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CLINICAL THERAPEUTICS

Age-Related Trends in Adults with Community-Onset Bacteremia

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ABSTRACT To understand the epidemiological variation in bacteremia characteristics among differently aged populations, adults with community-onset bacteremia during a 6-year period were studied in a retrospective cohort. A total of 2,349 bacteremic patients were stratified into four age categories: young adults (18 to 44 years old; 196 patients; 8.3%), adults (45 to 64 years old; 707 patients; 30.1%), the elderly (65 to 84 years old; 1,098 patients; 46.7%), and the oldest old (≥85 years old; 348 patients; 14.8%). Age-related trends in critical illness (a Pitt bacteremia score of ≥4) at bacteremia onset, antibiotic-resistant pathogens (extended-spectrum β-lactamase [ESBL]-producing *Escherichia coli*, *Klebsiella* species, and *Proteus mirabilis* [EKP]; methicillin-resistant *Staphylococcus aureus* [MRSA]; and levofloxacin nonsusceptible EKP), inappropriate empirical antibiotic therapy (EAT), and 4-week mortality rate were observed. Using a multivariate regression model, critical illness at bacteremia onset (adjusted odds ratio [AOR], 9.03; $P < 0.001$) and inappropriate EAT (AOR, 2.67; $P < 0.001$) were the two leading predictors of 4-week mortality. Moreover, ESBL-producing EKP (AOR, 12.94; $P < 0.001$), MRSA (AOR, 8.66; $P < 0.001$), and levofloxacin-nonsusceptible EKP (AOR, 4.27; $P < 0.001$) were linked to inappropriate EAT. In conclusion, among adults with community onset bacteremia, significant positive age-related trends were noted in antibiotic-resistant pathogens and bacteremia severity, which were related to the increasing incidence of inappropriate EAT and 4-week mortality with age. Thus, different empirical antimicrobial regimens should be considered for distinct age groups.

KEYWORDS community, appropriateness, empirical therapy, aging, bloodstream infections

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Bloodstream infection is a serious, life-threatening condition with a reported incidence of up to 16.9 cases per 1,000 hospital admissions (1–3). Importantly, the incidence of bacteremia and related mortality increases markedly with age (4), and elderly patients may present with nonspecific functional decline and atypical presentations, which make an accurate diagnosis challenging (5). Therefore, several studies have shown different clinical manifestations and outcomes between the elderly and younger adults in the literature (4, 6).

To achieve optimal outcomes, the successful management of elderly patients with bacteremia is required; this involves the elimination of the offending pathogen by the timely administration of appropriate antimicrobials and removal of the infection source (7, 8). To avoid a delay in administering appropriate antimicrobials to the elderly, understanding the differences in clinical characteristics, causative microorganisms,

bacteremia severity, and antimicrobial susceptibility between young adults and the elderly is necessary. Although age-related differences in pathogen distribution and antimicrobial susceptibilities have been previously assessed (6, 9), no study has investigated age-related trends in clinical characteristics among adults with bloodstream infections in terms of comorbidity severity, bacteremia severity and sources, types and antimicrobial susceptibilities of causative microorganisms, and patient outcomes. To achieve the appropriateness of empirical antibiotic therapy (EAT) for the elderly, we investigated adult patients with community-onset bacteremia to compare the clinical manifestations and short-term outcomes of patients stratified by age groups and to describe the age-related trends in causative microorganisms and antimicrobial susceptibilities.

RESULTS

Clinical presentations, bacteremia severity, and outcomes in different age groups. In accordance with the inclusion and exclusion criteria (see Fig. S1 in the supplemental material), the 2,349 patients with community-onset bacteremia were eligible and stratified into four categories by age: young adults (196 patients; 8.3%), adults (707 patients; 30.1%), the elderly (1,098 patients; 46.7%), and the oldest old (348 patients; 14.8%). Significantly positive linear-by-linear associations between age and the following variables were observed (Table 1): comorbidities with chronic kidney diseases, hypertension, neurological diseases, coronary artery diseases, or chronic obstructive pulmonary diseases; bacteremia due to pneumonia or biliary tract infections; critical illness (a Pitt bacteremia score of $\geq$4) at bacteremia onset; initial syndrome of severe sepsis; and the 2- and 4-week mortality rates. Otherwise, negative age-related trends in bacteremia due to intra-abdominal infections or bone and joint infections and mildly critical illness (a Pitt bacteremia score of 0) at bacteremia onset were observed.

