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Short versus long duration antimicrobial treatment for community-onset bacteraemia: A propensity score matching study

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ABSTRACT

The efficacy and safety of short-course intravenous (i.v.) antimicrobial therapy for bloodstream infections is unknown. Therefore, a retrospective 8-year cohort study including 1431 hospitalised adults was conducted to compare the outcomes of patients receiving short-course (5–10 days) and long-course (11–16 days) i.v. antibiotic therapy for community-onset bacteraemia. Of 1010 patients who received short-course therapy, 726 were matched with 363 patients in the long-course group through propensity score matching at a ratio of 1:2 based on independent predictors of 30-day mortality identified in the multivariate regression model. Following appropriate matching, similarities between the two groups in the proportion of baseline characteristics (age, sex, major co-morbidities, co-morbidity severity, bacteraemia severity at onset and major bacteraemia sources) and 30-day crude mortality rate after bacteraemia onset were observed. Notably, clinical outcomes within 30 days after the end of i.v. therapy, in terms of proportions of post-treatment overall infections (2.2% vs. 6.1%; $P=0.001$), infections caused by antimicrobial-resistant pathogens (ARPs) (1.7% vs. 4.4%; $P=0.007$), and thereby post-treatment crude mortality (1.4% vs. 3.6%; $P=0.009$), were lower in the short-course group. In conclusion, for adults with community-onset uncomplicated bacteraemia, short-course (5–10 days) i.v. antibiotic treatment did not result in an increased risk of mortality but instead decreased the odds of overall and ARP infections after the treatment course.

1. Introduction

Community-onset bacteraemia is an infectious disease that has an annual incidence of 0.82% worldwide [1] and is associated with high morbidity and mortality, resulting in significant healthcare costs [2]. Despite advances in supportive care and new techniques for rapid diagnosis, appropriate antimicrobial therapy remains the cornerstone for improved patient outcomes.

Most clinicians consider intravenous (i.v.) administration the preferred route for antibiotic therapy for bloodstream infections (BSIs). Traditionally, the duration of treatment for BSI is in the range of 7–14 days, but evidence supporting the optimal treatment duration within this timeframe has been challenged in recent years [3–5]. Intravenous antibiotic therapy has been associated with a risk of i.v. catheter-related infection, a labour burden on nursing staff, length of hospitalisation and administration cost. Furthermore, prolonged antimicrobial exposure has been associated with an increased likelihood of adverse drug events [6], *Clostridium difficile* infection (CDI) [6] and antimicrobial resistance [7]. Therefore, the ideal duration of i.v. antimicrobial therapy is one that optimises the clinical outcome while simultaneously minimising adverse drug events.

Studies evaluating therapeutic durations for bacteraemia have numerous limitations, such as small population size [4,8,9], a focus on specific co-morbidities [10] or specific pathogens [11–13], critically ill individuals [8,9,14] and a lack of appropriate objects

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for comparison [8,9,14]. Only one randomised controlled trial (RCT) focusing on overall bacteraemia (but in neonates) was identified through a search of the English language literature [15]. In addition, to avoid the influence of antimicrobial-resistant pathogens (ARPs) on the clinician's decision regarding the therapeutic course of i.v. antimicrobials, in this study we focused on adults with community-onset bacteraemia and conducted a long-term cohort study to compare the therapeutic efficacies of short- and long-course i.v. antibiotic therapy using propensity score (PS) matching.

2. Methods

2.1. Study design and sites

A retrospective 8-year (January 2007 to December 2014) cohort study was conducted in the emergency department (ED) of a 1200-bed medical centre in southern Taiwan. Hospitalised adults (age ≥18 years) with community-onset bacteraemia in the ED were included. The study was approved by the Institutional Review Board of National Cheng Kung University Hospital (Tainan, Taiwan) and was collectively reported by the format recommended by STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) [16].

2.2. Patient population

During the study period, patients who underwent blood culture sampling at the ED were screened for bacterial growth via a computer database. Of adults with bacterial growth, medical information was retrieved through a review of their medical charts. For patients with multiple bacteraemic episodes, only the first episode was considered. Patients were first excluded if they were found to have a contaminated blood culture sample or if they had been transferred from another hospital. For the remaining patients, those who met any of the following criteria were excluded: (i) non-hospitalised patients; (ii) i.v. therapy duration <5 days or >16 days; (iii) failure to receive appropriate antimicrobial therapy with an empirical agent or during the entire i.v. course; (iv) death during the i.v. course; (v) treatment with aminoglycoside monotherapy; and (vi) uncertain date of death.

2.3. Data collection

Data collection was performed by retrospectively reviewing the medical records of all eligible patients in the ED using a predetermined case report form that included patient demographics and clinical characteristics. The covariates included patient age, vital signs, co-morbidities, co-morbidity severity, laboratory data, duration and type of antimicrobial administration, bacteraemia source, bacteraemia severity (Pitt bacteraemia score) at onset [17,18] and length of ED stay. Furthermore, any further hospitalisation course, including duration, type and dosage of antimicrobial agents, length of hospitalisation and patient outcome, were also recorded. Medical records were reviewed by two authors and any discrepancies were discussed. The primary endpoints was crude mortality within 30 days of bacteraemia onset and the secondary endpoint was post-treatment mortality within 30 days after the discontinuation of i.v. antibiotic administration.

As in a relevant study [11], a cut-off value of 10 days was selected to categorise the duration of antimicrobial therapy. Primary exposure was the duration of i.v. antibiotic treatment, dichotomised to short-course (5–10 days) and long-course (11–16 days) therapy, after the first day of therapy, which was the day that blood cultures were obtained (i.e. ED arrival). Therapeutic efficacy (i.e. clinical outcomes) within 30 days after discontinuation of i.v. antibiotic therapy studied for two groups included post-treatment crude mortality, recurrent bacteraemia, CDI, post-treatment overall infections and post-treatment ARP infections.

