Clinical Benefit of Empiric High-Dose Levofloxacin Therapy for Adults With Community-onset Enterobacteriaceae Bacteremia

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ABSTRACT

Purpose: Levofloxacin is commonly prescribed to treat varied community-acquired gram-negative infections; knowledge of the therapeutic efficacies of high-dose (HD) administration is helpful to improve patient care.

Methods: In this 6-year cohort, adults with community-onset Enterobacteriaceae bacteremia were retrospectively studied in 2 hospitals. To overcome the confounding factors in the dosage choice of empiric administration, patients receiving empiric intravenous HD (750 mg/d) therapy were matched with those receiving the conventional dose (CD; 500 mg/d) by using individual propensity scores, calculated by the independent predictors of 30-day crude mortality.

Findings: Initially, more patients with critical illness (Pitt bacteremia score [PBS] $\geq$4) at bacteremia onset and comorbid malignancies and the higher 15- and 30-day mortality rate were recorded in 136 patients receiving HD therapy, compared to 103 receiving CD therapy. After appropriate matching, differences in patient demographic and clinical characteristics between the HD (n = 103) and CD (n = 103) groups were nonsignificant. Consequently, crude mortality rates at 3, 15, or 30 days after onset of bacteremia did not differ. However, the period of time to defervescence, total intravenous antimicrobial administration, and hospital stay was shorter in the HD group than in the CD group. Similarly, regardless if patients had more critical illness (PBS $\geq$2) or stabilized illness (PBS <2), the advantage of empiric HD therapy on defervescence remained significant. Within 60 days after discontinuation of intravenous levofloxacin therapy, the proportion of recurrent bacteremia, posttreatment overall infections, and posttreatment crude mortality was similar between the HD and CD groups.

Implications: For adults with community-onset Enterobacteriaceae bacteremia, empiric administration of HD levofloxacin was as effective as CD levofloxacin in reducing mortality and, notably, led to more rapid defervescence compared with CD administration. (*Clin Ther*. 2019;41:1996–2007) © 2019 Published by Elsevier Inc.

Key Words: bacteremia, defervescence, empiric therapy, Enterobacteriaceae, high-dose, levofloxacin.

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INTRODUCTION

Bloodstream infections are associated with elevated morbidity and mortality, which results in considerable health care costs.[1] Community-onset bacteremia is a familiar infectious problem with an annual incidence of 0.82%,[2] and it includes various infection types such as urosepsis, pneumonia, soft-tissue infections, and intra-abdominal infections.[3] The Enterobacteriaceae family, particularly *Escherichia coli* and *Klebsiella pneumoniae*, account for the majority of the causative microorganisms in the community-onset bloodstream infections.[4]

Levofloxacin is a broad-spectrum antibiotic that is effective against both gram-negative and gram-positive aerobes.[5] It is used in clinical settings largely because of its potency in treating numerous community-onset infections.[6] Generally, a high-dose (HD), short course of levofloxacin therapy was evidenced for the treatment of patients with community-acquired pneumonia,[7] acute bacterial sinusitis,[8] complicated urosepsis, and acute pyelonephritis.[9] However, for empiric therapy for bacteremia, no clinical report has verified the beneficial effects of an HD therapy (750 mg/d) with levofloxacin, with a conventional dose (CD, 500 mg/d) therapy as the comparators. We therefore compared the therapeutic efficacies of empiric HD and CD levofloxacin in community-onset Enterobacteriaceae bacteremia.

PATIENTS AND METHODS

Study Design

Data for this multicenter cohort were retrospectively collected from January 2010 to December 2015 at emergency departments of 2 hospitals in southern Taiwan. One study hospital is a university-affiliated medical center with 1200 beds and another is a teaching hospital with 800 beds. The study was approved by the Institutional Review Board of National Cheng Kung University Hospital (A-ER-100-182, 5th edition revision), and the requirement of obtaining informed consent was waived. The reporting of the present study was adequate by the format recommended by the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.

Patient Population

Over the 6-year study period, patients having blood cultures sampled during the emergency department stay were screened for bacterial growth by using a computer database. Medical information was retrieved for those adults with the growth of blood cultures. Adult patients (aged $\geq$18 years) with community-onset Enterobacteriaceae bacteremia and empirically received intravenous (IV) levofloxacin therapy were included after exclusion of those having hospital-onset bacteremia. For the remaining patients with multiple episodes of bloodstream infections, only the first episode was considered. To further study the difference in clinical characteristics and outcomes between the HD and CD groups, patients in the levofloxacin group were excluded if they were treated with inappropriate empiric therapy, those having inadequate levofloxacin dosing, or if their clinical information or outcome was incomplete. Consequently, the remaining patients were categorized as the HD and CD groups according to dose administration.

