Effects of Inappropriate Empirical Antimicrobial Therapy on the Outcomes of Patients with Community-Onset Bacteremia: Age Matters

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Abstract

Background: Studies have reported the effects of delayed administration of appropriate empirical antimicrobial (AEA) on the prognosis of patients with bloodstream infections; however, whether there is an age-related difference in these effects remains debated.

Methods: In this 4-year multicenter cohort study, patients with community-onset bacteremia were retrospectively included and categorized into “middle aged” (45–64 years), “old” (65–74 years), and “very old” (≥ 75 years) groups. To determine the timing of AEA administration for each patient, all causative microorganisms were prospectively obtained. For each age group, the effects of delayed AEA administration on 30-day mortality were investigated after adjustment for the independent predictors of 30-day mortality determined using a logistic regression model.

Results: Significant differences were observed in the distribution of comorbidity types, comorbidity severity, bacteremia sources, bacteremia severity, and causative microorganisms among 968 (33.2%) middle-aged, 683 (23.4%) old, and 1,265 (43.4%) very old patients. Although significant effects (adjusted odds ratio [AOR], 1.002; $P = 0.07$) of delayed AEA administration on prognosis were not observed in middle-aged patients, each hour of AEA delay resulted in an average increase in the 30-day crude mortality of 0.036% (AOR, 1.0036; $P < 0.001$) and 0.38% (AOR, 1.0038; $P < 0.001$) in old and very old patients, respectively. Practically in critically ill patients, each hour of delayed AEA administration resulted in an average increase of 0.03% (AOR, 1.003; $P = 0.04$), 0.4% (AOR, 1.004; $P < 0.001$), and 0.5% (AOR, 1.005; $P = 0.001$) in 30-day crude mortality in middle-aged, old, and very old patients, respectively.

Conclusions: Regardless of bacteremia severity, the adverse effects of delayed AEA administration on the survival of patients with community-onset bacteremia increased with patients' age. To achieve favorable outcomes, rapid AEA administration is recommended in older patients.

Introduction

Community-onset bacteremia is a common problem encountered by emergency department (ED) physicians. The annual incidence of community-onset bacteremia was 0.82% in a population-based study [1], and its high morbidity and mortality of up to 40% can result in considerable healthcare costs [2, 3]. The hemodynamic support and early administration of appropriate antimicrobial therapy can offer survival benefits for patients with bacteremia, particularly those with critical illness at the onset of bacteremia [4–6]. However, because of an increased proportion of causative microorganisms harboring antimicrobial resistance genes [7], rapid administration of appropriate empirical antimicrobials (AEAs) remains challenging for ED physicians.

Appropriate management has always been difficult in older patients with bloodstream infections because bacteremia incidence and mortality markedly increase with age [8] and older patients may present with nonspecific functional decline and atypical presentation [9]. Moreover, a recent study reported that age-related differences in bacteremia severity and antimicrobial-resistant isolates cause an increased delay in

AEA administration [10]. Because the severity of bacteremia increases with patients' age, we hypothesized that the prognostic effects of delayed AEA administration would be enhanced with age. Therefore, in this study, we investigated and compared the effects of delayed AEA administration on short-term outcomes of adults aged ≥ 45 years with community-onset bacteremia among different age groups.

Materials And Methods

Study design and sites

Between January 2015 and December 2018, we conducted a 4-year multicenter retrospective cohort study at the EDs of three hospitals, namely a university-affiliated medical center (1,300 beds) and two teaching hospitals (one with 460 beds and one with 380 beds) in southern Taiwan. The cohort consisted of patients aged ≥ 45 years who had developed community-onset bacteremia in the ED. This study was approved by the institutional review board of the study hospital, and the requirement of obtaining informed consent was waived. Clinical information was obtained and reported according to the Strengthening the Reporting of Observational Studies in Epidemiology.

Patient selection

From a database search, we identified adult patients who had undergone blood culture sampling at the ED during the study period. We retrieved the medical information of patients with bacterial growth in their blood cultures. We excluded patients aged < 45 years and those with contaminated blood cultures, fungemia, mycobacteremia, hospital-onset bacteremia or bacteremia prior to arrival at the ED, an uncertain mortality date, and incomplete chart records. Among patients who had multiple episodes of bloodstream infections during the study period, we examined only the first episode. The primary study endpoint was crude 30-day mortality after arrival at the ED (i.e., onset of bacteremia).

Data collection

We retrospectively collected the demographic and clinical data of eligible patients by using a predetermined form. Clinical data were jointly collected by a board-certified ED physician and an infectious disease physician who were trained in reviewing medical charts and blinded to the aim and hypothesis of this study. Any discrepancy in the recording of clinical data was resolved through discussion between the two physicians. The following patient information was collected: age, vital signs, laboratory data, comorbidity types and severity (according to the Charlson comorbidity index [CCI]), severity of bacteremia (according to the Pitt bacteremia score [PBS]), duration and types of antimicrobial agents administered, and length of ED stay. Moreover, data regarding the length of hospital stay, durations and types of antimicrobial agents administered, imaging study findings, timing and types of surgical and radiological interventions, causative microorganisms, bacteremia diagnosis, and 30-day mortality were collected.