2.4. Definitions

As previously described [17,19], an episode of bacteraemia in the community setting was diagnosed as community-onset bacteraemia, which included healthcare-acquired and community-acquired BSIs. More than one bacterial species isolated from the same BSI episode was regarded as polymicrobial bacteraemia. Based on previous criteria [20], contamination of blood culture sampling was considered if a potentially contaminating pathogen was isolated.

According to a previous description [17,19], antimicrobial therapy was considered appropriate when all of the following criteria were fulfilled: (i) the route and dosage of antimicrobial agents were as recommended in the *Sanford guide* [21]; and (ii) bacteraemia pathogens were in vitro susceptible to the administered antimicrobial agent based on the breakpoints of the Clinical and Laboratory Standards Institute (CLSI) issued in 2016 [22]. Empirical antibiotic therapy was regarded as appropriate if the period between ED arrival and administration of appropriate i.v. antimicrobial was ≤24 h [23].

Defervescence following antimicrobial administration was defined as an afebrile state in which the tympanic body temperature was maintained at <37.0 °C for ≥24 h [19], and the period between defervescence and appropriate administration of empirical antimicrobials was considered the time to defervescence. Bacteraemia severity was graded according to the Pitt bacteraemia score using a previously validated scoring system [17,18]. As per previous classifications [18,24], patients with a Pitt bacteraemia score of 0 were regarded as stabilised illness, whereas those with Pitt bacteraemia scores of 1–3 and ≥4 were regarded as moderate and critical illness, respectively. Co-morbidities were defined according to previous criteria [25], and malignancies included haematological malignancies and solid tumours. Co-morbidity severity was assessed using a previously delineated McCabe classification in which co-morbidities were graded as rapidly fatal (death expected within 1 year), ultimately fatal (death expected in a 5-year period) and non-fatal, according to the criteria of McCabe and Jackson [18,19,26].

Like previous definitions [11], removal of infected hardware, drainage of infected fluid collections, or resolution of obstruction for biliary or urinary sources was referred to as appropriate control of the bacteraemia source. Recurrent bacteraemia was defined as a new episode of the documented BSI caused by the same micro-organism and in vitro susceptibility as the index bacteraemia episode [27]. ARPs were defined as micro-organisms with antimicrobial resistance that seldom exist in the community, such as Enterobacteriaceae, *Pseudomonas* spp., *Vibrio* spp. or *Aeromonas* spp. resistant to extended-spectrum cephalosporins or fluoroquinolones, methicillin-resistant *Staphylococcus aureus* (MRSA), ampicillin-resistant enterococci and penicillin-resistant streptococci. CDI was defined as a positive test for *C. difficile* in the setting of clinical criteria for infection or symptom relief after oral vancomycin or metronidazole administration [28].

2.5. Microbiological methods

Blood cultures were incubated in a BD BACTEC™ 9240 instrument (Becton Dickinson Diagnostic Systems, Sparks, MD) for 5 days at 35 °C. Bacteraemic aerobic isolates were prospectively collected. Bacterial species was identified using a VITEK®2 system (bioMérieux Inc., Durham, NC), and antimicrobial susceptibility was determined by the disk diffusion method based on the performance standards of the CLSI [22]. For the Gram-negative aerobes,

the tested drugs included ampicillin/sulbactam, cefazolin, cefuroxime, cefotaxime, cefepime, ertapenem and levofloxacin. Penicillin, cefotaxime and levofloxacin were tested for streptococci, and cefoxitin and ampicillin were studied for staphylococci and enterococci, respectively. If the patient was empirically or definitively treated by other agents, the susceptibility of the indicated agent was determined. For *Escherichia coli, Klebsiella* spp. and *Proteus mirabilis* (EKP), production of extended-spectrum β-lactamases (ESBLs) was detected by a phenotypic confirmatory test using cephalosporin/clavulanic acid combination disks [29].

2.6. Statistical analyses

Statistical analyses were performed using IBM SPSS Statistics for Windows v.20.0 (IBM Corp., Armonk, NY). Fisher's exact test or Pearson's χ^2 test was used for categorical variables, and an independent *t*-test or Mann–Whitney test was used for continuous variables. To determine independent predictors with adjusted odds ratio, the variables of 30-day mortality identified in the univariate analysis with a *P*-value of <0.1 were included in a stepwise and backward multivariable logistic regression model. A two-sided *P*-value of <0.05 was considered statistically significant.

A PS-matched analysis was performed to control for confounding variables in the choice of the therapeutic course of i.v. antimicrobials. The PS was calculated by the independent predictors of 30-day crude mortality after bacteraemia onset identified by a multivariable logistic regression model. Patients receiving long-course therapy were matched at a ratio of 1:2 with those receiving short-course therapy using individual PSs. Matching by the closest total scores was done manually based on a tolerance interval approach. As previously described [30], the matching tolerance was a PS difference of 0.2, implying that a patient with long-course therapy was matched to one with short-course therapy when the estimated probability of the latter receiving long-course therapy was within 20% of the estimated probability of his or her counterpart of short-course therapy.

3. Results

3.1. Demographics and clinical characteristics of the overall cohort

A total of 1431 adults with community-onset bacteraemia were included based on the inclusion and exclusion criteria, including 1010 (70.6%) treated by short-course antimicrobial therapy and 421 (29.4%) treated by long-course antimicrobial therapy (Fig. 1). Their mean ± standard deviation (S.D.) age was 68.0 ± 15.8 years, and 743 (51.9%) were female. The mean ± S.D. duration of hospital stay was 11.4 ± 7.2 days and the 30-day crude mortality rate was 1.2% (17 patients). The five most common co-morbidities included hypertension (706 patients; 49.3%), diabetes mellitus (543; 37.9%), malignancy (383; 26.8%), neurological disease (308; 21.5%) and chronic kidney disease (240; 16.8%).