Data Collection

By retrospective review of medical records, all demographic and clinical data were collected in a predetermined case form. Data included age, sex, initial syndrome, laboratory data, and vital signs at the emergency department; bacteremia sources; bacteremia severity (a Pitt bacteremia score) at onset; the duration and type of antimicrobial administration; the length of hospitalization; comorbidities; comorbidity severity (McCabe classification); the date of defervescence; and patient outcomes. The medical records were inspected by 2 authors, and any discrepancy was discussed for collection. The adverse drug reactions (ADRs) of IV levofloxacin administration such as central nervous system (eg, dizziness, headache, delirium, conscious alteration), gastrointestinal (eg, nausea, vomiting, diarrhea), and cardiac (eg, Torsades de pointes) events were collected during IV levofloxacin therapy. The primary and secondary end points were 30-day mortality after bacteremia onset and 60 days after discontinuation of empiric IV levofloxacin therapy, respectively. Early outcomes were measured by using time to defervescence, the length of antimicrobial therapy, the length of hospital stay, and a 30-day crude mortality rate. Within 60 days after discontinuation of empiric IV levofloxacin therapy, late outcomes studied for the 2 groups included recurrent bacteremia, posttreatment overall infections, and posttreatment crude mortality.

Definitions

The episode of bacteremia in the community was diagnosed as community-onset bacteremia,[3,10] which included nursing home or long-term health care facilities. More than one bacterial species isolated from the same episode of the bloodstream infection was regarded as polymicrobial bacteremia.

As with previous descriptions,[3,10] the antibiotic therapy was considered adequate when the following criteria were fulfilled: (1) the route and dosage of antimicrobial agents were administered based on the Sanford Guide[11]; and (2) causative microorganisms were susceptible *in vitro* to the administered antimicrobial agents in accordance with the susceptibility breakpoint of the Clinical and Laboratory Standards Institute issued in 2018.[12] The period between arrival at the emergency department and administration of adequate IV antimicrobial agents was measured as the time to appropriate antibiotic[3]; and the empiric antimicrobial therapy was regarded as appropriate if time to appropriate antibiotic was ≤24 hours.[3,13]

After antimicrobial administration, an afebrile state in which tympanic body temperature was maintained at <37.0 °C for at least 24 hours was defined as defervescence[10]; the period between defervescence and appropriate administration of empiric antimicrobials was defined as time to defervescence. Consistent with previous definitions,[14] the removal of infected hardware, drainage of infected fluid collection, or resolution of obstruction of biliary or urinary sources was considered appropriate control of bacteremia. The Pitt bacteremia score, a previously validated scoring system, was graded for bacteremia severity.[15] Patients having a Pitt bacteremia score ≥4 were regarded as having critical illness. A comorbidity was defined per an previous description,[16] and the severity of comorbid diseases was assessed according to the previously delineated McCabe classification.[17] Recurrent bacteremia was defined as a new episode of the documented bloodstream infection caused by the same microorganism and *in vitro* susceptibility as the index bacteremia episode.

Microbiologic Methods

Enterobacteriaceae were identified by using the Gram-Negative Identification Card in the VITEK 2 system (BioMérieux, Lyon, France). Antimicrobial susceptibilities were assessed by using the disk diffusion method and interpreted based on Clinical and Laboratory Standards Institute breakpoints issued in 2018.[12]

Statistical Analyses

SPSS version 23.0 (IBM SPSS Statistics, IBM Corporation, Armonk, New York) was used for statistical analyses. The Fisher exact test or Pearson χ^2 test was performed for categorical variables, and an independent *t* test or Mann–Whitney test was used for continuous variables. To identify the independent determinant of 30-day mortality, the predictor of 30-day mortality with a *P* value <0.1, recognized by the univariate analysis, was processed in a stepwise and backward logistic regression model. A two-sided *P* value <0.05 was considered significant.

A propensity score–matched analysis was performed to overcome confounding variables in the dosage choice of empiric antimicrobial administration. The propensity score was calculated by using the independent determinants of 30-day crude mortality. Patients empirically receiving HD therapy were manually matched with those receiving CD therapy by using the closest total propensity scores. As with previous descriptions,[18] the matching tolerance for the propensity score difference was $P < 0.2$.

RESULTS

Demographic and Clinical Characteristics of the Study Cohort

Initially, 1985 causative microorganisms in 1888 patients were included in this cohort (Figure 1). Of these microorganisms (Figure 2), most were *E coli* (1243 isolates [62.6%]), followed by *Klebsiella* species (448 [22.6%]), *Enterobacter* species (90 [4.5%]), *Proteus* species (69 [3.5%]), *Salmonella* species (64 [3.2%]), *Morganella morganii* (21 [1.1%]), *Citrobacter* species (18 [0.9%]), *Serratia* species (16 [0.8%]), *Providencia* species (7 [0.4%]), *Pantoea* species (4 [0.2%]), and others (5 [0.3%]). Overall, levofloxacin was active against 76.2%–100.0% of Enterobacteriaceae causing community-onset bacteremia, with an average susceptibility rate of 85.1%.