Microbiological methods

Blood cultures were incubated in a Bactec 9240 instrument (Becton Dickinson Diagnostic Systems, Sparks, MD, USA), and the causative microorganism was identified using a semiautomated system (Vitek 2 system, bioMérieux, Durham, NC, USA). After the causative microorganism had been identified, it was stored for further susceptibility testing, which was performed using the disk diffusion method for aerobes and the agar dilution method for anaerobes in accordance with the guidelines of the Clinical and Laboratory Standards Institute (CLSI) [11]. The susceptibility of Gram-negative aerobes to the following antibiotics was tested: ampicillin/sulbactam, piperacillin/tazobactam, levofloxacin, moxifloxacin, cefazolin, cefuroxime, cefotaxime, ceftazidime, cefepime, ertapenem, and imipenem. For streptococci and enterococci, the tested antibiotics were penicillin and ampicillin, respectively. Furthermore, the susceptibility of anaerobes to ampicillin/sulbactam, piperacillin/tazobactam, metronidazole, and moxifloxacin was tested. To determine the timing of AEA administration for each patient, provided that empirical antibiotics were not included in the initial susceptibility panel, the susceptibility to the indicated antibiotic was tested.

Definitions

Eligible patients were categorized as “middle aged” (45–64 years), “old” (65–74 years), and “very old” (≥ 75 years) according to the cut-off age used in a previous study [12]. Community-onset bacteremia refers to bacteremic episodes with onset in the community and includes healthcare facility–acquired and community-acquired bacteremia [4, 13]. According to a previously described criterion [14], contaminated blood cultures are defined as those exhibiting the growth of potential contaminating pathogens.

According to previous studies [4, 13], antimicrobial therapy is appropriate when the following criteria are fulfilled: (i) the route and dosage of antimicrobial agents administered adhere to the recommendations in the Sanford Guide [15] and (ii) all bacteremia-causing pathogens in one episode of bacteremia are susceptible to the antimicrobials administered in vitro according to the CLSI criteria [11]. Time to appropriate antibiotic was defined as the period between the onset of bacteremia (arrival at the ED) and the administration of the first dose of appropriate antimicrobials [4, 13].

The severity of bacteremia was determined according to the PBS, which was calculated using a previously validated scoring system based on the following variables assessed during the first 24 hours after ED arrival: vital signs, usage of vasopressor agents, mental status, receipt of mechanical ventilation, and cardiac arrest [4, 13]. Patients with a PBS of ≥ 4 were categorized as critically ill. Comorbidities were defined as described previously [16], and malignancies included hematological malignancies and solid tumors. The severity of comorbidities was examined using the CCI [17], and patients with a CCI of ≥ 5 were regarded as having severe comorbidities. Crude mortality was defined as death from all causes.

Statistical analyses

Statistical analyses were performed using the Statistical Package for Social Science for Windows (version 23.0; Chicago, IL, USA). Categorical and continuous clinical variables were compared using the Pearson chi-square test or Fisher’s exact test, if the expected value was < 5 , and the independent *t*-test, respectively. Spearman’s correlation coefficients were calculated to analyze age-related trends in clinical

covariates and outcomes. To investigate the effects of delayed AEA administration on 30-day mortality, the significant predictors of 30-day mortality recognized by the univariate analysis and the continuous covariate of “time to appropriate antibiotic” were jointly processing under the model of hierarchical logistic regression. The E-value was calculated to examine the potential effect of unmeasured confounders in our study [18]. A two-sided *P* value of < 0.05 was considered significant.

Results

Demographic characteristics of the entire cohort

Of 6,102 patients with bacterial growth in their blood cultures, 2,916 were diagnosed as having community-onset bacteremia. Of these 2,916 patients, 968 (33.2%), 683 (23.4%), and 1,265 (43.4%) were middle aged, old, and very old, respectively (Fig. 1). The median (interquartile range [IQR]) length of ED stay of the entire cohort was 15.7 (6.0–26.8) hours. Most (2,370, 81.3%) patients were admitted to general wards, and 304 (10.4%) patients were admitted to intensive care units; 100 (3.4%) patients died in the ED. Only 142 (4.9%) patients were directly discharged from the ED and subsequently followed up at outpatient clinics. Of all the patients, 609 (21.2%) were critically ill (i.e., PBS ≥ 4) upon ED arrival. The median (IQR) length of hospital stay was 10 (6–18) days, and the 15- and 30-day crude mortality rates were 12.0% (349 patients) and 15.4% (449), respectively.

Initial manifestations and clinical outcomes in different age groups

Table 1 presents a comparison of clinical manifestations and outcomes between the middle-aged, old, and very old groups. Significant differences were noted in the proportion of male patients, the proportion of nursing-home residents, major comorbidities, bacteremia severity (PBS), major bacteremia sources, types of empirical antimicrobials administered, and presence of polymicrobial bacteremia among the three groups. In addition, we observed a positive age-related trend (all $\gamma = 1.00$, $P < 0.01$) in bacteremia severity; the proportion of nursing-home residents; comorbidities of hypertension, heart failure, or coronary artery diseases; presence of polymicrobial bacteremia and bacteremic pneumonia; and 30-day crude mortality rates.

Table 1

Clinical characteristics and outcomes of 2,916 adults with community-onset bacteremia, categorized by patient age.

