2013) 8:e69581. doi: 10.1371/journal.pone.0069581

201. Paul M, Shani V, Muchtar E, Kariv G, Robenshtok E, Leibovici L. Systematic review and meta-analysis of the efficacy of appropriate empiric antibiotic therapy for sepsis. *Antimicrob Agents Chemother.* (2010) 54:4851–63. doi: 10.1128/AAC.00627-10

202. Marquet K, Liesenborgs A, Bergs J, Vleugels A, Claes N. Incidence and outcome of inappropriate in-hospital empiric antibiotics for severe infection: a systematic review and meta-analysis. *Crit Care.* (2015) 19:1–12. doi: 10.1186/s13054-015-0795-y

203. Raman G, Avendano E, Berger S, Menon V. Appropriate initial antibiotic therapy in hospitalized patients with gram-negative infections: systematic review and meta-analysis. *BMC Infect Dis.* (2015) 15:1–11. doi: 10.1186/s12879-015-1123-5

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