Based on the inclusion and exclusion criteria (Figure 1), 239 patients empirically receiving IV levofloxacin monotherapy were eligible; the leading

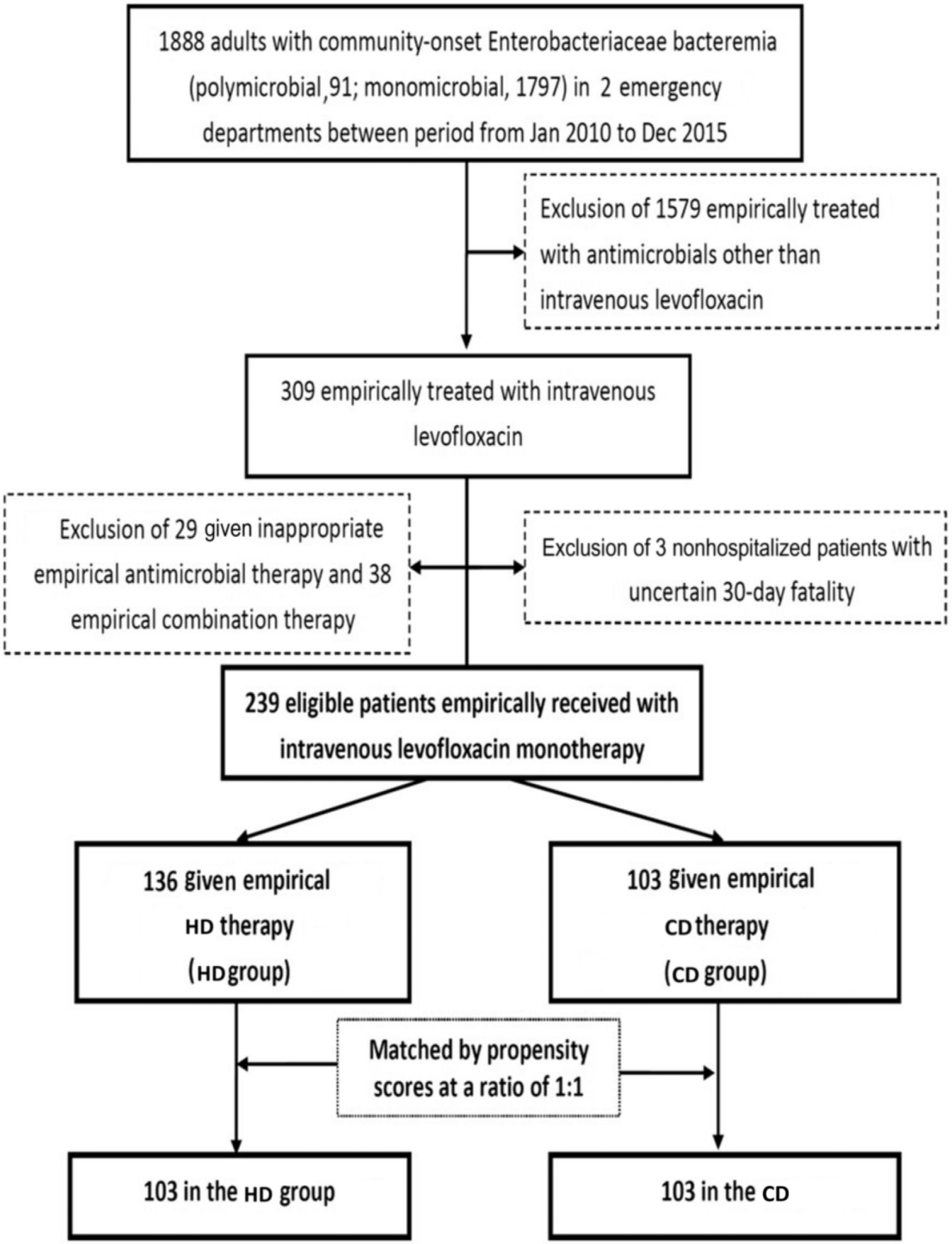

Figure 1. The flowchart of patient selections. CD = conventional dose; HD = high-dose.