Clinical variable	Patient number (%)			<i>P</i> value
	Middle age n = 968	Old age n = 683	Very old age n = 1265	
Gender, male	534 (55.2)	309 (45.2)	644 (50.9)	< 0.001
Residence at a nursing home	27 (2.8)	31 (4.5)	115 (9.1)	< 0.001
Charlson comorbidity index ≥ 5	267 (27.6)	186 (28.7)	334 (26.4)	0.54
Major comorbidity				
Diabetes mellitus	365 (37.7)	320 (46.9)	483 (38.2)	< 0.001
Hypertension	343 (35.4)	376 (55.1)	816 (64.5)	< 0.001
Malignancy	308 (31.8)	239 (35.0)	351 (27.7)	0.003
Liver cirrhosis	170 (17.6)	95 (13.9)	100 (7.9)	< 0.001
Chronic kidney disease	144 (14.9)	131 (19.2)	276 (21.8)	< 0.001
Neurological disease	87 (9.0)	140 (20.5)	497 (39.3)	< 0.001
Heart failure	49 (5.1)	58 (8.5)	152 (12.0)	< 0.001
Coronary artery disease	39 (4.0)	88 (12.9)	181 (14.3)	< 0.001
Major source of bacteremia				
Urinary tract	291 (30.1)	240 (35.1)	431 (34.1)	0.05
Intra-abdominal	130 (13.4)	78 (11.4)	133 (10.5)	0.10
Pneumonia	115 (11.9)	88 (12.9)	244 (19.3)	< 0.001

BLI = β -lactamase inhibitor; IQR = interquartile range; IV = intravenous. Boldface indicates statistical significance ($P < 0.05$).

Clinical variable	Patient number (%)			<i>P</i> value
	Middle age n = 968	Old age n = 683	Very old age n = 1265	
Skin and soft-tissue	111 (11.5)	52 (7.6)	108 (8.5)	0.01
Primary bacteremia	80 (8.3)	56 (8.2)	72 (5.7)	0.03
Biliary tract	59 (6.1)	63 (9.2)	140 (11.1)	< 0.001
Liver abscess	43 (4.4)	24 (3.5)	31 (2.5)	0.03
Polymicrobial bacteremia	74 (7.6)	64 (9.4)	151 (11.9)	0.003
Inadequate source control during antibiotic therapy	34 (3.5)	20 (2.9)	39 (3.1)	0.77
Pitt bacteremia score ≥ 4 at onset	168 (17.4)	144 (21.1)	297 (23.5)	0.005
Major empirical antibiotic				
Third-generation cephalosporin	368 (38.0)	283 (41.4)	448 (35.4)	0.03
First-generation cephalosporin	124 (12.8)	55 (8.1)	124 (9.8)	0.005
Second-generation cephalosporin	123 (12.7)	87 (12.7)	172 (13.6)	0.79
Fourth-generation cephalosporin	107 (11.1)	70 (10.2)	126 (10.0)	0.70
Aminopenicillin/BLI	87 (9.0)	54 (7.9)	146 (11.5)	0.02
Fluoroquinolone	66 (6.8)	49 (7.2)	95 (7.5)	0.82
Glycopeptide	65 (6.7)	41 (6.0)	61 (4.8)	0.15
Ureidopenicillin/BLI	29 (3.0)	31 (4.5)	71 (5.6)	0.01
Carbapenem	27 (2.8)	24 (3.5)	42 (3.3)	0.67
Ureidopenicillin	21 (2.2)	20 (2.9)	31 (2.5)	0.62
Duration, day, median (IQR)				
Time to appropriate antibiotic administration, hours	2 (1–7)	2 (1–7)	2 (1–10)	0.82
IV antimicrobial therapy, days	8 (5–15)	5 (5–15)	8.5 (5–15)	0.11

BLI = β -lactamase inhibitor; IQR = interquartile range; IV = intravenous. Boldface indicates statistical significance ($P < 0.05$).

Clinical variable	Patient number (%)			<i>P</i> value
	Middle age n = 968	Old age n = 683	Very old age n = 1265	
Length of hospitalization, days	10 (6–17)	10 (6–18)	10 (6–17)	0.13
Crude mortality rate				
15-day	111 (11.5)	75 (11.0)	163 (12.9)	0.39
30-day	138 (14.3)	104 (15.2)	207 (16.4)	0.39
BLI = β -lactamase inhibitor; IQR = interquartile range; IV = intravenous. Boldface indicates statistical significance ($P < 0.05$).				

Distribution of causative microorganisms in different age groups

Of the total 3,281 causative microorganisms (middle-aged, old, and very old: 1,065, 762, and 1,454 isolates, respectively), the 10 most commonly detected were *Escherichia coli* (1,222, 37.2%), *Klebsiella* species (474, 14.4%), *Staphylococcus aureus* (375, 11.4%), *Streptococcus* species (355, 10.8%), *Pseudomonas* species (114, 3.5%), *Enterococcus* species (106, 3.2%), *Enterobacter cloacae* (89, 2.7%), *Proteus* species (76, 2.3%), *Salmonella* species (51, 1.6%), and *Aeromonas* species (45, 1.4%). Notably, dissimilar distributions were observed in six of the most commonly detected microorganisms, namely *E. coli*, *Klebsiella* species, *S. aureus*, *Aeromonas* species, *Proteus* species, and enterococci, among the three age groups (Supplemental Table 1).