Causative microorganism and antimicrobial susceptibility in different age groups. A total of 2,655 bacteremia isolates obtained from 2,349 patients were stratified into four categories: young adults (215 isolates; 8.1%), adults (779 isolates; 29.3%), the elderly (1,245 isolates; 46.9%), and the oldest old (416 isolates; 15.7%). Of 10 leading microorganisms, an age-related trend was not disclosed in all species but only in *Proteus mirabilis* (Table 2). However, certain age-related trends were observed in antimicrobial susceptibilities (Table 3). As age increased, susceptibilities to cefazolin, cefuroxime, cefotaxime, and levofloxacin decreased, and the percentages of extended-spectrum β-lactamase (ESBL) producers increased in two common Gram-negative pathogens, *Escherichia coli* and *Klebsiella pneumoniae*. Additionally, the proportions of methicillin-resistant *Staphylococcus aureus* (MRSA) increased, and susceptibilities to penicillin or levofloxacin in *Streptococcus* species decreased with age.

Empirical antimicrobial agents in different age groups. Because 180 patients received combinative EAT and 22 were not treated by antimicrobials before the reporting of blood cultures, 2,507 antimicrobial agents prescribed to 2,349 patients in four age groups were displayed (Table 4). Cephalosporin was the most common class of antimicrobial therapy, accounting for nearly one-third (66.9%; 1,678/2,507) of all empirically administered drugs; third-generation cephalosporins composed nearly half (52.4%; 880/1,678) of all cephalosporins. Approximately 9% (209) of all cases were empirically treated by aminopenicillins/beta-lactamase inhibitors (BLIs), and there was an age-related trend with borderline significance ($P = 0.057$). Notably, there was a positive age-related trend in the incidence of inappropriate EAT.

Clinical predictors linked to inappropriate EAT. Several clinical and microbiological factors associated with inappropriate EAT were examined by univariate analysis (Table 5). The factors associated with inappropriate EAT included nursing home residents; previous antimicrobial use; polymicrobial bacteremia; ESBL-producing EKP, levofloxacin-nonsusceptible EKP, MRSA, or *Pseudomonas* species as causative microorganisms; bacteremia due to vascular-line infections; and preexisting neurological diseases, chronic kidney disease, or diabetes mellitus. In contrast, bacteremia due to liver abscess was often treated by appropriate EAT. The multivariate regression analyses

TABLE 1 Age-related trends in various clinical characteristics and outcomes of 2,349 patients with community-onset bacteremia

Characteristic	No. (%) of patients				*P* value[a]
	Young adults (18–44 yr; *n* = 196)	Adults (45–64 yr; *n* = 707)	Elderly (65–84 yr; *n* = 1,098)	Oldest old (≥85 yr; *n* = 348)	
Gender, male	105 (53.8)	397 (56.2)	509 (46.4)	198 (56.9)	0.987
Nursing home residents	4 (2.0)	22 (3.1)	62 (5.6)	45 (12.9)	0.073
Recent events within 4 weeks before ED arrival					
Hospitalization	36 (18.4)	179 (25.3)	265 (24.1)	71 (20.4)	0.807
Antimicrobial therapy	27 (13.8)	137 (19.4)	227 (20.7)	55 (15.8)	0.704
Invasive procedures[b] or surgery	6 (3.1)	55 (7.8)	93 (8.5)	18 (5.2)	0.636
Polymicrobial bacteremia	17 (8.7)	55 (7.8)	116 (10.6)	52 (14.9)	0.125
Major comorbidity					
Malignancy	35 (17.9)	213 (30.1)	345 (31.4)	66 (19.0)	0.917
Liver cirrhosis	27 (13.8)	127 (18.0)	133 (12.1)	14 (4.0)	0.223
Chronic kidney disease	**25 (12.8)**	**99 (14.0)**	**221 (20.1)**	**74 (21.3)**	**0.045**
Hypertension	**15 (7.7)**	**231 (32.7)**	**656 (59.7)**	**216 (62.1)**	**0.042**
Diabetes mellitus	10 (5.1)	255 (36.1)	491 (44.7)	119 (34.2)	0.282
Neurological disease	**7 (3.6)**	**56 (7.9)**	**297 (27.0)**	**162 (46.6)**	**0.030**
Urological disease	8 (3.1)	23 (3.3)	88 (8.0)	45 (12.9)	0.051
Coronary artery disease	**1 (0.5)**	**27 (3.8)**	**144 (13.1)**	**51 (14.7)**	**0.046**
Chronic obstructive pulmonary disease	**0 (0)**	**16 (2.3)**	**56 (5.1)**	**40 (11.5)**	**0.032**
Ultimately or rapidly fatal comorbidity (McCabe classification)	42 (21.4)	197 (27.9)	273 (24.9)	52 (14.9)	0.480
Major sources of bacteremia					
Urinary tract infection	46 (23.5)	210 (29.7)	379 (34.5)	113 (32.5)	0.143
Intra-abdominal infection	**38 (19.4)**	**108 (15.3)**	**136 (12.4)**	**30 (8.6)**	**0.002**
Skin and soft-tissue infection	27 (13.8)	85 (12.0)	86 (7.8)	46 (13.2)	0.714
Primary bacteremia	25 (12.8)	62 (8.8)	72 (6.6)	22 (6.3)	0.066
Pneumonia	**19 (9.7)**	**77 (10.9)**	**162 (14.8)**	**67 (19.3)**	**0.026**
Bone and joint infection	**16 (8.2)**	**34 (4.8)**	**37 (3.4)**	**5 (1.4)**	**0.017**
Biliary tract infection	**7 (3.6)**	**46 (6.5)**	**121 (11.0)**	**46 (13.2)**	**0.008**
Severity-of-illness marker at bacteremia onset (Pitt bacteremia score)					
≥4 points	**26 (13.3)**	**121 (17.1)**	**233 (21.2)**	**96 (27.6)**	**0.008**
0 points	**66 (33.7)**	**203 (28.7)**	**289 (26.3)**	**75 (21.6)**	**0.008**
Initial syndrome					
Severe sepsis	**53 (27.0)**	**286 (40.5)**	**510 (46.4)**	**174 (50.0)**	**0.043**
Septic shock	28 (14.3)	142 (20.1)	226 (20.6)	83 (23.9)	0.052
Length (days, mean ± SD)					
Time to defervescence[c]	6.9 ± 7.9	7.8 ± 8.8	7.5 ± 8.4	7.5 ± 8.8	0.487
Total hospital stay	16.9 ± 25.5	14.5 ± 15.7	15.1 ± 16.5	14.0 ± 15.5	0.174
Crude mortality rate					
2 wk	**10 (5.1)**	**72 (10.2)**	**116 (10.6)**	**53 (15.2)**	**0.040**
4 wk	**19 (9.7)**	**99 (14.0)**	**158 (14.4)**	**64 (18.4)**	**0.038**