There were 91 polymicrobial episodes, therefore a total of 1549 causative micro-organisms were collected in the overall cohort (Table 1). The top ten pathogens were *E. coli, Klebsiella* spp., *Streptococcus* spp., *S. aureus, Enterobacter* spp., *Proteus* spp., *Pseudomonas* spp., *Salmonella* spp., *Aeromonas* spp. and *Enterococcus* spp. Among them, EKP isolates (including 707 *E. coli*, 244 *Klebsiella* spp. and 30 *P. mirabilis*) and Enterobacteriaceae accounted for 63.3% (981 isolates) and 70.6% (1094) of the total causative micro-organisms, respectively. Notably, only 6/109 *S. aureus* isolates (5.5%) were MRSA; ESBL-producers and levofloxacin-resistant isolates only accounted for 2.7% (26/981) of EKP and 6.9% (76/1094) of Enterobacteriaceae, respectively. Ceftazidime-resistant isolates accounted for 2.9% (1/35) of *Pseudomonas* spp., and penicillin-resistant isolates accounted 3.0% (5/164) of streptococci.

In the overall cohort, the eight most commonly administered agents for empirical antimicrobial therapy were third-generation cephalosporins (3GCs), second-generation cephalosporins (2GCs), first-generation cephalosporins (1GCs), aminopenicillin/β-lactamase inhibitors (BLIs), fourth-generation cephalosporins (4GCs), fluoroquinolones, ureidopenicillin/BLIs and carbapenems (Table 2). For definitive therapy, the leading agent administered was 1GCs, and other common agents included 3GCs, 2GCs, fluoroquinolones, narrow-spectrum penicillins, aminopenicillin/BLIs, carbapenems and 4GCs.

3.2. Comparison of baseline characteristics in the overall cohort

Table 3 presents a comparison of the clinical characteristics at bacteraemia onset for the overall cohort in the short- and long-course groups. A higher proportion of female patients as well as bacteraemia due to urinary tract infection (UTI) or intra-abdominal infection (IAI) was observed in the short-course group, whereas in the long-course group a higher proportion of patients were nursing home residents and had inadequate source control, polymicrobial bacteraemia, severe bacteraemia (Pitt bacteraemia score ≥4 at onset), ultimately or rapidly fatal co-morbidities, the co-morbidities diabetes mellitus or neurological disease, and bacteraemia due to pneumonia or liver abscess.

3.3. Comparisons of causative micro-organisms and antimicrobial agents in the overall cohort

The proportion of causative micro-organisms and ARPs in the overall cohort between the short- and long-course group are compared in Table 1. Dissimilarity of the micro-organism proportions for *E. coli, Klebsiella* spp., *S. aureus, Enterobacter* spp. and *Enterococcus* spp. was observed. Among the ARPs, a higher proportion of levofloxacin-resistant Enterobacteriaceae was observed in the long-course group.

A comparison of the antimicrobial classes administered for empirical and definitive therapy between the short- and long-course groups in the overall cohort is shown in Table 2. Significantly dissimilar proportions of empirical antimicrobial therapy included 2GCs, 1GCs, 4GCs, fluoroquinolones, ureidopenicillin/BLIs and carbapenems. Similarly, a significant difference in the antimicrobial proportion was also observed in numerous definitive antimicrobial classes, such as 1GCs, 2GCs, fluoroquinolones, narrow-spectrum penicillins, carbapenems and 4GCs.

3.4. Predictors of 30-day crude mortality

Several predictors of 30-day crude mortality were identified in the univariate analysis, including Pitt bacteraemia score ≥4 at bacteraemia onset, bacteraemia caused by UTI, causative micro-organisms of *E. coli* or *Klebsiella* spp., and ultimately or rapidly fatal co-morbidities (Table 4).

Of the ten predictors of 30-day crude mortality identified in the univariate analysis with $P < 0.1$, only three variables remained significant in the multivariate regression model (Table 4), including Pitt bacteraemia score ≥4 at onset, bacteraemia caused by UTI, and ultimately or rapidly fatal co-morbidities.

3.5. Comparison of causative micro-organisms and antimicrobial agents in the matched cohort

A comparison of the proportion of causative micro-organisms and ARPs between the short- and long-course groups after adequate PS matching is shown in Table 1. A higher proportion of *E. coli* and a lower percentage of *S. aureus* were observed in the short-course group compared with the long-course group. Notably,