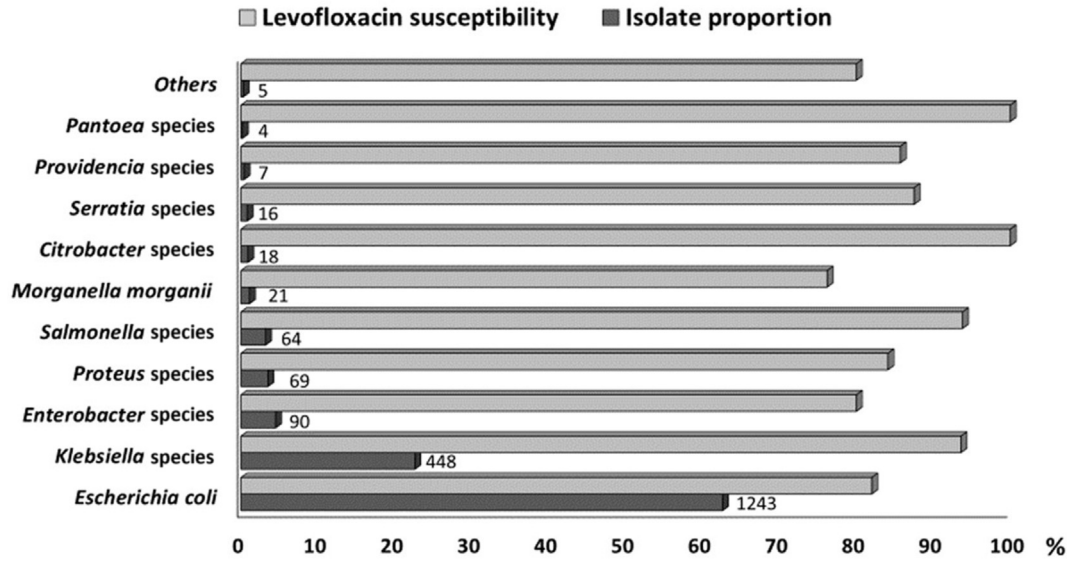

Figure 2. The microorganism proportion and levofloxacin susceptibility of 1985 causative microorganisms in 1888 adults with community-onset Enterobacteriaceae bacteremia. The numeric figures indicate isolate numbers in each pathogen.

comorbidities included hypertension (126 patients [52.7%]), diabetes mellitus (80 [33.5%]), malignancies (80 [33.5%]), chronic kidney diseases (49 [20.5%]), neurologic disorders (37 [15.5%]), liver cirrhosis (23, [9.6%]), coronary artery diseases (22 [9.2%]), and urologic diseases (17 [7.1%]). The most common source of bacteremia was urinary tract infections (93 [38.9%]), followed by biliary tract infections (55 [23.0%]), intra-abdominal infections (45 [18.8%]), primary bacteremia (16 [6.7%]), pneumonia (13 [5.4%]), and liver abscess (11 [4.6%]). The proportion of critically ill patients at bacteremia onset was 9.6% (23 patients), and the 15- and 30-day crude mortality rate was 4.6% (11 patients) and 6.7% (16), respectively. The median (interquartile range) length of IV antimicrobial therapy and hospitalization was 7 (4−11) days and 8.0 (5.2−13.0) days.

Baseline Characteristics in the HD and CD Groups

The 239 eligible patients empirically treated with IV levofloxacin were categorized into the HD (136 patients [56.9%]) and CD (103 patients [43.1%]) groups, as shown in Figure 1. The comparisons between the 2 groups of clinical characteristics recorded at the onset of bacteremia and clinical outcomes are listed in Table 1. Higher frequencies of critical illness (Pitt bacteremia score ≥4) at bacteremia onset and comorbid malignancies, as well as the higher 3-, 15-, and 30-day crude mortality rate, were exhibited in the HD group.

Predictors of 30-Day Mortality

The relationship of clinical variables, including sex, age, bacteremia sources, bacteremia severity, causative microorganisms, comorbidity types, and severity of comorbidities, with 30-day crude mortality was studied according to univariate analysis in 239 patients (Table 2). Several variables were positively associated with 30-day mortality: male sex, inadequate source control, critical illness (Pitt bacteremia score ≥4) at bacteremia onset, a comorbidity of malignancy or liver cirrhosis, a causative microorganism of *Enterobacter* species, and bacteremic pneumonia. In addition, bacteremia due to a urinary tract infection was linked to a better outcome.

Consequently, only 3 significant determinants of 30-day crude mortality—critical illness (Pitt bacteremia score ≥4), comorbid liver cirrhosis, and bacteremic

Table 1. Clinical characteristics and mortality rates of the high-dose (HD) and conventional dose (CD) groups in overall and matched cohorts.