[a]Calculated by Pearson's correlation. Boldface indicates statistical significance, i.e., a *P* value of <0.05.
[b]Including endoscopic retrograde cholangiopancreatography, bronchoscopy, panendoscopy, and colonoscopy.
[c]Only 1,905 febrile patients at admission were calculated.

identified six predictors of inappropriate EAT, including nursing home residents (adjusted odds ratio [AOR], 1.66; $P = 0.049$); previous antimicrobial use (AOR, 2.53; $P < 0.001$); polymicrobial bacteremia (AOR, 1.53; $P = 0.01$); causative microorganisms of ESBL-producing EKP (AOR, 11.83; $P < 0.001$), MRSA (AOR, 7.88 $P < 0.001$), or levofloxacin-nonsusceptible EKP (AOR, 4.21; $P < 0.001$); and underlying neurological diseases (AOR, 1.38; $P = 0.03$).

Clinical predictors of 4-week mortality. For the included patients, the associations of clinical variables with 4-week mortality, in terms of patient demography, character-

TABLE 2 Age-related trends in species distribution of major pathogens in adults with community-onset bacteremia

Microorganism (*n*)	No. (%) of isolates				*P* value[a]
	Young adults (18–44 yr; *n* = 215)	Adults (45–64 yr; *n* = 779)	Elderly (65–84 yr; *n* = 1,245)	Oldest old (≥85 yr; *n* = 416)	
Escherichia coli (968)	62 (28.8)	264 (33.9)	494 (39.7)	148 (35.6)	0.251
Klebsiella pneumoniae (354)	17 (7.9)	123 (15.8)	164 (13.2)	50 (12.0)	0.619
Staphylococcus aureus (312)	30 (14.0)	114 (14.6)	124 (10.0)	44 (10.6)	0.182
Pseudomonas aeruginosa (84)	9 (4.2)	16 (2.1)	46 (3.7)	13 (3.1)	0.757
***Proteus mirabilis* (62)**	**2 (0.9)**	**16 (2.1)**	**28 (2.2)**	**16 (3.8)**	**0.046**
Salmonella enteritidis (54)	12 (5.6)	18 (2.3)	20 (1.6)	4 (1.0)	0.095
Enterococcus faecalis (54)	5 (2.3)	7 (0.9)	30 (2.4)	12 (2.9)	0.503
Viridians streptococci (53)	6 (2.8)	21 (2.7)	19 (1.5)	7 (1.7)	0.133
Streptococcus agalactiae (52)	3 (1.4)	22 (2.8)	19 (1.5)	8 (1.9)	0.960
Streptococcus pneumoniae (22)	5 (2.3)	8 (1.0)	12 (1.0)	2 (0.5)	0.095