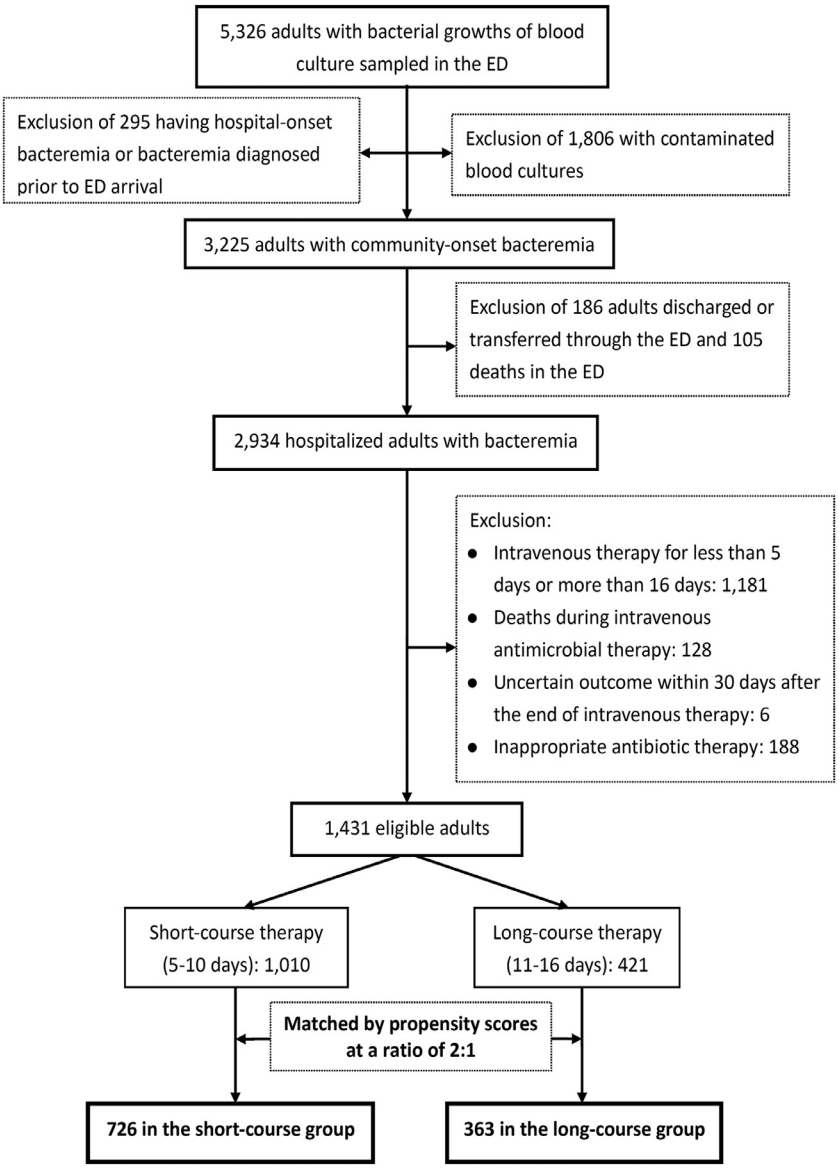

Fig. 1. Flowchart of patient selection. ED, emergency department; IV, intravenous.

among the ARPs, there was a significantly higher proportion of ESBL-producing EKP in the long-course group.

A comparison of antimicrobial classes administered for empirical and definitive therapy in the matched cohort between the short- and long-course groups is shown in Table 2. For empirical therapy, a dissimilarity in antimicrobial proportions was only observed for fluoroquinolones. For definitive antimicrobial classes, a higher proportion of carbapenems and a lower proportion of 1GCs and 2GCs was observed in the long-course group.

3.6. Baseline characteristics and clinical outcomes in the matched cohort

Of the 1010 patients who underwent short-course therapy, 726 were matched with 363 patients in the long-course group with the closest PS based on the three independent predictors of 30-day mortality, as indicated in Table 3. Following appropriate matching, no significant differences in the patient proportion between the groups were observed in terms of older age, sex, nursing home residence, major co-morbidities, severity of co-morbidities, bacteraemia severity at onset and major bacteraemia sources. The 30-day crude mortality rate after bacteraemia onset was also similar in the two groups. Dissimilar proportions were only observed in the co-morbidity neurological disease. Notably, the length of sequential oral antimicrobial therapy, time to defervescence and the proportion of inadequate source control were similar between the groups.

Within 30 days after the discontinuation of i.v. antimicrobial therapy, a similar proportion of recurrent BSIs and CDIs between the two groups was observed; however, lower rates of post-treatment crude mortality, post-treatment overall infections and post-treatment ARP infections were observed in the short-course group compared with the long-course group (Fig. 2).

4. Discussion

Even in less severe types of bacteraemia, such as catheter-related BSI, most clinicians consider an i.v. administration duration of 7–14 days to be an adequate treatment course for enterococci or Gram-negative bacterial infections; moreover, the therapeutic duration should be extended to 4–6 weeks if *S. aureus* is the causative micro-organism [3,31]. For severe bacteraemia caused by

Table 1
Top ten causative micro-organisms and top five antimicrobial-resistant pathogens in the short- and long-course intravenous antimicrobial treatment groups in the overall and matched cohorts.