Characteristic	Patient No. (%)					
	Overall Cohort			Matched Cohort		
	HD Group (n = 136)	CD Group (n = 103)	*P*	HD Group (n = 103)	CD Group (n = 103)	*P*
Male sex	50 (36.8%)	45 (43.7%)	0.28	36 (35.0%)	45 (43.7%)	0.20
Elderly (age ≥65 y)	81 (59.6%)	63 (61.2%)	0.80	57 (55.3%)	63 (61.2%)	0.40
Nursing home residents	3 (2.2%)	4 (3.9%)	0.45	2 (1.9%)	4 (3.9%)	0.68
Polymicrobial bacteremia	8 (5.9%)	3 (2.9%)	0.36	5 (4.9%)	3 (2.9%)	0.72
Length of levofloxacin therapy, mean (SD)	3.4 (1.7)	3.9 (2.3)	0.06	3.6 (1.6)	3.9 (2.3)	0.10
Pitt bacteremia score ≥4 at onset	18 (13.2%)	5 (4.9%)	0.03	7 (6.8%)	5 (4.9%)	0.55
Inadequate source control during antimicrobial therapy	2 (1.5%)	3 (2.9%)	0.65	1 (1.0%)	3 (2.9%)	0.62
Fatal comorbidity (McCabe classification)	24 (17.6%)	19 (18.4%)	0.87	13 (12.6%)	19 (18.4%)	0.25
Major comorbidity						
Hypertension	72 (52.9%)	54 (52.4%)	0.94	57 (55.3%)	54 (52.4%)	0.68
Malignancy	54 (39.7%)	26 (25.2%)	0.02	28 (27.2%)	26 (25.2%)	0.75
Diabetes mellitus	40 (29.4%)	40 (38.8%)	0.13	28 (27.2%)	40 (38.8%)	0.08
Chronic kidney diseases	26 (19.1%)	23 (22.3%)	0.54	22 (21.4%)	23 (22.3%)	0.87
Neurologic diseases	17 (12.5%)	20 (19.4%)	0.14	13 (12.6%)	20 (19.4%)	0.18
Liver cirrhosis	17 (12.5%)	6 (5.8%)	0.08	9 (8.7%)	6 (5.8%)	0.42
Coronary artery diseases	12 (8.8%)	10 (9.7%)	0.82	9 (8.7%)	10 (9.7%)	0.81
Urologic disorders	11 (8.1%)	6 (5.8%)	0.50	10 (9.7%)	6 (5.8%)	0.30
Major bacteremia sources						
Urinary tract infections	53 (39.0%)	40 (38.8%)	0.98	44 (42.7%)	40 (38.8%)	0.57
Biliary tract infections	34 (25.0%)	21 (20.4%)	0.40			
Intra-abdominal infections	27 (19.9%)	18 (17.5%)	0.64	20 (19.4%)	18 (17.5%)	0.72
Primary bacteremia	8 (5.9%)	8 (7.8%)	0.56	3 (2.9%)	8 (7.8%)	0.12
Pneumonia	7 (5.1%)	6 (5.8%)	0.82	5 (4.9%)	6 (5.8%)	0.75
Crude mortality rate						
3-day	7 (5.1%)	0	0.02	2 (1.9%)	0	0.50
15-day	11 (8.1%)	0	0.003	3 (2.9%)	0	0.25
30-day	14 (10.3%)	2 (1.9%)	0.01	3 (2.9%)	2 (1.9%)	1.00

pneumonia—were shown in the multivariate regression model (Table 2).

Clinical Characteristics and Outcomes of the Matched Patients

Of the 136 patients empirically receiving HD levofloxacin therapy, 103 patients were matched with 103 patients in the CD group, with the closest propensity scores using 3 independent determinants of crude mortality. After adequate matching (Table 1), no significant differences in patient proportions were noted between the HD and CD groups in terms of elderly age, sex, nursing home residence, empiric combination therapy, bacteremia severity, major comorbidities, comorbidity severity, and bacteremia sources. Of note, similarity of length

Table 2. Risk factors of 30-day crude mortality.

Variable	No. (%) of Patients		Univariate Analysis		Multivariate Analysis	
	Death (n = 16)	Survival (n = 223)	OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*
Male sex	11 (68.8)	84 (37.7)	3.64 (1.22−10.84)	0.001	NS	NS
Inadequate source control during antimicrobial therapy	2 (12.5)	3 (1.3)	10.48 (1.62−67.90)	0.04	11.16 (0.85−147.34)	0.07
Comorbidities						
Malignancy	11 (68.8)	69 (30.9)	4.91 (1.64−14.67)	0.002	NS	NS
Liver cirrhosis	4 (25.0)	19 (8.5)	3.58 (1.05−12.19)	0.05	9.44 (1.67−53.42)	0.01
Pitt bacteremia score ≥4 at onset	9 (56.3)	14 (6.3)	19.19 (6.22−59.19)	<0.001	17.14 (3.93−74.71)	<0.001
Causative microorganism of *Enterobacter* species	3 (18.8)	11 (4.9)	4.45 (1.10−17.93)	0.06	5.88 (0.85−40.79)	0.07
Bacteremia sources						
Pneumonia	5 (31.3)	8 (3.6)	12.22 (3.43−43.55)	<0.001	14.56 (2.27−93.32)	0.005
Urinary tract infections	0	93 (41.7)	—	0.001	NS	NS

NS = not significant (after processing backward multivariate regression); OR = odds ratio.

of empiric levofloxacin administration and the 3-, 15-, and 30-day crude mortality rates between the 2 matched groups was observed.

An extreme low proportion of ADRs during empiric administration of IV levofloxacin was observed in the matched cohort. The leading ADRs were central nervous system events (4 patients [1.9%]), followed by gastrointestinal events (2 patients [1.0%]). Notably, the similarity of varied ADRs, in terms of central nervous system (HD vs CD, 3 of 103 [2.9%] vs 1 of 103 [1.0%]; $P = 0.62$) and gastrointestinal events (HD vs CD, 1 of 103 [1.0%] vs 1 of 103 [1.0%]; $P = 1.00$), was shown between the HD and CD groups.