[a]Calculated by Pearson's correlation. Boldface indicates statistical significance, i.e., a *P* value of <0.05.

istics and severity of bacteremia, inappropriate EAT, resistant microorganisms, comorbidities, comorbidity severity (McCabe classification), and bacteremia source, were examined by univariate analysis (Table 6). A fatal outcome within 4 weeks after bacteremia onset was related to male gender; nursing home residency; ultimately or rapidly fatal comorbidities (McCabe classification); critical illness (a Pitt bacteremia score of ≥4) at bacteremia onset; polymicrobial bacteremia; causative microorganisms of *K. pneumoniae*, *Pseudomonas* species, or ESBL-producing EKP; bacteremic pneumonia; comorbidities with malignancies, neurological diseases, or liver cirrhosis; and inappropriate EAT. Furthermore, the following variables were negatively associated with

TABLE 3 Trends in the susceptibility of the five leading microorganisms in patients with community-onset bacteremia

Microorganism[a]	Susceptibility[b] (%)				*P* value[c]
	Young adults (18–44 yr)	Adults (45–64 yr)	The elderly (65–84 yr)	Oldest old (≥85 yr)	
Escherichia coli	*n* = 62	*n* = 264	*n* = 494	*n* = 148	
Cefazolin-S	**64.5**	**56.8**	**55.3**	**48.6**	**0.027**
Cefuroxime-S	**79.0**	**78.0**	**72.1**	**66.2**	**0.035**
Cefotaxime-S	**98.4**	**90.2**	**88.9**	**83.1**	**0.034**
Levofloxacin-S	**90.3**	**84.1**	**82.0**	**68.9**	**0.049**
ESBL producer	**3.2**	**4.5**	**5.9**	**9.5**	**0.035**
Klebsiella pneumoniae	*n* = 17	*n* = 123	*n* = 164	*n* = 50	
Cefazolin-S	**88.2**	**79.7**	**73.2**	**62.0**	**0.006**
Cefuroxime-S	**94.1**	**93.5**	**86.0**	**82.0**	**0.041**
Cefotaxime-S	**100**	**95.9**	**91.5**	**88.0**	**0.001**
Levofloxacin-S	**100**	**95.1**	**90.9**	**86.0**	**<0.001**
ESBL producer	**0**	**4.1**	**5.5**	**12.0**	**0.031**
Staphylococcus aureus	*n* = 30	*n* = 114	*n* = 124	*n* = 44	
Methicillin-R	**6.9**	**31.6**	**37.9**	**59.1**	**0.021**
Streptococcus species	*n* = 27	*n* = 90	*n* = 125	*n* = 47	
Penicillin-S	**96.3**	**94.4**	**93.6**	**89.4**	**0.047**
Cefotaxime-S	96.3	94.4	94.4	97.9	0.673
Levofloxacin-S	**100**	**98.9**	**96.8**	**93.6**	**0.023**
Pseudomonas aeruginosa	*n* = 9	*n* = 16	*n* = 46	*n* = 13	
Ceftazidime-S	77.8	100	100	84.6	0.765
Cefepime-S	77.8	100	100	84.6	0.765
Levofloxacin-S	88.9	87.5	91.3	84.6	0.542

[a]S, susceptible.
[b]*n* indicates the number of isolates in various age groups.
[c]Calculated by Pearson's correlation. Boldface indicates statistical significance, i.e., a *P* value of <0.05.

TABLE 4 Trends in empirical antimicrobial therapy in adults with community-onset bacteremia

