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Original Article

Predictors of time to appropriate antibiotics for septic patients in intensive care units

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Abstract: This study assessed the amount of time that passed from diagnosis of sepsis to first administration of an appropriate antibiotic (TDFAA, hours). The aim of this study was to determine potential factors that affect TDFAA in patients admitted to intensive care units (ICUs), secondary to sepsis. Retrospective medical data and outcomes of patients with sepsis were assessed. Study outcomes included hospital and ICU mortality rates and morbidity severity, using factors such as ICU stay and duration of vasopressor use. Multivariate linear regression with stepwise model selection was performed to investigate factors associated with TDFAA. A total of 541 patients were included. Percentages of polymicrobial infections and multidrug-resistant organisms were higher with TDFAA of 24-48 hours than any other TDFAA (all $P<0.001$). Percentages of patients with prior antibiotic exposure were higher with TDFAA of 1-24 hours than any other TDFAA. Duration of previous antibiotic use was also significantly higher with TDFAA of >48 hours than any other TDFAA. After adjusting for other factors identified in stepwise model selection, TDFAA was longer in patients with multidrug-resistant organisms, septic shock, and increased Charlson comorbidity scores, as well as those on mechanical ventilation. Multidrug-resistant bacterial infections, comorbidities, mechanical ventilation, and septic shock were independent predictors of TDFAA. Therefore, careful administration, determination, and selection of antibiotic therapy are warranted for patients based on comorbidities and ventilator use, as well as the presence of septic shock.

Keywords: Antibiotics, ICU, sepsis, appropriate

Introduction

Severe sepsis affects multiple organ systems and is often observed in various environments [1]. Early, immediate, and appropriate antibiotic therapy is necessary to treat sepsis [2, 3]. Current guidelines for sepsis include the Surviving Sepsis Campaign that began in 2004 and was updated in 2017 [2, 4-6]. According to the Surviving Sepsis Campaign, two major treatment guidelines include obtaining blood collections prior to antibiotics and aiming to administer broad-spectrum antibiotics within 1 hour of recognizing septic shock or severe sepsis without septic shock [2, 4, 6].

Timing of antibiotic administration is important in treating severe infections. Without timely treatment, patient outcomes significantly worsen, including hospital mortality and length of stay [7]. Recent antibiotic exposure within the last 3 months, drug intolerances, and pathogen susceptibility patterns in different environments are factors that affect sepsis treatment [6]. Kumar et al. found that mortality was time-dependent, as survival was reduced by 7.6% with each 1-hour delay in administering appropriate antibiotics to patients with severe sepsis [4, 8]. Moreover, administration of appropriate antibiotic therapy for sepsis is defined as sufficiently dosed antibiotic treatment covering the causative microorganism [9].

Previous studies have demonstrated that inappropriate antibiotic use for sepsis could lead to the emergence of multidrug-resistant (MDR) organisms [10-12]. Patients with septic shock have a five-fold increased mortality rate if in-

appropriate antibiotics are initiated [11]. Thus, administering inappropriate antibiotic therapy could lead to nosocomial infections, increasing incidence of resistant bacteria in intensive care units (ICUs), with poorer outcomes [13].

This study assessed the amount of time that passed from diagnosis of sepsis to administration of the first appropriate antibiotic (TDFAA, hours). This study aimed to determine possible factors that affect TDFAA in patients admitted to the ICU, secondary to sepsis.

Patients and methods

Study and patients

This retrospective study assessed medical data and outcomes of patients with sepsis, treated at the Taipei Tzu Chi Hospital, from January 1, 2014, to December 31, 2016. Initial antibiotic use, sepsis severity scores, infection type, and other clinical data were obtained from medical charts. The Taipei Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Institutional Review Board approved this study on September 6, 2017 (protocol: 06-X21-082).

Patient selection

Patients were included if they had culture-positive sepsis and were admitted to the medical ICU. Electronic medical records were screened to identify ICD-9-CM (785.52, 995.91, 995.92) and ICD-10-CM codes (A41, R65.20, R65.21). Sepsis was redefined as life-threatening organ dysfunction because of a dysregulated host response to infection.

Inclusion criteria were sepsis diagnosis, medical ICU admission, and acute ≥2-point change in total SOFA scores, attributable to infection [14]. All included patients had documented infections (clinically identified infection type, clinical symptoms/signs compatible with pathogen culture results, and antibiotic susceptibility results).

Exclusion criteria included acute SOFA changes <2 points, systemic inflammatory response not microbe-induced (acute pancreatitis, burns, trauma, etc.), tuberculosis, viral or fungal infections [15], infection after admission (i.e., new infection >48 hours after admission), and not administered an appropriate antibiotic before death. Patients that were administered appropriate antibiotics but uncertainty existed regarding whether the antibiotic was adequate were also excluded (e.g., MDR *Pseudomonas aeruginosa* [MDR-PA] for <14 days).