Methicillin-resistant *S. aureus* and ampicillin-susceptible enterococci accounted for 39.4% (148 isolates) of the total *S. aureus* isolates and 85.8% (91) of the total enterococci isolates, respectively. Furthermore, 93.5% (332) of the streptococci were susceptible to penicillin. Overall, cefazolin, cefuroxime, ampicillin/sulbactam, moxifloxacin, cefotaxime, levofloxacin, ceftazidime, ertapenem, cefepime, piperacillin/tazobactam, and imipenem were active against 50.6%, 71.2%, 74.3%, 81.3%, 78.1%, 82.2%, 83.6%, 88.9%, 93.0%, 94.6%, and 99.3% of Gram-negative aerobes, respectively. Ampicillin/sulbactam, moxifloxacin, piperacillin/tazobactam, and metronidazole were active against 78.0%, 87.5%, 94.0%, and 97.6% of the total anaerobes, respectively.

Predictors of 30-day mortality in overall patients

In the univariate analysis (Table 2), the following variables were found to be positively associated with 30-day mortality: male sex; residence at a nursing home; polymicrobial bacteremia; critical illness (PBS $\geq$ 5) at onset; inadequate source control; bacteremic pneumonia; *S. aureus*, *Klebsiella* species, or *Pseudomonas* species as the causative microorganisms; severe comorbidities (CCI $\geq$ 5); and

comorbidities of malignancies, liver cirrhosis, and neurological diseases. Other predictors of 30-day mortality included bacteremia due to liver abscesses, urinary or biliary tract infections, *E. coli* as the causative microorganism, and comorbidities of hypertension and diabetes mellitus.

Table 2
Risk factors of 30-day crude mortality in overall patients.

Variable	Patient number (%)		Univariate analysis		Multivariate analysis	
	Death n = 449	Survival n = 2467	OR (95% CI)	P value	Adjusted OR (95% CI)	P value
Time to appropriate antibiotic administration (hours)	–	–	–	–	1.003 (1.002–1.004)	< 0.001
Gender, male	267 (59.5)	1220 (49.5)	1.50 (1.22–1.84)	< 0.001	1.05 (0.82–1.36)	0.68
Residence at a nursing home	56 (12.5)	117 (4.7)	2.86 (2.05–4.01)	< 0.001	1.74 (1.11–2.73)	0.02
Polymicrobial bacteremia	78 (17.4)	211 (8.6)	2.25 (1.70–2.98)	< 0.001	1.48 (1.01–2.17)	0.04
Pitt bacteremia score ≥ 4	290 (64.6)	319 (12.9)	12.28 (9.79–15.40)	< 0.001	10.29 (7.92–13.37)	< 0.001
Inadequate source control during antibiotic therapy	78 (17.4)	211 (8.6)	2.08 (1.30–3.33)	< 0.001	2.75 (1.52–4.99)	0.001
Source of bacteremia						
Pneumonia	173 (38.5)	274 (11.1)	5.02 (4.00–6.30)	< 0.001	1.85 (1.36–2.52)	< 0.001
Urinary tract infection	50 (11.1)	912 (37.0)	0.21 (0.16–0.29)	< 0.001	0.35 (0.24–0.52)	< 0.001
Biliary tract infection	22 (4.9)	240 (9.7)	0.48 (0.31–0.75)	0.001	0.42 (0.24–0.73)	0.002
Liver abscess	7 (1.6)	91 (3.7)	0.41 (0.19–0.90)	0.02	0.28 (0.11–0.68)	0.005
Causative microorganism						

OR = odds ratio; CI = confidence interval. Boldface indicates statistical significance ($P < 0.05$) in the hierarchical logistic regression model.

Variable	Patient number (%)		Univariate analysis		Multivariate analysis	
<i>Escherichia coli</i>	112 (24.9)	1110 (45.0)	0.41 (0.32–0.51)	< 0.001	0.91 (0.66–1.25)	0.55
<i>Klebsiella</i> species	102 (22.7)	369 (15.0)	1.67 (1.31–2.14)	< 0.001	1.24 (0.88–1.77)	0.22
<i>Staphylococcus aureus</i>	78 (17.4)	298 (12.1)	1.53 (1.17–2.01)	0.002	1.12 (0.78–1.62)	0.55
<i>Pseudomonas</i> species	37 (8.2)	77 (3.1)	2.79 (1.86–4.18)	< 0.001	1.81 (1.03–3.16)	0.04
Charlson comorbidity index $\geq$ 5	214 (47.7)	583 (23.6)	2.94 (2.39–3.62)	< 0.001	1.74 (1.25–2.41)	0.001
Comorbidity						
Malignancy	216 (48.1)	682 (27.6)	2.43 (1.98–2.98)	< 0.001	1.79 (1.29–2.47)	< 0.001
Hypertension	214 (47.7)	1321 (53.5)	0.79 (0.65–0.97)	0.02	1.09 (0.84–1.42)	0.52
Diabetes mellitus	154 (34.3)	1014 (41.1)	0.71 (0.60–0.84)	0.007	0.77 (0.59–1.01)	0.06
Neurological disease	129 (28.7)	595 (24.1)	1.27 (1.01–1.59)	0.04	1.42 (1.03–1.97)	0.03
Liver cirrhosis	84 (18.7)	281 (11.4)	1.79 (1.37–2.34)	< 0.001	1.62 (1.13–2.32)	0.009
OR = odds ratio; CI = confidence interval. Boldface indicates statistical significance ($P < 0.05$) in the hierarchical logistic regression model.						