Antibiotic	No. (%) of patients				
	Young adults (18–44 yr; *n* = 216)	Adults (45–64 yr; *n* = 762)	Elderly (65–84 yr; *n* = 1,167)	Oldest old (≥85 yr; *n* = 362)	*P* value[a]
Cephalosporins (*n* = 1,678)	135 (62.5)	528 (69.3)	794 (68.0)	221 (61.0)	0.816
First generation (*n* = 256)	31 (14.4)	85 (11.2)	101 (8.7)	39 (10.8)	0.271
Second generation (*n* = 316)	24 (11.1)	93 (12.2)	161 (13.8)	38 (10.5)	0.982
Third generation (*n* = 880)	66 (30.6)	272 (35.7)	424 (36.3)	118 (32.6)	0.682
Fourth generation (*n* = 226)	14 (6.5)	78 (10.2)	108 (9.3)	26 (7.2)	0.911
Aminopenicillins/BLIs (*n* = 209)	10 (4.6)	61 (8.0)	102 (8.7)	36 (9.9)	0.057
Fluoroquinolones (*n* = 182)	17 (7.9)	56 (7.3)	83 (7.1)	26 (7.2)	0.174
Glycopeptides (*n* = 144)	24 (11.1)	47 (6.2)	59 (5.1)	14 (3.9)	0.072
Ureidopenicillins/BLIs (*n* = 103)	7 (3.2)	17 (2.2)	55 (4.7)	24 (6.6)	0.144
Carbapenems (*n* = 77)	8 (3.7)	17 (2.2)	37 (3.2)	15 (4.1)	0.654
Ureidopenicillins (*n* = 49)	3 (1.4)	12 (1.6)	17 (1.5)	17 (4.7)	0.210
Inappropriate EAT[b]	**28/196 (14.3)**	**110/707 (15.6)**	**206/1,098 (18.8)**	**88/348 (25.3)**	**0.049**

[a]Calculated by Pearson's correlation. Boldface indicates statistical significance, i.e., a *P* value of <0.05.
[b]One hundred eighty patients received a combination of empirical antimicrobial therapy, and 22 were not treated by antimicrobials before blood culture results were available.

4-week mortality: *E. coli* as the causative microorganism; bacteremia due to urinary tract infections, biliary tract infections, or liver abscess; and comorbidities with hypertension.

With the exclusion of four predictors independently linked to inappropriate EAT (Table 5), such as nursing home residents, polymicrobial bacteremia, ESBL-producing EKP, and comorbidities with neurological diseases, significant predictors of 4-week mortality recognized by the univariate analyses were included in the multivariate regression. Consequently, seven independent predictors of 4-week mortality were identified: ultimately and rapidly fatal comorbidities (McCabe classification; AOR, 2.13; $P < 0.001$); inappropriate EAT (AOR, 2.60; $P < 0.001$); critical illness at bacteremia onset (a Pitt bacteremia score of ≥4; AOR, 10.69; $P < 0.01$); bacteremia because of pneumonia (AOR, 2.00; $P < 0.001$) or urinary tract infections (AOR, 0.37; $P < 0.001$); and comorbidities with malignancy (AOR, 1.95; $P = 0.001$) or liver cirrhosis (AOR, 1.86; $P < 0.001$).

TABLE 5 Clinical predictors of inappropriate empirical antimicrobial therapy in adults with community-onset bacteremia

Variable	Analysis result[a]			
	Univariate		Multivariate[b]	
	OR (95% CI)	*P* value	AOR (95% CI)	*P* value
Nursing home residents	2.33 (1.60–3.40)	<0.001	1.66 (1.01–2.12)	0.049
Antimicrobial use within 4 wk before ED arrival	2.28 (1.80–2.89)	<0.001	**2.53 (1.60–4.02)**	**<0.001**
Polymicrobial bacteremia	2.55 (1.91–3.41)	<0.001	**1.53 (1.10–2.12)**	**0.01**
Causative microorganism				
ESBL-producing EKP	14.00 (8.39–23.35)	<0.001	**11.83 (6.68–20.96)**	**<0.001**
Methicillin-resistant *S. aureus*	10.90 (7.27–16.32)	<0.001	**7.88 (5.12–12.15)**	**<0.001**
Levofloxacin nonsusceptible EKP	7.30 (5.39–9.89)	<0.001	**4.21 (3.04–5.85)**	**<0.001**
Pseudomonas species	3.71 (2.40–5.71)	<0.001	NS	NS
Bacteremia source				
Vascular-line infection	2.56 (1.64–4.00)	<0.001	NS	NS
Liver abscess	0.17 (0.05–0.54)	0.001	NS	NS
Comorbidities				
Neurological disease	1.85 (1.47–2.33)	<0.001	**1.38 (1.03–1.86)**	**0.03**
Chronic kidney disease	1.41 (1.09–1.82)	0.008	NS	NS
Diabetes mellitus	1.24 (1.00–1.54)	0.046	NS	NS

[a]Calculated by chi-square or multivariate regression tests. Boldface indicates statistical significance, i.e., a *P* value of <0.05.
[b]NS, no significance (after processing the backward multivariate regression).