For early outcomes, the mean period of the time to defervescence (4.0 vs. 7.1 days; $P < 0.001$), total IV antibiotic therapy (6.3 vs 11.5 days; $P < 0.001$), and hospital stays (7.6 vs 13.7 days; $P < 0.001$) were shorter in the HD group than in the CD group (Figure 3A). Focusing on the late outcome, the patient proportion of recurrent bacteremia (HD vs CD, 0 of 103 [0%] vs 2 of 103 [1.9%]; $P = 0.50$), the posttreatment overall infection rate (HD vs CD, 2 of 103 [1.9%] vs 5 of 103 [4.9%]; $P = 0.45$), and the posttreatment crude mortality rate (HD vs CD, 2 of 103 [1.9%] vs 4 of 103 [3.9%]; $P = 0.68$) were similar between the 2 groups.

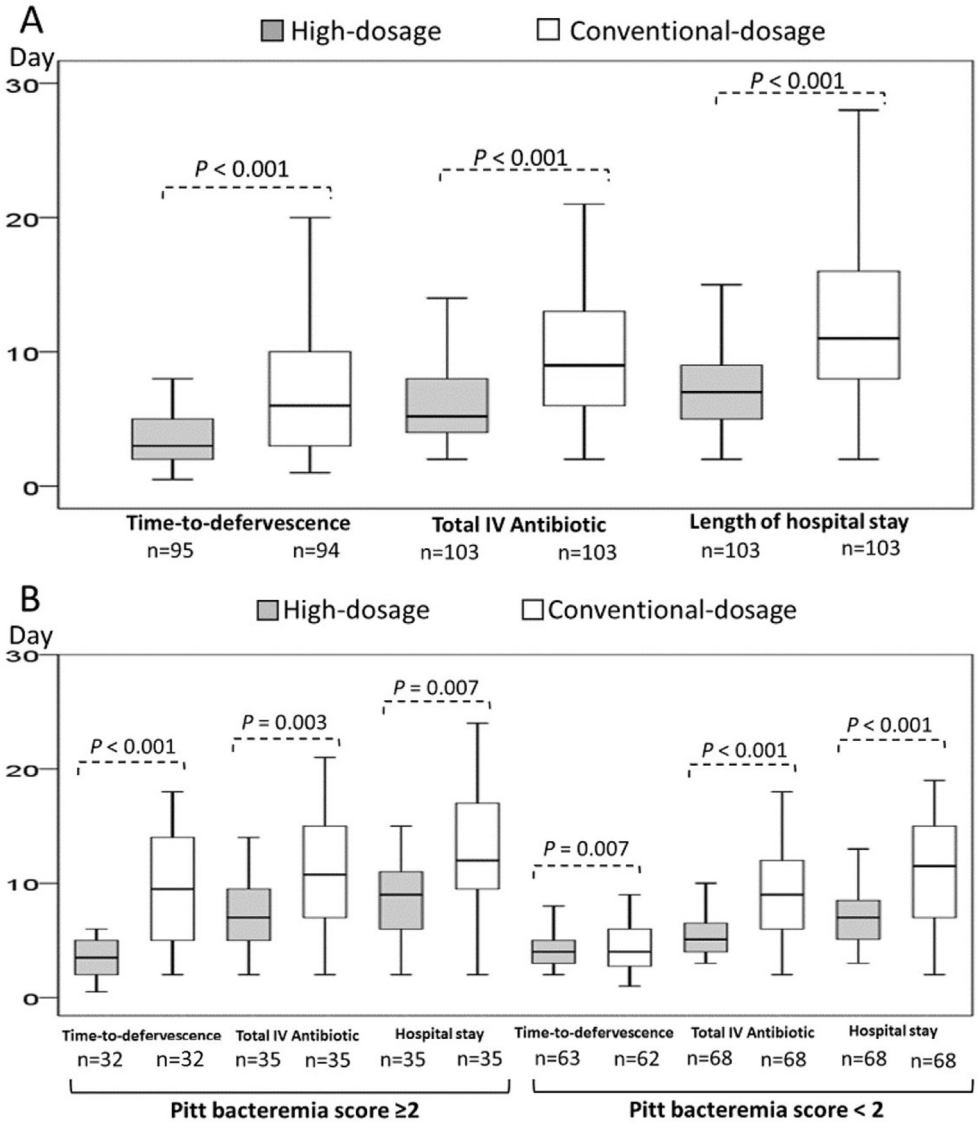

Figure 3. Boxplots of intravenous (IV) high-dose (HD) or conventional dose (CD) levofloxacin for comparisons of the time to defervescence, length of hospital stay, and IV antimicrobial therapy in (A) all matched adults and (B) subgroups having more critical illness (Pitt bacteremia score $\geq$4) and stabilized illness (Pitt bacteremia score <2) at bacteremia onset.