Consequently, the following independent determinants of 30-day crude mortality were recognized in the multivariate regression model (Table 2): residence at a nursing home; polymicrobial bacteremia; critical illness at the onset (PBS $\geq$ 4); inadequate source control; bacteremic pneumonia; bacteremia due to urinary or biliary tract infections; *Pseudomonas* bacteremia; severe comorbidities; and comorbidities of malignancies, neurological diseases, or liver cirrhosis. Notably, each hour of delayed AEA administration was associated with an average increase of 0.3% in 30-day crude mortality (adjusted odds ratio [AOR], 1.003; $P < 0.001$)

Effects of delayed AEA administration on patient survival in different age groups

Among the 968 patients in the middle-aged group (Table 3), the predictors of 30-day mortality determined in the multivariate analysis included critical illness (PBS ≥ 4) at onset, bacteremic pneumonia, severe comorbidities (CCI ≥ 5), and comorbid malignancies. However, the adverse effect of the hour AEA delay on 30-day mortality was not significant (AOR, 1.002; $P = 0.07$). In the old age group, the effect of the hour AEA delay on 30-day mortality remained significant (AOR, 1.0036; $P < 0.001$) in the multivariate regression model after adjusting for all the predictors of 30-day mortality recognized in the univariate analysis (Table 3). Furthermore, among 1,265 patients in the very old group, the effect of the hour AEA delay on 30-day mortality remained significant (AOR, 1.0038; $P < 0.001$) in the multivariate regression model after adjusting for all the predictors of 30-day mortality recognized in the univariate analysis (Table 3).

Table 3
Predictors of 30-day crude mortality in middle-aged, old, and very old patients, respectively.

Variable	Patient number (%)		Univariate analysis		Multivariate analysis	
	Death	Survival	OR (95% CI)	P value	Adjusted OR (95% CI)	P value
The middle-aged patient (n = 968)	n = 138	n = 830				
Time to appropriate antibiotic administration (hours)	–	–	–	–	1.002 (1.002–1.004)	0.07
Gender, male	96 (69.6)	438 (52.8)	2.05 (1.39–3.01)	< 0.001	1.18 (0.70–2.00)	0.53
Residence at a nursing home	10 (7.2)	17 (2.0)	3.74 (1.67–8.34)	0.001	1.53 (0.54–4.33)	0.42
Polymicrobial bacteremia	23 (16.7)	51 (6.1)	3.06 (1.80–5.19)	< 0.001	1.64 (0.77–3.66)	0.20
Pitt bacteremia score ≥ 4	85 (61.6)	83 (10.0)	14.43 (9.57–21.78)	< 0.001	12.58 (7.74–20.45)	< 0.001
Source of bacteremia						
Pneumonia	52 (37.7)	63 (7.6)	7.36 (4.79–11.31)	< 0.001	3.82 (2.15–6.78)	< 0.001
Urinary tract infection	16 (11.6)	275 (33.1)	0.27 (0.15–0.46)	< 0.001	1.65 (0.81–3.35)	0.17
Liver abscess	1 (0.7)	42 (5.1)	0.14 (0.02–1.00)	0.02	0.14 *0.02–1.25)	0.08
Causative microorganism						
<i>Klebsiella</i> species	34 (24.6)	137 (16.5)	1.65 (1.08–2.54)	0.02	1.20 (0.63–2.27)	0.53
<i>Escherichia coli</i>	33 (23.9)	332 (40.0)	0.47 (0.31–0.71)	< 0.001	0.88 (0.50–1.55)	0.65
<i>Pseudomonas</i> specie	11 (8.0)	17 (2.0)	4.14 (1.90–9.05)	0.001	1.14 (0.36–3.58)	0.83
Charlson comorbidity index ≥ 5	75 (54.3)	192 (23.1)	3.96 (2.73–5.74)	0.001	2.34 (1.285–4.30)	0.006

OR = odds ratio; CI = confidence interval. Boldface indicates statistical significance ($P < 0.05$) in the hierarchical logistic regression model.

Variable	Patient number (%)		Univariate analysis		Multivariate analysis	
Comorbidity						
Malignancy	80 (58.0)	228 (27.5)	3.64 (2.51–5.28)	< 0.001	1.90 (1.04–3.50)	0.04
Diabetes mellitus	40 (29.0)	325 (39.2)	0.63 (0.43–0.94)	0.02	0.83 (0.50–1.39)	0.49
Liver cirrhosis	36 (26.1)	134 (16.1)	1.83 (1.20–2.80)	0.004	1.64 (0.92–2.93)	0.09
The old patient (n = 683)	n = 104	n = 579				
Time to appropriate antibiotic administration (hours)	–	–	–	–	1.0036 (1.002–1.006)	< 0.001
Gender, male	61 (58.7)	248 (42.8)	1.89 (1.24–2.89)	0.003	1.04 (0.62–1.75)	0.88
Pitt bacteremia score ≥ 4	65 (62.5)	79 (13.6)	10.55 (6.64–16.75)	< 0.001	10.84 (6.24–18.85)	< 0.001
Source of bacteremia						
Pneumonia	35 (33.7)	53 (9.2)	5.03 (3.07–8.26)	< 0.001	1.71 (0.90–3.26)	0.10
Urinary tract infection	16 (15.4)	224 (38.7)	0.29 (0.17–0.50)	< 0.001	0.46 (0.22–0.96)	0.04
Causative microorganism						
<i>Escherichia coli</i>	22 (21.2)	255 (44.0)	0.34 (0.21–0.56)	< 0.001	0.57 (0.30–1.08)	0.08
<i>Staphylococcus aureus</i>	19 (18.3)	65 (11.2)	1.77 (1.01–3.10)	0.04	1.21 (0.59–2.51)	0.61
Pseudomonas species	10 (9.6)	19 (3.3)	3.14 (1.41–6.95)	0.007	3.38 (1.24–9.28)	0.02
<i>Proteus</i> species	5 (4.8)	9 (1.6)	3.20 (1.05–9.74)	0.048	4.96 (0.98–20.53)	0.06
Charlson comorbidity index ≥ 5	49 (47.1)	147 (25.4)	2.62 (1.71–4.02)	< 0.001	1.57 (0.86–2.87)	0.14