Micro-organism	Overall cohort [*n* (%)]				Matched cohort [*n* (%)]			
	Total (*n* = 1549)	Short-course (*n* = 1080)	Long-course (*n* = 469)	*P*-value*	Total (*n* = 1180)	Short-course (*n* = 779)	Long-course (*n* = 401)	*P*-value*
Causative micro-organism								
Escherichia coli	707 (45.6)	**555 (51.4)**	**152 (32.4)**	**<0.001**	501 (42.5)	**363 (46.6)**	138 (34.4)	**<0.001**
Klebsiella spp.	244 (15.8)	**148 (13.7)**	**96 (20.5)**	**0.001**	191 (16.2)	115 (14.8)	76 (19.0)	0.06
Streptococcus spp.	164 (10.6)	115 (10.6)	49 (10.4)	0.91	138 (11.7)	98 (12.6)	40 (10.0)	0.19
Staphylococcus aureus	109 (7.0)	**49 (4.5)**	**60 (12.8)**	**<0.001**	87 (7.4)	**41 (5.3)**	**46 (11.5)**	**<0.001**
Enterobacter spp.	42 (2.7)	**30 (2.8)**	**12 (2.6)**	**<0.001**	36 (3.1)	26 (3.3)	10 (2.5)	0.43
Proteus spp.	37 (2.4)	24 (2.2)	13 (2.8)	0.52	27 (2.3)	14 (1.8)	13 (3.2)	0.12
Pseudomonas spp.	35 (2.3)	25 (2.3)	10 (2.1)	0.82	28 (2.4)	20 (2.6)	8 (2.0)	0.54
Salmonella spp.	31 (2.0)	23 (2.1)	8 (1.7)	0.58	24 (2.0)	17 (2.2)	7 (1.7)	0.62
Aeromonas spp.	29 (1.9)	23 (2.1)	6 (1.3)	0.26	21 (1.8)	16 (2.1)	5 (1.2)	0.32
Enterococcus spp.	25 (1.6)	**12 (1.1)**	**13 (2.8)**	**0.02**	18 (1.5)	8 (1.0)	10 (2.5)	0.05
Antimicrobial-resistant pathogens								
LVX-R Enterobacteriaceae	76/1094 (6.9)	**46/803 (5.7)**	**30/291 (10.3)**	**<0.001**	60/806 (7.4)	35/553 (6.3)	25/253 (9.9)	0.08
ESBL-producing EKP	26/981 (2.7)	6/254 (2.4)	20/727 (2.8)	0.74	21/719 (2.9)	4 /492 (0.8)	**17/227 (7.5)**	**<0.001**
Methicillin-R *S. aureus*	6/109 (5.5)	4/49 (8.2)	2/60 (3.3)	0.27	4/87 (4.6)	2/41 (4.9)	2/46 (4.3)	1.00
Penicillin-R streptococci	5/164 (3.0)	4/115 (3.5)	1/49 (2.0)	1.00	5/138 (3.6)	4/98 (4.1)	1/40 (2.5)	1.00
CAZ-R *Pseudomonas* spp.	1/35 (2.9)	1/25 (4.0)	0/10 (0)	1.00	1/28 (3.6)	1/20 (5.0)	0/8 (0)	1.00

LVX, levofloxacin; R, resistant; ESBL, extended-spectrum β-lactamase; EKP, *E. coli*, *Klebsiella* spp. and *Proteus mirabilis*; CAZ, ceftazidime.
* Boldface indicates statistical significance ($P < 0.05$).

Table 2
Leading empirical and definitive antimicrobials in the short- and long-course intravenous antimicrobial treatment groups in the overall and matched cohorts.

Antimicrobial agent	Overall cohort [*n* (%)]				Matched cohort [*n* (%)]			
	Total (*n* = 1431)	Short-course (*n* = 1010)	Long-course (*n* = 421)	*P*-value*	Total (*n* = 1089)	Short-course (*n* = 726)	Long-course (*n* = 363)	*P*-value*
Empirical antimicrobials								
Third GCs	624 (43.6)	444 (44.0)	180 (42.8)	0.68	473 (43.4)	319 (43.9)	154 (42.4)	0.63
Second GCs	208 (14.5)	**167 (16.5)**	**41 (9.7)**	**0.001**	150 (13.8)	110 (15.2)	40 (11.0)	0.06
First GCs	144 (10.1)	**122 (12.1)**	**22 (5.2)**	**<0.001**	80 (7.3)	61 (8.4)	19 (5.2)	0.06
Aminopenicillin/BLIs	126 (8.8)	80 (7.9)	46 (10.9)	0.07	103 (9.5)	65 (9.0)	38 (10.5)	0.42
Fourth GCs	122 (8.5)	**72 (7.1)**	**50 (11.9)**	**0.003**	101 (9.3)	59 (8.1)	42 (11.6)	0.07
Fluoroquinolones	74 (5.2)	**64 (6.3)**	**10 (2.4)**	**0.002**	56 (5.1)	**47 (6.5)**	**9 (2.5)**	**0.005**
Ureidopenicillin/BLIs	49 (3.4)	**18 (1.8)**	**31 (7.4)**	**<0.001**	30 (2.8)	15 (2.1)	15 (4.1)	0.05
Carbapenems	43 (3.0)	**21 (2.1)**	**22 (5.2)**	**0.001**	29 (2.7)	15 (2.1)	14 (3.9)	0.08
Definitive antimicrobials								
First GCs	447 (31.2)	**349 (34.6)**	**98 (23.3)**	**<0.001**	307 (28.2)	**220 (30.3)**	**87 (24.0)**	**0.03**
Third GCs	304 (21.2)	206 (20.4)	98 (23.3)	0.23	232 (21.3)	148 (20.4)	84 (23.1)	0.30
Second GCs	213 (14.9)	**175 (17.3)**	**38 (9.0)**	**<0.001**	164 (15.1)	**130 (17.9)**	**34 (9.4)**	**<0.001**
Fluoroquinolones	131 (9.2)	**105 (10.4)**	**26 (6.2)**	**0.01**	105 (9.6)	79 (10.9)	26 (7.2)	0.05
Narrow-spectrum penicillins	73 (5.1)	**38 (3.8)**	**35 (8.3)**	**<0.001**	72 (6.6)	41 (5.6)	31 (8.5)	0.07
Aminopenicillin/BLIs	69 (4.8)	51 (5.0)	18 (4.3)	0.53	58 (5.3)	43 (5.9)	15 (4.1)	0.22
Carbapenems	67 (4.7)	**22 (2.2)**	**45 (10.7)**	**<0.001**	55 (5.1)	**16 (2.2)**	**39 (10.7)**	**<0.001**
Fourth GCs	65 (4.5)	**38 (3.8)**	**27 (6.4)**	**0.03**	55 (5.1)	30 (4.1)	25 (6.9)	0.05

GC, generation cephalosporin; BLI, β-lactamase inhibitor.
* Boldface indicates statistical significance ($P < 0.05$).

other foci, such as infective endocarditis and central nervous system (CNS) infection, a short duration of i.v. antimicrobial administration remains a challenge [3]. To ensure patient safety when receiving short-course parenteral antimicrobial therapy, a bacteraemia cohort was retrospectively recruited in the current study. In addition, the choices of treatment duration of primary care clinicians may be influenced by numerous clinical variables, such as the severity of co-morbidities, bacteraemia source, control of complicated bacteraemia and bacteraemia severity. Therefore, evaluating treatment effects from observational data can be problematic because several prognostic factors may influence treatment decisions. We attempted to overcome this confounder by indication using PS matching and derived two well-matched groups, with the sole difference between them being the duration of antibiotic therapy. After matching, long-course i.v. therapy resulted in high rates of post-treatment overall and ARP infections and thereby higher post-treatment mortality within 30 days after the end of i.v. therapy.