TABLE 6 Risk factors of 28-day mortality in adults with community-onset bacteremia

	Analysis result[a]			
	Univariate		Multivariate[b]	
Variable at bacteremia onset	OR (95% CI)	*P* value	AOR (95% CI)	*P* value
Gender, male	1.52 (1.21–1.94)	<0.001	NS	NS
Nursing home residents	2.87 (1.95–4.23)	<0.001		
Ultimately or rapidly fatal comorbidity (McCabe classification)	3.50 (2.76–4.45)	<0.001	2.13 (1.52–2.98)	<0.001
Polymicrobial bacteremia	2.30 (1.68–3.16)	<0.001		
Inappropriate EAT	2.12 (1.63–2.75)	<0.001	2.60 (1.88–3.60)	<0.001
Pitt bacteremia score of ≥4	11.82 (9.14–15.28)	<0.001	10.69 (8.00–14.28)	<0.001
Causative microorganism				
ESBL-producing EKP	3.25 (2.02–5.27)	<0.001		
Pseudomonas species	2.88 (1.81–4.57)	<0.001	NS	NS
Klebsiella pneumoniae	1.83 (1.38–2.44)	<0.001	NS	NS
Escherichia coli	0.45 (0.35–0.58)	<0.001	NS	NS
Bacteremia source				
Pneumonia	4.74 (3.63–6.18)	<0.001	2.00 (1.41–2.82)	<0.001
Urinary tract infection	0.24 (0.17–0.34)	<0.001	0.37 (0.25–0.55)	<0.001
Biliary tract infection	0.57 (0.35–0.91)	0.02	NS	NS
Liver abscess	0.31 (0.11–0.85)	0.02	NS	NS
Major comorbidities				
Malignancy	2.67 (2.11–3.38)	<0.001	1.95 (1.34–2.83)	0.001
Neurological disease	1.42 (1.09–1.84)	0.008		
Liver cirrhosis	2.00 (1.49–2.70)	<0.001	1.86 (1.36–2.26)	<0.001
Hypertension	0.74 (0.59–0.94)	0.01	NS	NS

[a]Calculated by chi-square or multivariate regression tests.
[b]NS, no significance (after processing the backward multivariate regression).

Notably, inappropriate EAT and bacteremia severity at onset were the two leading variables independently linked to 4-week mortality. Furthermore, of these significant independent predictors, age-related trends were only disclosed in critical illness at bacteremia onset, inappropriate EAT, and bacteremic pneumonia (Fig. 1).

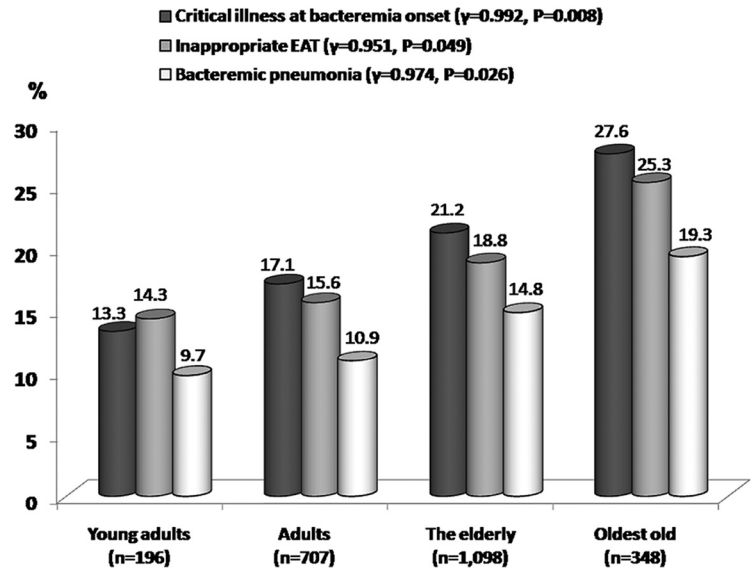

FIG 1 Positive age-related trends in three independent predictors of 4-week crude mortality. *r* indicates the correlation coefficients recognized by Pearson's correlation.

DISCUSSION

Although several studies questioned the survival benefit of early appropriate antimicrobial therapy (10), previous investigations have suggested that the early administration of appropriate antimicrobials could result in a favorable prognosis in bacteremia patients (11, 12); similarly, the importance of EAT appropriateness was highlighted in this cohort. Generally, with the increased severity of bacteremia, the importance of appropriate EAT should be vigorously emphasized (12), and the time to appropriate EAT administration should be as short as possible (13). With our study findings showing that bacteremic severity increased with age, the appropriateness of EAT should be strongly encouraged for the elderly.