Clinical Characteristics and Outcomes of the Matched Subgroups

The 206 matched patients were categorized into the more critically ill (Pitt bacteremia score $\geq$2, a total of 70 patients) and stabilized (Pitt bacteremia score <2, a total of 136 patients) subgroups. Within the 2 severity subgroups, no significant differences in the major proportion were noted between the HD and CD patients, in terms of elderly age, sex, nursing home residence, bacteremia severity, major comorbidities, comorbidity severity, bacteremia sources, and crude mortality rates (Table 3). The

Table 3. Clinical characteristics and outcomes of the high-dose (HD) and conventional dose (CD) groups in the matched cohort with more critical illness (Pitt bacteremia score ≥2) and stabilized illness (Pitt bacteremia score <2). Values are given as no. (%) of patients.

Characteristics	Pitt Bacteremia Score ≥2			Pitt Bacteremia Score <2		
	HD Group (n = 35)	CD Group (n = 35)	*P*	HD Group (n = 68)	CD Group (n = 68)	*P*
Male sex	15 (42.9)	15 (42.9)	1.00	21 (30.9)	30 (44.1)	0.11
Elderly (age ≥65 y)	20 (57.1)	20 (57.1)	1.00	37 (54.4)	43 (63.2)	0.30
Nursing home residents	1 (2.9)	2 (5.7)	1.00	1 (1.5)	2 (2.9)	1.00
Polymicrobial bacteremia	2 (5.7)	0	0.49	3 (4.4)	3 (4.4)	1.00
Fatal comorbidity (McCabe classification)	8 (22.9)	9 (25.7)	0.78	5 (7.4)	10 (14.7)	0.17
Major comorbidities						
Hypertension	18 (51.4)	17 (48.6)	0.84	39 (57.4)	37 (54.4)	0.73
Malignancy	12 (34.3)	10 (28.6)	0.61	16 (23.5)	16 (23.5)	1.00
Diabetes mellitus	10 (28.6)	13 (37.1)	0.45	18 (26.5)	27 (39.7)	0.10
Neurologic diseases	7 (20.0)	5 (14.3)	0.53	6 (8.8)	15 (22.1)	0.03
Chronic kidney diseases	5 (14.3)	8 (22.9)	0.36	17 (25.0)	15 (22.1)	0.69
Liver cirrhosis	2 (5.7)	2 (5.7)	1.00	7 (10.3)	4 (5.9)	0.35
Major bacteremia sources						
Urinary tract infections	15 (42.9)	18 (51.4)	0.47	29 (42.6)	22 (32.4)	0.22
Biliary tract infections	7 (20.0)	3 (8.6)	0.17	14 (20.6)	18 (26.5)	0.42
Intra-abdominal infections	4 (11.4)	4 (11.4)	1.00	16 (23.5)	14 (20.6)	0.68
Pneumonia	3 (8.6)	2 (5.7)	1.00	2 (2.9)	4 (5.9)	0.68
Primary bacteremia	2 (5.7)	3 (8.6)	1.00	5 (7.4)	5 (7.4)	1.00
Crude mortality rate						
7-day	3 (8.6)	0	0.24	0	0	1.00
30-day	3 (8.6)	0	0.24	0	2 (2.9)	0.50

dissimilar proportion between the HD and CD groups was only exhibited in comorbid neurologic disease among the more stabilized subgroup.

Regardless of the more critically ill and stabilized subgroups, a shorter period of time to defervescence, total IV antibiotic therapy, and hospital stays was reported in the HD group compared with the CD group (Figure 3B). Furthermore, a significant difference in time to defervescence was also found between the HD and CD groups, according to Kaplan–Meier curves for febrile patients in the more critically ill and stabilized subgroups (Figure 4).

DISCUSSION

Generally, HD levofloxacin therapy for various community-acquired infections has decreased hospital stay duration and medical costs.[19] This multicenter cohort including a long-term period and patients with varied dosage administration was therefore performed. Because patients with a less critical illness at bacteremia onset were more likely to receive empiric HD levofloxacin than CD levofloxacin, we performed propensity score matching to overcome this potential bias. After appropriate matching, no differences in clinical characteristics, particularly in bacteremia and comorbidity severity, and thereby clinical outcome were similarly observed between the 2 groups; however, time to defervescence and the length of IV antimicrobial administration and hospital stay were shorter in patients given empiric HD levofloxacin than in those given CD levofloxacin. In further analyses of the severity