OR = odds ratio; CI = confidence interval. Boldface indicates statistical significance ($P < 0.05$) in the hierarchical logistic regression model.

Variable	Patient number (%)		Univariate analysis		Multivariate analysis	
Comorbid Malignancy	55 (52.9)	184 (31.8)	2.41 (1.58–3.68)	< 0.001	2.53 (1.36–4.72)	0.003
The very old patients (n = 1265)	n = 207	n = 1058				
Time to appropriate antibiotic administration (hours)	–	–	–	–	1.0038 (1.002–1.005)	< 0.001
Residence at a nursing home	35 (16.9)	80 (7.6)	2.49 (1.62–3.82)	< 0.001	1.73 (0.98–3.05)	0.06
Polymicrobial bacteremia	41 (19.8)	110 (10.4)	2.13 (1.43–3.16)	< 0.001	1.22 (0.70–2.11)	0.48
Pitt bacteremia score ≥ 4	140 (67.6)	157 (14.8)	1.88 (1.37–2.56)	< 0.001	9.41 (6.33–13.97)	< 0.001
Inadequate source control during antibiotic therapy	18 (8.7)	21 (2.0)	4.70 (2.50–8.99)	< 0.001	4.64 (2.03–10.60)	< 0.001
Source of bacteremia						
Pneumonia	86 (41.5)	158 (14.9)	0.05 (2.93–5.60)	< 0.001	1.29 (0.83–2.01)	0.26
Urinary tract infection	18 (8.7)	413 (39.0)	0.15 (0.09–0.25)	< 0.001	0.19 (0.10–0.36)	< 0.001
Biliary tract infection	8 (3.9)	132 (12.5)	0.28 (0.14–0.59)	< 0.001	0.25 (0.11–0.60)	0.002
Causative microorganism						
<i>Escherichia coli</i>	57 (27.5)	523 (49.4)	0.39 (0.28–0.54)	0.001	1.22 (0.76–1.97)	0.40
Klebsiella species	46 (22.2)	126 (11.9)	2.11 (1.45–3.08)	< 0.001	1.78 (1.04–3.04)	0.04
<i>Staphylococcus aureus</i>	34 (16.4)	100 (9.5)	1.88 (1.24–2.87)	0.003	1.10 (0.612–1.96)	0.76
<i>Pseudomonas</i> species	16 (7.7)	41 (3.9)	2.08 (1.14–3.78)	0.01	1.99 (0.87–4.55)	0.10
<i>Proteus</i> species	14 (6.8)	36 (3.4)	2.06 (1.09–3.89)	0.02	2.78 (0.93–4.55)	0.06

OR = odds ratio; CI = confidence interval. Boldface indicates statistical significance ($P < 0.05$) in the hierarchical logistic regression model.

Variable	Patient number (%)		Univariate analysis		Multivariate analysis	
Charlson comorbidity index ≥ 5	90 (43.5)	244 (23.1)	2.57 (1.88–3.50)	< 0.001	1.34 (0.82–2.18)	0.24
Comorbidity						
Hypertension	121 (58.5)	695 (65.7)	0.74 (0.54–1.00)	0.047	0.94 (0.63–1.38)	0.74
Malignancy	81 (39.1)	270 (25.5)	1.88 (1.37–2.56)	< 0.001	1.57 (0.99–2.51)	0.06
Liver cirrhosis	31 (15.0)	69 (6.5)	2.53 (1.61–3.97)	< 0.001	2.61 (1.40–4.89)	0.003
Urological disease	16 (7.7)	137 (12.9)	0.56 (0.33–0.97)	0.04	0.57 (0.30–1.10)	0.10
OR = odds ratio; CI = confidence interval. Boldface indicates statistical significance ($P < 0.05$) in the hierarchical logistic regression model.						

Effects of delayed AEA administration on the survival of critically ill patients in different age groups

Among the 168 critically ill patients ($\text{PBS} \geq 4$) in the middle-aged group (Table 4), the adverse effect of the AEA delay (every hour) on 30-day mortality was significant (AOR, 1.003; $P = 0.04$) after adjustment for the following predictors of 30-day mortality recognized in the univariate analysis: polymicrobial bacteremia; bacteremic pneumonia; bacteremia due to urinary tract infections and liver abscesses; severe comorbidities ($\text{CCI} \geq 5$); and comorbidities of malignancies, diabetes mellitus, and liver cirrhosis. Among the 144 and 297 critically ill patients in the old and very old groups, the adverse effect of AEA delay (every hour) on 30-day mortality remained significant (AOR, 1.004; $P < 0.001$ and AOR, 1.005; $P < 0.001$, respectively) after respective adjustment for the predictors of 30-day mortality recognized in the univariate analysis (Table 4).