Generally, the increasing incidence and adverse influence of multidrug-resistant microorganisms, such as ESBL producers and MRSA, have been documented in the community (14, 15). Similar to the SENTRY Antimicrobial Surveillance Program (9), the MRSA proportion here increased with age. Additionally, there were several reports that demonstrated a high colonization rate of MRSA in the elderly or nursing home residents (16, 17). Thus, the age-related correlation with MRSA bacteremia was not unexpected in our study. Moreover, positive age-related trends in ESBL producers and levofloxacin-nonsusceptible *E. coli* and *K. pneumoniae* were observed. Because the relationship of bacterial infections due to ESBL producers or fluoroquinolone-resistant pathogens and antimicrobial exposure has been well established (15, 18), it is our suspicion that the frequent emergency department (ED) visits or hospitalization of the elderly in the community and their subsequent antibiotic exposure contributed to a substantial risk of infection with multidrug-resistant organisms. More importantly, despite the occurrence of antimicrobial-resistant microorganisms increasing with age, the EAT profile was similar among the four age groups in the ED. Consequently, the age-related trend for inappropriate EAT was determined. The results indicated that for individuals with suspected or documented bacteremia in the ED, it is critical to consider patient age for EAT. For the elderly with risk factors of inappropriate EAT (i.e., recent antimicrobial therapy or underlying neurological disease), the spectrum of EAT may be broader than that for younger adults.

In this cohort, we focused on the cases of community-onset, rather than community-acquired, bacteremia for several reasons. First, community-onset bacteremia is not an uncommon and treatable infectious disease (19). Second, by definition, cases of community-acquired bacteremia should have no recent hospitalization within the past month, no recent invasive procedure before admission, no regular dialysis, and no indwelling intravascular devices (20). However, it is difficult to recognize the true category of patients from the community in overcrowded EDs (21). Accordingly, the patients visiting EDs with bacteremia can be regarded without argument as having community-onset bacteremia, as shown in our published ED-based studies (22–25).

In our cohort, of the seven independent predictors of 4-week mortality identified, the three leading predictors were inappropriate EAT, a critical illness at bacteremia onset, and bacteremic pneumonia, which all had a high AOR and a positive age-related trend. These significant prognostic variables may contribute to the positive age-related trend in 4-week mortality among adults with community-onset bacteremia.

There are several limitations inherent to the design of this study. First, multiple univariate hypothesis tests for age-related trends with no adjustment of covariates for multivariate testing were performed in the current study, increasing the likelihood that some trends are false positives. Therefore, the multivariate regression tests for 4-week mortality and inappropriate EAT were presented here. Second, despite the fact that a large cohort was analyzed using the linear-by-linear association test, the factors contributing to the age-related trend were complicated and not clarified as easily as the primary contributors. Using *E. coli* and *K. pneumoniae* as the samples, they were generally the leading pathogens linked to intra-abdominal, urinary, and biliary tract infections. Because of a positive age-related trend in biliary tract infections and a negative trend in intra-abdominal infections, we suspected that the contradictory

age-related trends in the abovementioned bacteremic sources partially contribute to the absence of an age-related trend in *E. coli* or *K. pneumoniae* bacteremia. Third, the present study was a retrospective study; thus, there may have been some selection bias as a result of patient loss and incomplete clinical information. To diminish the patient number without complete clinical information and reduce the errors of information retrieval, two authors reviewed the medical records of eligible patients. Moreover, we used telephone follow-ups to collect outcome data after discharge. Only 16 (0.7% of 2,365) patients lacking outcome information were excluded, and such a selection bias was expected to minimally influence the study results. Finally, although the present study was conducted in a single center and our findings, particularly on antimicrobial susceptibility, may not be generalized to other areas, it included more than two thousand adults in a 6-year period and at least could be regarded as representative data of community-onset bacteremia in southern Taiwan.

In conclusion, for adults with community-onset bacteremia, age-related differences in bacteremia severity and antimicrobial-resistant microorganisms were evident and contributed to the risk of inappropriate EAT and subsequent mortality in the elderly. With regard to a positive age-related trend in bacteremia severity, the importance of appropriate EAT should be augmented with aging. To facilitate the early administration of broad-spectrum antimicrobials, clinically validated algorithms are warranted for the reliable identification of bacterial infections due to antimicrobial-resistant pathogens in the elderly.

MATERIALS AND METHODS

Study design. This retrospective cohort study was conducted at the emergency department (ED) of the medical center. The study hospital is a tertiary-care, 1,300-bed, university-based medical center with an approximate annual ED census of 70,000 patients. This study was approved by the hospital's institutional review board (ER-100-182), and the requirement for informed consent was waived. This analysis was reported using the format recommended by STROBE (26). Partial clinical information in this study cohort has been published (13, 22–24).