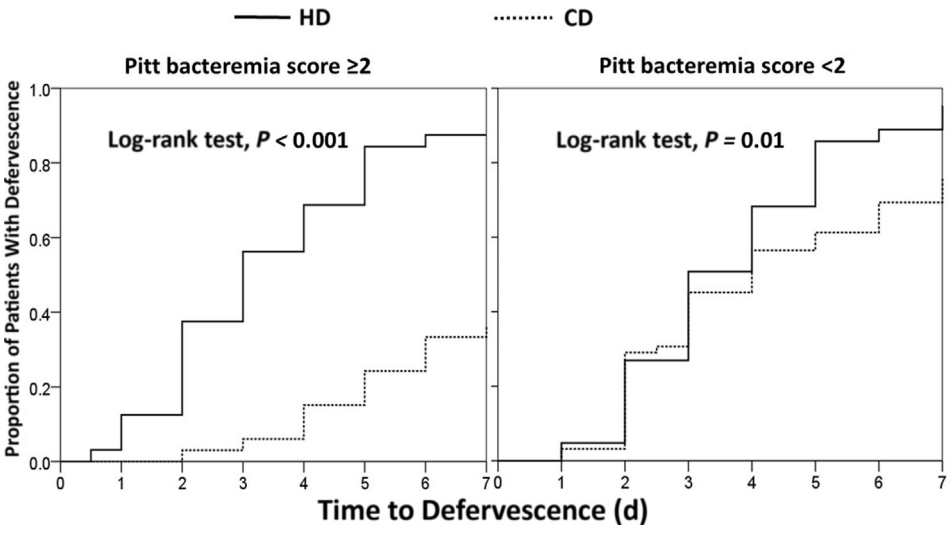

Figure 4. Kaplan–Meier curves of time to defervescence in 203 survivors within 1 week after bacteremia onset who were empirically treated with intravenous high-dose (HD) or conventional dose (CD) levofloxacin in subgroups with more critical illness (Pitt bacteremia score $\geq$2) and stabilized illness (Pitt bacteremia score <2).

subgroups (ie, more critically ill and stabilized patients), the advantage of empiric HD administration on rapid defervescence and the length of hospitalization remained significant.

Levofloxacin is a concentration-dependent bactericidal agent; thus, therapeutic success is linked to AUC/MIC and C_{max}/MIC rather than to time of concentration greater than the MIC.[19] In addition, a high C_{max}/MIC is associated with a shorter treatment duration without compromising efficacy, thereby preventing resistance to infection. Consequently, an HD, short-course paradigm decreases the total concentration of antimicrobials to which causative microorganisms are unnecessarily exposed; this has been tested and verified for numerous infection types. In the present study, the notable association of a high C_{max}/MIC and therapeutic success might also be established, as indicated by a rapid defervescence time. Importantly, consistent with HD, short-course reports in which the short length of levofloxacin therapy was prospectively adopted in the study design,[7,8] the rapid defervescence time after empiric HD levofloxacin therapy rightfully resulted in a shorter duration of IV antibiotic administration and hospital stay.

Despite levofloxacin resistance emerging in the community,[5,6] the susceptibility to levofloxacin remained >80% for the species of Enterobacteriaceae family in the community-onset bloodstream infections studied here, which is consistent with studies in Taiwan and the Asia–Pacific region.[20,21] Thus, it is reasonable to administer levofloxacin as an initial antimicrobial agent to treat community-onset bacteremia for rapid defervescence time and shorter hospital stay. However, these advantages of levofloxacin therapy should be interpreted cautiously, because numerous patients with critical illness at bacteremia onset and fatal patients were excluded under the processing of propensity score matching; accordingly, the matched patients were not representative of the entire population in a community.

This study has several limitations. First, to achieve impartial comparisons between HD and CD therapy, patients having incomplete clinical data and those who received inadequate empiric therapy were excluded. However, only a minor proportion of the entire cohort was excluded; this bias was considered to have a negligible influence on our results. Second, adverse events due to IV administration (eg, phlebitis)

or levofloxacin itself (eg, dizziness, nausea, headache) were not analyzed in this study. However, we believe that these events may result in an increased length of antibiotic therapy and hospital stay. Thus, the length of hospital stay was also analyzed as a parameter to assess the efficacy of antibiotic therapy. Finally, because of the short-course administration of empiric levofloxacin, the disadvantages of HD levofloxacin prescription on promoting bacterial resistance or *Clostridium difficile* infections were not evaluated; these topics warrant further clinical investigations. However, the HD expenses resulting in a rapid defervescence time and early discharge were herein demonstrated.

CONCLUSIONS

Regardless of more critically ill and stabilized patients, the survival outcome with HD levofloxacin therapy was similar to that of CD therapy. However, HD levofloxacin resulted in more rapid defervescence and shorter hospitalization for adults having community-onset Enterobacteriaceae bacteremia.

DISCLOSURES

This study was funded by several institutions and hospitals. These study sponsors did not participate in the collection, analysis, and interpretation of data; in the writing of the manuscript; or in the decision to submit the manuscript for publication. All authors have indicated that they have no conflicts of interest regarding the content of this article.

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Drs. C.-C. Lee, Ko, and Tang conceived the study idea and designed the study. Drs. C.-C. Lee, Hsieh, and Yang provided methodologic and statistical advice on study design and data analysis. Dr. C.-C. Lee drafted the manuscript. Drs. Ko and Tang revised it carefully from a professional point of view. Drs. C.-C. Lee, Yang, C.-H. Lee, Hsieh, and Hong supervised the data collection and chart reviews, and all authors read and approved the final manuscript.

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