In recent years, an increasing trend of antibiotic administration has been observed worldwide; thus, a global crisis of resistance acquisition has developed [7], in part because of the collateral damage of antimicrobial use [32]. One method to halt the increase in antimicrobial resistance may be a reduction in antibiotic consumption if their clinical efficacy is not impaired. Limiting treatment duration may be the most clinically efficient method for reducing antimicrobial consumption. In addition, long-term i.v. administration can result in catheter-related complications, such as BSI and phlebitis, which are serious public-health problems [5]. To our knowledge, numerous review articles have indicated that shorter courses of antibiotic therapy are highly successful in

Table 3
Clinical characteristics and 30-day mortality rates in the short- and long-course intravenous (i.v.) antimicrobial treatment groups in the overall and matched cohorts[a].

Characteristic	Overall cohort [*n* (%)]			Matched cohort [*n* (%)]		
	Short-course (*n* = 1010)	Long-course (*n* = 421)	*P*-value*	Short-course (*n* = 726)	Long-course (*n* = 363)	*P*-value*
Female sex	**558 (55.2)**	**185 (43.9)**	**<0.001**	367 (50.6)	163 (44.9)	0.08
Patient age (years) (mean ± S.D.)	68.2 ± 15.6	67.7 ± 16.3	0.57	68.7 ± 15.4	68.3 ± 16.1	0.68
Nursing home resident	**33 (3.3)**	**29 (6.9)**	**0.002**	26 (3.6)	21 (5.8)	0.09
Inadequate source control during i.v. antibiotic course	**14 (1.4)**	**19 (4.5)**	**<0.001**	10 (1.4)	10 (2.8)	0.11
Sequential oral therapy after i.v. administration (days) (mean ± S.D.)	5.9 ± 1.5	6.0 ± 1.4	0.08	5.9 ± 1.5	6.0 ± 1.4	0.11
Time to defervescence (days) (mean ± S.D.)	5.5 ± 3.5	5.7 ± 4.2	0.31	5.7 ± 3.7	5.7 ± 4.2	0.98
Polymicrobial bacteraemia	**55 (5.4)**	**36 (8.6)**	**0.03**	42 (5.8)	28 (7.7)	0.22
Pitt bacteraemia score at onset			**<0.001**			0.30
0	**317 (31.4)**	**118 (28.0)**		227 (31.3)	100 (27.5)	
1–3	**589 (58.3)**	**227 (53.9)**		406 (55.9)	207 (57.0)	
≥4	**104 (10.3)**	**76 (18.1)**		93 (12.8)	56 (15.4)	
Co-morbidity severity (McCabe classification)			**0.02**			0.44
Ultimately or rapidly fatal	**201 (19.9)**	**107 (25.4)**		155 (21.3)	85 (23.4)	
Non-fatal	**809 (80.1)**	**314 (74.6)**		571 (78.7)	278 (76.6)	
Major co-morbidities						
Hypertension	503 (49.8)	203 (48.2)	0.59	344 (47.4)	173 (47.7)	0.93
Diabetes mellitus	**354 (35.0)**	**189 (44.9)**	**0.001**	288 (39.7)	162 (44.6)	0.12
Malignancy	259 (25.6)	124 (29.5)	0.14	199 (27.4)	105 (28.9)	0.60
Neurological disease	**195 (19.3)**	**113 (26.8)**	**0.002**	**142 (19.6)**	**96 (26.4)**	**0.01**
Chronic kidney disease	171 (16.9)	69 (16.4)	0.80	127 (17.5)	58 (16.0)	0.53
Liver cirrhosis	130 (12.9)	50 (11.9)	0.61	95 (13.1)	44 (12.1)	0.65
Urological disorder	89 (8.8)	44 (10.5)	0.33	67 (9.2)	41 (11.3)	0.28
Coronary artery disease	87 (8.6)	44 (10.5)	0.27	71 (9.8)	40 (11.0)	0.52
Major bacteraemia source						
Urinary tract	**447 (44.3)**	**119 (28.3)**	**<0.001**	253 (34.8)	117 (32.2)	0.39
Intra-abdominal	**142 (14.1)**	**42 (10.0)**	**0.04**	109 (15.0)	40 (11.0)	0.07
Primary bacteraemia	104 (10.3)	31 (7.4)	0.08	78 (10.7)	27 (7.4)	0.08
Biliary tract	100 (9.9)	46 (10.9)	0.56	87 (12.0)	43 (11.8)	0.95
Pneumonia	**76 (7.5)**	**71 (16.9)**	**<0.001**	74 (10.2)	48 (13.2)	0.14
Soft tissue	66 (6.5)	40 (9.5)	0.05	58 (8.0)	32 (8.8)	0.64
Liver abscess	**32 (3.2)**	**32 (7.6)**	**<0.001**	28 (3.9)	23 (6.3)	0.07
30-day crude mortality rate	9 (0.9)	8 (1.9)	0.11	7 (1.0)	7 (1.9)	0.25

S.D., standard deviation.
[a] Data are given as number (%) unless otherwise stated.
* Boldface indicates statistical significance ($P < 0.05$).