Bacterial growth in blood cultures obtained from adults in the ED between January 2008 and December 2013 was screened in a computer database. Among adult patients with bacteremia, clinical information was retrieved from medical records and recorded in a predetermined case record form. Patients were excluded if they had hospital-onset bacteremia, contaminated blood cultures, bacteremia diagnosed prior to visiting the ED, inappropriate dosage or route of antimicrobial administration during all hospitalizations, or incomplete clinical information. The most inaccurate records of several variables, such as bacteremia severity, initial sepsis-related syndrome, and laboratory data, were captured within 24 h after ED arrival. Two authors reviewed the medical records of eligible patients for the above-described clinical information. If any discrepancies were observed, both authors inspected the medical records simultaneously, and a decision was reached through consensus. If there were multiple bacteremic episodes, only the first episode of each patient was included. The primary endpoint was crude 4-week mortality. To avoid underestimating the mortality rate, if a patient was not followed up at the outpatient clinic after discharge, outcome information was retrieved by telephone contact. Patients unable to be reached by telephone were excluded.

Microbiological methods. Bacteremic aerobic isolates in the study period were prospectively collected. Bacteremic isolates were identified by the GNI card of the Vitek 2 system (bioMerieux, Lyon, France). For these stored isolates, antimicrobial susceptibility was determined by the disk diffusion method, based on the performance standards of the Clinical and Laboratory Standards Institute (CLSI) in 2016 (27). For Gram-negative bacilli, the tested drugs included cefazolin, cefuroxime, cefotaxime, ceftazidime, and levofloxacin. For streptococci, the tested drugs included penicillin, cefotaxime, and levofloxacin. If a patient was empirically treated with agents not described above, the susceptibility for these agents was measured. Cefoxitin susceptibility was measured to identify methicillin-resistant *Staphylococcus aureus* (MRSA). For *Escherichia coli*, *Klebsiella* species, and *Proteus mirabilis* (EKP), the presence of extended-spectrum β-lactamases (ESBLs) was detected by a phenotypic confirmatory test with cephalosporin-clavulanate combination disks, as recommended by the 2009 CLSI guidelines (28).

Definitions. Similar to a previous categorization (4), our patients were stratified by age as young adults (18 to 44 years), adults (45 to 64 years), the elderly (65 to 84 years), and the oldest old (≥85 years). Community-onset bacteremia indicates that the place of onset of the bacteremic episode is the community and includes long-term health care facilities and community-acquired bacteremia, as previously described (22–25). Blood culture samples with potential contaminating pathogens were regarded as being contaminated according to previously described criteria (29). The sources of bacteremia were determined clinically based on the presence of an active infection site coincident with bacteremia or the isolation of a microorganism from other clinical specimens prior to or on the same date as the bacteremia onset.

As previously defined (13, 23), the antimicrobial therapy was considered appropriate when all of the following criteria were fulfilled: (i) antimicrobial agents were administered according to the route and

dosage recommended in the Sanford guide (30) and (ii) bacteremic pathogens were susceptible *in vitro* to the administered antimicrobial agent based on the contemporary CLSI breakpoints (27). Inappropriate EAT was defined as >48 h for the time to appropriate antibiotic (13, 31), which was the period between ED arrival and the administration of appropriate antimicrobial therapy. The bacteremic severity was graded by the Pitt bacteremia score (13, 23). Patients with a high Pitt bacteremia score (≥4) were categorized as critically ill (13), whereas those with a Pitt bacteremia score of 0 and 1 to 3 were categorized as being mildly and moderately ill, respectively. Comorbidities were defined as in previous reports (32), and malignancies included hematological malignancies and solid tumors. The severity of underlying diseases was assessed by a previously delineated McCabe classification system (33).

Statistical analyses. Statistical analyses were performed using the Statistical Package for the Social Sciences for Windows (Chicago, IL, USA), version 20.0. The age-related trends in clinical characteristics and the outcomes were analyzed by the equivalent linear-by-linear association test (i.e., Pearson's correlation). A univariate analysis for the predictors of 4-week mortality with odds ratios (ORs), 95% confident intervals (CIs), and *P* values was conducted using a chi-square test or Fisher's exact test. To assess the independent predictor (adjusted odds ratio [AOR] and 95% CI) of short-term mortality or inappropriate EAT, variables with a *P* value of less than 0.05 in the univariate analysis were included in a stepwise and backward multivariable logistic regression model. A *P* value of less than 0.05 was considered significant.

SUPPLEMENTAL MATERIAL

Supplemental material for this article may be found at https://doi.org/10.1128/AAC.01050-17.

SUPPLEMENTAL FILE 1, PDF file, 0.3 MB.

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We have no conflicts of interest to declare.

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