Table 4
Predictors of 30-day crude mortality in critically ill middle-aged, old, and very old patients.

Variable	Patient number (%)		Univariate analysis		Multivariate analysis	
	Death	Survival	OR (95% CI)	P value	Adjusted OR (95% CI)	P value
The middle-aged patient (n = 168)	n = 85	n = 83				
Time to appropriate antibiotic administration (hours)	–	–	–	–	1.003 (1.000–1.006)	0.04
Polymicrobial bacteremia	20 (23.5)	7 (8.4)	3.34 (1.33–8.40)	0.008	2.83 (0.99–8.11)	0.05
Source of bacteremia						
Pneumonia	36 (42.4)	12 (14.5)	4.35 (2.06–9.18)	< 0.001	3.45 (1.46–8.12)	0.005
Urinary tract infection	7 (8.2)	24 (28.9)	0.22 (0.09–0.55)	0.001	0.31 90.11–0.89)	0.03
Liver abscess	1 (1.2)	9 (10.8)	0.10 (0.01–0.79)	0.009	0.16 (0.02–1.45)	0.10
Charlson comorbidity index ≥ 5	37 (43.5)	24 (28.9)	1.90 (1.00–3.59)	0.049	1.44 (0.58–3.63)	0.44
Comorbidity						
Malignancies	41 (48.2)	27 (32.5)	1.93 (1.03–3.61)	0.04	1.20 (0.46–3.12)	0.71
Diabetes mellitus	23 (27.1)	36 (43.4)	0.48 (0.25–0.92)	0.03	0.69 (0.30–1.57)	0.37
Liver cirrhosis	21 (24.7)	10 (12.0)	2.40 (1.05–5.46)	0.03	2.33 (0.896–6.07)	0.08
The old patient (n = 144)	n = 65	n = 79				

OR = odds ratio; CI = confidence interval. Boldface indicates statistical significance ($P < 0.05$) in the hierarchical logistic regression model.

Variable	Patient number (%)		Univariate analysis		Multivariate analysis	
	Death	Survival	OR (95% CI)	P value	Adjusted OR (95% CI)	P value
Time to appropriate antibiotic administration (hours)	–	–	–	–	1.004 (1.002–1.006)	< 0.001
Source of bacteremia						
Pneumonia	28 (43.1)	21 (26.6)	2.09 (1.04–4.21)	0.04	1.68 (0.74–3.82)	0.21
Urinary tract infection	9 (13.8)	23 (29.1)	0.39 (0.17–0.92)	0.03	0.88 (0.32–2.43)	0.81
Causative microorganism						
<i>Escherichia coli</i>	15 (23.1)	35 (44.3)	0.38 (0.18–0.78)	0.008	0.45 (0.19–1.06)	0.07
<i>Pseudomonas</i> species	4 (6.2)	0 (0)	–	0.04	–	1.00
The very old patient (n = 297)	n = 140	n = 157				
Time to appropriate antibiotic administration (hours)	–	–	–	–	1.005 (1.002–1.007)	0.001
Inadequate source control during hospitalization	12 (8.6)	4 (2.5)	3.59 (1.13–11.39)	0.02	2.74 (0.79–9.49)	0.11
Source of bacteremia						
Pneumonia	66 (47.1)	54 (34.4)	1.70 (1.07–2.72)	0.03	1.30 (0.72–2.32)	0.39
Urinary tract infection	10 (7.1)	53 (33.8)	0.15 (0.07–0.31)	< 0.001	0.22 (0.10–0.50)	< 0.001
Causative microorganism of <i>Klebsiella</i> species	34 (24.3)	21 (13.4)	2.08 (1.14–3.79)	0.02	1.58 (0.81–3.06)	0.18

OR = odds ratio; CI = confidence interval. Boldface indicates statistical significance ($P < 0.05$) in the hierarchical logistic regression model.

Variable	Patient number (%)		Univariate analysis		Multivariate analysis	
	Death	Survival	OR (95% CI)	<i>P</i> value	Adjusted OR (95% CI)	<i>P</i> value
Comorbidity						
Neurological disease	67 (47.9)	96 (61.1)	0.58 (0.37–0.93)	0.02	0.60 (0.35–12.02)	0.06
Liver cirrhosis	16 (11.4)	7 (4.5)	2.77 (1.10–6.94)	0.03	2.33 (0.88–6.22)	0.09
OR = odds ratio; CI = confidence interval. Boldface indicates statistical significance ($P < 0.05$) in the hierarchical logistic regression model.						

Discussion

Similar to the findings of previous studies [4–6], we observed a significant effect of delayed AEA administration on patient survival in the overall cohort. The results of the subgroup analysis revealed that the adverse effects of delayed AEA administration on the prognosis of middle-aged patients were not significant; however, we found that each hour of delay in AEA administration resulted in an average increase of 0.36% and 0.38% in the 30-day crude mortality of old and very old patients, respectively. Moreover, in critically ill patients, each hour of delayed AEA administration contributed to an average increase of 0.3%, 0.4%, and 0.5% in 30-day crude mortality in middle-aged, old, and very old patients, respectively. In sum, regardless of bacteremia severity, the effects of delayed AEA administration on short-term mortality increased with patients' age.