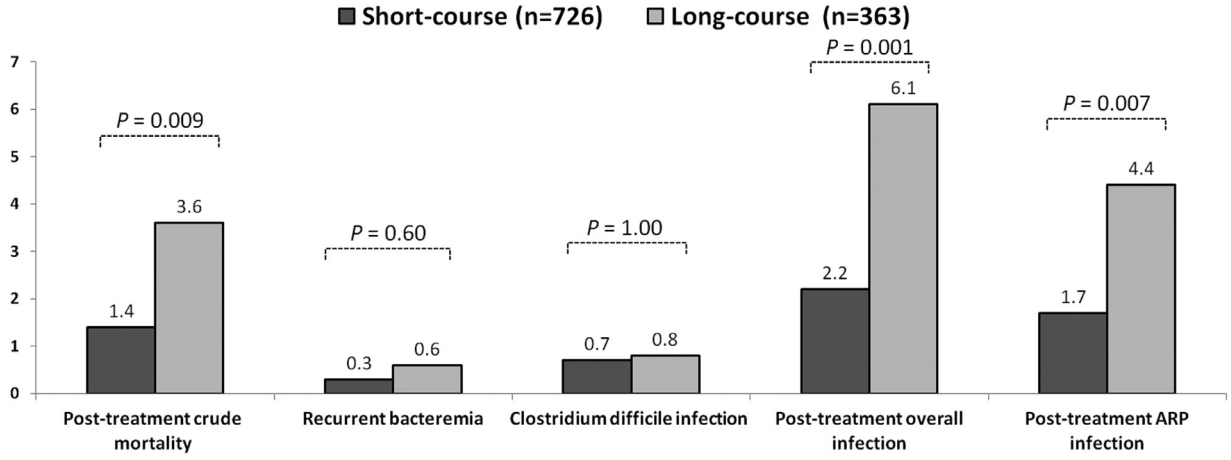

Fig. 2. Clinical outcomes within 30 days after the end of intravenous (i.v.) antibiotic therapy in matched patients receiving short-course and long-course i.v. antibiotic therapy. ARP, antimicrobial-resistant pathogen.

meningococcal meningitis, community-acquired pneumonia, pyelonephritis, infective endocarditis, complicated IAI, soft tissue infection and ventilator-associated pneumonia [3–5]. These findings have been revealed by relevant investigations that produced high-quality evidence (i.e. RCTs) to identify optimal antibiotic prescribing practices. However, little progress by comprehensive and well-designed studies has been made to refine treatment ranges and to standardise antibiotic administration practices for overall BSI. Using appropriate PS matching in the current cohort, a safe form of short-term therapy that protected against resistance for all adults with community-onset bacteraemia was demonstrated.

A meta-analysis of numerous RCTs including patients with various infections, such as urosepsis, pneumonia, IAI and soft tissue infection, found that clinical cure and survival in patients receiving short-course antibiotic treatment were similar to those in patients receiving prolonged courses of treatment [4]. In the current cohort, such infection types accounted for the majority of bacteraemia sources. In addition, advantages of short-course antibiotic

Table 4
Risk factors for 30-day crude mortality in the overall cohort[a].

Characteristic at bacteraemia onset	No. (%) of patients		Univariate analysis		Multivariate analysis	
	Death ($n = 17$)	Survival ($n = 1414$)	OR (95% CI)	*P*-value*	Adjusted OR (95% CI)	*P*-value*
Older age	10 (58.8)	863 (61.0)	0.91 (0.35–2.41)	0.85	–	–
Male sex	12 (70.6)	676 (47.8)	2.62 (0.92–7.48)	0.06	NS	NS
Nursing home resident	2 (11.8)	60 (4.2)	3.01 (0.67–13.46)	0.17	–	–
Inadequate source control during i.v. antibiotic course	1 (5.9)	32 (2.3)	2.67 (0.35–20.98)	0.33	–	–
Polymicrobial bacteraemia	3 (17.6)	88 (6.2)	3.23 (0.91–11.45)	0.09	NS	NS
Pitt bacteraemia score ≥4	6 (35.3)	174 (12.3)	**3.89 (1.42–10.64)**	**0.01**	**3.62 (1.29–10.18)**	**0.02**
Bacteraemia source						
Intra-abdominal	5 (29.4)	179 (12.7)	2.88 (1.00–8.26)	0.06	NS	NS
Pneumonia	4 (23.5)	143 (10.1)	2.74 (0.88–8.50)	0.09	NS	NS
Biliary tract	2 (11.8)	144 (10.2)	1.18 (0.27–5.19)	0.69	–	–
Soft tissue	2 (11.8)	104 (7.4)	1.68 (0.38–7.44)	0.36	–	–
Urinary tract	1 (5.9)	565 (40.0)	**0.09 (0.01–0.71)**	**0.004**	**0.14 (0.09–0.99)**	**0.049**
Primary bacteraemia	1 (5.9)	134 (9.5)	0.60 (0.08–4.54)	1.00	–	–
Liver abscess	0 (0)	64 (4.5)	–	1.00	–	–
Major causative micro-organism						
Klebsiella spp.	7 (41.2)	236 (16.7)	**3.49 (1.32–9.27)**	**0.02**	2.46 (0.90–6.71)	0.08
Escherichia coli	3 (17.6)	704 (49.8)	**0.22 (0.06–0.76)**	**0.008**	NS	NS
Streptococcus spp.	2 (11.8)	159 (11.2)	1.05 (0.24–4.65)	1.00	–	–
Staphylococcus aureus	1 (5.9)	108 (7.6)	0.76 (0.10–5.75)	1.00	–	–
ESBL-producing EKP	0 (0)	26 (1.8)	–	1.00	–	–
Ultimately or rapidly fatal co-morbidities (McCabe classification)	9 (52.9)	299 (21.1)	**4.20 (1.61–10.97)**	**0.004**	**3.59 (1.35–9.55)**	**0.01**
Co-morbidities						
Malignancy	7 (41.2)	376 (26.6)	1.93 (0.73–5.11)	0.18	–	–
Hypertension	6 (35.3)	700 (49.5)	0.56 (0.21–1.51)	0.24	–	–
Liver cirrhosis	5 (29.4)	175 (12.4)	2.95 (1.03–8.47)	0.05	NS	NS
Neurological disease	5 (29.4)	303 (21.4)	1.53 (0.53–4.37)	0.43	–	–
Diabetes mellitus	4 (23.5)	539 (38.1)	0.50 (0.16–1.54)	0.22	–	–
Chronic kidney disease	2 (11.8)	238 (16.8)	0.66 (0.15–2.90)	0.58	–	–
Urological disorder	2 (11.8)	131 (9.3)	1.31 (0.30–5.77)	0.67	–	–

OR, odds ratio; CI, confidence interval; i.v., intravenous; ESBL, extended-spectrum β-lactamase; EKP, *E. coli, Klebsiella* spp. and *Proteus mirabilis;* NS, not significant (after processing the backward multivariate regression).

[a] Only variables identified in the univariate analysis with a *P*-value of <0.1 were included in a stepwise and backward multivariable logistic regression model.

* Boldface indicates statistical significance ($P < 0.05$).

treatment for bacteraemia caused by Enterobacteriaceae [11], *Pseudomonas aeruginosa* [12] and Gram-negative bacilli [13] have recently been reported; these causative micro-organisms comprised the majority (>80%) in our original and matched cohorts. Accordingly, based on our results, short-course therapy is a rightfully recommended strategy for overall community-onset bacteraemia.

In the matched cohort, the proportion of major bacteraemia courses was similar between the long- and short-term groups; however, a higher proportion of *E. coli* and a lower proportion of ESBL-producers were observed in the short-course group. Therefore, it was reasonable to administer higher frequencies of 1GCs and 2GCs as well as lower frequencies of carbapenems as definitive therapy. More importantly, the effect of causative micro-organisms with a heterogenous distribution in the matched cohort, such as *E. coli, S. aureus* and ESBL-producing EKP, on patient mortality was trivial in the multivariate analysis. Furthermore, a proportion difference in the aforementioned definitive antimicrobial classes was observed between the two matched groups; discrepancies in the therapeutic efficacy of various antimicrobial classes might result in bias. As in numerous published studies dealing with the clinical benefits of short-course therapy for specific BSIs [8,9,11], administration of in vitro-active antibiotics at an appropriate dosage was emphasised here and it is difficult to assess its influence on the results.

To assess the collateral damage of long-term antimicrobial use and to evaluate the incidence of causative micro-organisms harbouring antibiotic resistance genes that are unusual in the community, this study defined the term ARPs as the rare occurrence of antimicrobial resistance in the community. Indeed, an extremely low incidence rate of the leading two ARPs collected in this cohort, such as ESBL-producing EKP and fluoroquinolone-resistant Enterobacteriaceae, was observed. Accordingly, community-onset bacteraemia was selected as the research target to avoid the influence of ARPs on the clinician's decision to extend the therapeutic course; furthermore, it was reasonable to regard ARP occurrence as one of the patient outcomes after i.v. antimicrobial therapy in the study design.

Several limitations should be considered when interpreting these findings. First, although the reason that clinicians chose a short-term course was not comprehensively obtained and analysed in the present retrospective cohort, we believe a similar response to antimicrobial therapy was exhibited in the long- and short-course groups because the time to defervescence in two groups was not significantly different. Second, because of the limitations of the therapeutic period, several infections that traditionally require long-term i.v. antimicrobial therapy, such as CNS infections, necrotizing soft-tissue infections and infective endocarditis, were excluded. Third, because patients who died during i.v. therapy or who received a longer therapeutic course (>16 days) were excluded from the analysis, we believe that numerous patients with critical illness at bacteraemia onset were not enrolled for PS matching. Therefore, the findings might not be generalisable to critically ill patients upon arrival in the ED. Fourth, the heterogenous distribution of causative micro-organisms between the longer-course and short-course groups was not discussed here, but the impact of antimicrobial resistance on the therapeutic course should be neglected owing to the low prevalence of resistant isolates in the entire cohort. Finally, only 2.3% (33/1431) of patients in the cohort had inadequate source control during antimicrobial therapy, indicating that the majority (1083/1431; 75.7%) of eligible

patients had 'uncomplicated' bacteraemia. Accordingly, we were unable to make inferences on the optimal duration of therapy for patients with inadequate source control. RCTs that rightfully enrol patients to assess this question further are required to elucidate unsolved problems.

5. Conclusions

Focusing on adults with community-onset uncomplicated bacteraemia, this study suggests that 5–10 days of i.v. antibiotic treatment was not associated with either an increased risk of mortality or decreased odds of post-treatment overall and ARP infections compared with longer antibiotic treatment courses. Accordingly, short-course i.v. therapy was safe and the incorporation of such strategies into antibiotic stewardship programmes should be encouraged.

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Competing interests

None declared.

Ethical approval

This study was approved by the Institutional Review Board of National Cheng Kung University Hospital (Tainan, Taiwan) [ER-100-182]. The requirement of obtaining informed consent was waived.

Availability of data and materials

Data are available from the corresponding author on reasonable request.

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