Studies have reported age-related differences in the distribution of comorbidities, bacteremia sources, and causative microorganisms [8, 10, 19, 20]. Consistent with these findings, a positive age-related trend in bacteremia severity, comorbidity severity, and short-term mortality was observed in the present study. Accordingly, physicians adopted different empirical antimicrobials for patients in different age groups, leading to similar durations of the time to appropriate antibiotic among the different age groups included in this study.

Numerous studies have reported a trend of delay in antimicrobial administration affecting the short-term prognosis of patients with bacteremia in various settings, such as those with community-onset bacteremia [4, 13], severe illness [21], nosocomial bacteremia [22], neutropenia [23], and specific causative microorganisms (i.e., *Pseudomonas aeruginosa* [24], *S. aureus* [25], and extended-spectrum beta-lactamase-producing Enterobacteriaceae [26]). Notably, the findings of the present study indicate that regardless of whether a patient was critically ill, the adverse effects of delay in AEA administration on patient survival increased with patients' age. Accordingly, in older patients with bacteremia episodes, faster AEA administration is recommended. To administer AEAs, epidemiological surveillance of

causative microorganisms and susceptibilities or application of the biomolecular technique of rapid pathogen identification is essential for older patients.

Similar to previous studies [4, 27, 28] that have emphasized that severe bacteremia requires earlier AEA administration to achieve favorable outcomes and therapeutic efficacy, we found that each hour of AEA delay resulted in a higher increase in 30-day crude mortality in critically ill patients than in overall patients; that is, middle-aged (0.3% vs. nonsignificant), old (0.4% vs. 0.36%), and very old (0.5% vs. 0.38%) groups. Therefore, regardless of patients' age, rapid AEA administration is crucial for preventing more severe episodes of bacteremia. Early identification of critically ill patients with bloodstream infections among ED patients through the use of a scoring algorithm, such as the Mortality Emergency Department Sepsis score [29] or quick Sequential Organ Failure Assessment [30], is crucial. These tools can assist in accurately assessing bacteremia severity at onset and identifying patients with a high mortality risk.

This study has several limitations. First, consistent with the findings of previous studies regarding the appropriateness of empirical antimicrobial administration [5, 13, 31, 32], no detailed components of the Surviving Sepsis Campaign were evaluated as covariates. However, this study investigated the adverse effects of inadequate source control for complicated bacteremia that are superior to the findings of reports regarding this campaign. Second, because previous studies have reported the neglected difference in therapeutic efficacies between narrow- and broad-spectrum antimicrobials administered as the appropriate empirical agent [33, 34], the differential efficacy between various AEAs was not considered herein owing to the study design being based on previous findings [5, 13, 31, 32]. Third, to investigate the effects of AEA timing on patient prognosis, patients with undetectable antimicrobial administration, incomplete clinical information, or uncertain date of death were excluded. Selection bias may have occurred as a result of the small sample size in this study. Fourth, the retrospective nature of this study made it prone to recall bias during data collection. To reduce this bias, all clinical information was randomly retrieved by two physicians who were blinded to the study hypothesis, and they inspected medical records together to resolve any discrepancies. Fifth, a low E-value was obtained for the prognostic effects of delayed AEA administration on various age groups; thus, unmeasured confounders in our cohort should be trivial. Finally, because study hospitals were located in southern Taiwan, the results of this study should be validated in other communities with variable bacteremia sources, causative microorganisms, or antibiotic-resistant isolates.

Conclusions

Regardless of bacteremia severity, the adverse effects of delayed AEA administration on patient mortality increased with patients' age. Furthermore, each hour of AEA delay resulted in a higher increase in 30-day crude mortality in critically ill patients than in overall patients in various age groups. Therefore, to achieve favorable outcomes in older patients with bacteremia, particularly those who are critically ill, rapid pathogen identification is necessary for prompt AEA administration.

Abbreviations

AEA: appropriate empirical antimicrobial; AOR: adjusted odds ratio; CI: confidence interval; CCI: Charlson comorbidity index; CLSI: Clinical and Laboratory Standards Institute; ED: emergency department; IQR: interquartile range; OR: odds ratio; PBS: Pitt bacteremia score

Declarations

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Availability of data and materials

Available from the corresponding author on reasonable request.

Authors' contributions

CCL and WK conceived the study idea and designed the study. CCL, CYH, CCH, and CHL supervised the data collection and chart reviews. CCL provided the data of microbiological analyses. CCL, PC, and CHL provided methodological and statistical advice on the study design and data analysis. CCL and WK provided expertise in infectious disease. CCL drafted this manuscript. WK revised it carefully from a professional point of view. All authors read and approved the final manuscript.

Conflicting interests

The authors have no conflict of interest to declare.

Consent for publication

All authors have provided consent for publication of the manuscript.

Ethics approval and consent to participate.

The study was approved by the institutional review board of National Cheng Kung University Hospital (B-ER-109-144), Madou Sin-Lau Hospital (SLH 9919-108-006), and Tainan Sin-Lau Hospital (SLH 9919-108-009); and the requirement of obtaining informed consent was waived.

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Figures

Figure 1

Flowchart of patient selection.

Supplementary Files

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