The following septic shock definition was used: sepsis with persisting hypotension requiring vasopressors to maintain a mean arterial pressure ≥65 mmHg and serum lactate >2 mmol/L (18 mg/dL) despite adequate volume resuscitation [14].

Antibiotic administration and determination of appropriate treatment

Antibiotics were administered by the end of the first hour after sepsis diagnosis but before ICU admission. Chosen antibiotics were reassessed within 30 minutes of ICU admission. Antibiotic selection was based on 2012 International Guidelines for Management of Severe Sepsis and Septic Shock [6]. The choice of empirical antimicrobial therapy depended on complex issues, including patient history, drug intolerances, recent antibiotic administration within 3 months, underlying diseases, clinical syndrome, pathogen susceptibility patterns in the laboratory data, and bacteria previously documented to colonize/infect. For patients with severe infections, including respiratory failure and septic shock, combination therapies with an extended-spectrum beta-lactam and an aminoglycoside or a fluoroquinolone for PA bacteremia were administered. Patients with septic shock from bacteremia with *Streptococcus pneumoniae* were administered a beta-lactam and macrolide combination. Antibiotics were deemed appropriate if the etiologic organism was sensitive to the therapeutic agent, per susceptibility testing results available 2-5 days after collection [16].

Following Clinical and Laboratory Standards Institute guidelines, all pathogens were tested to determine the minimum inhibitory concentration of the antibiotic through qualitative interpretation (susceptible, intermediate, resistant) using VITEK®2 (bioMérieux, Lyon, France). Furthermore, α- and β-hemolytic streptococci and *Haemophilus influenzae* were tested using BBL™ Sensi-Disc™ susceptibility test disks, following manufacturer instructions (Becton Dickinson and Company, Franklin Lakes, NJ, USA). MDR pathogens were confirmed twice using Sensi-Disc™ susceptibility test disks.

Table 1. Comparison of TDFAA groups regarding pathogens and resistance phenotypes

	TDFAA				*P*-value
	≤1 h (N=326)	1-24 h (N=92)	24-48 h (N=74)	>48 h (N=49)	
Gender					0.823
Female	148 (45.4%)	43 (46.74%)	38 (51.35%)	22 (44.9%)	
Male	178 (54.6%)	49 (53.26%)	36 (48.65%)	27 (55.1%)	
Pathogens					
Acinetobacter species	20 (6.13%)	9 (9.78%)	15 (20.27%)	5 (10.2%)	0.002*
Citrobacter koseri	6 (1.84%)	1 (1.09%)	2 (2.7%)	1 (2.04%)	0.833
Enterobacter species	7 (2.15%)	1 (1.09%)	2 (2.7%)	2 (4.08%)	0.632
Enterococcus faecalis	9 (2.76%)	5 (5.43%)	5 (6.76%)	4 (8.16%)	0.106
Enterococcus faecium	4 (1.23%)	8 (8.7%)	8 (10.81%)	3 (6.12%)	<0.001*
Escherichia coli	76 (23.31%)	34 (36.96%)	14 (18.92%)	9 (18.37%)	0.017*
Haemophilus influenza	15 (4.6%)	1 (1.09%)	3 (4.05%)	0 (0%)	0.234
Klebsiella species	61 (18.71%)	18 (19.57%)	17 (22.97%)	13 (26.53%)	0.561
Other streptococcal species	34 (10.43%)	5 (5.43%)	3 (4.05%)	2 (4.08%)	0.115
Proteus species	9 (2.76%)	3 (3.26%)	3 (4.05%)	3 (6.12%)	0.498
Pseudomonas aeruginosa	48 (14.72%)	25 (27.17%)	15 (20.27%)	9 (18.37%)	0.048*
Staphylococcus aureus	59 (18.1%)	18 (19.57%)	14 (18.92%)	15 (30.61%)	0.241
Streptococcus pneumonia	22 (6.75%)	1 (1.09%)	2 (2.7%)	2 (4.08%)	0.115
Polymicrobial	60 (18.4%)	50 (54.35%)	38 (51.35%)	22 (44.9%)	<0.001*
Multidrug-resistant organisms					<0.001*
No	287 (88.04%)	45 (48.91%)	19 (25.68%)	18 (36.73%)	
Yes	39 (11.96%)	47 (51.09%)	55 (74.32%)	31 (63.27%)	
Resistance phenotypes					
Aminoglycoside resistant GNB	6 (1.84%)	0 (0%)	0 (0%)	1 (2.04%)	0.418
Carbapenem-resistant GNB	7 (2.15%)	7 (7.61%)	9 (12.16%)	2 (4.08%)	0.001*
Cefepime-resistant GNB	0 (0%)	3 (3.26%)	1 (1.35%)	0 (0%)	0.015*
Ciprofloxacin-resistant GNB	18 (5.52%)	13 (14.13%)	4 (5.40%)	5 (10.2%)	0.033
Extended-spectrum beta-lactamase resistant GNB	13 (3.99%)	27 (29.35%)	25 (33.78%)	14 (28.57%)	<0.001*
Methicillin-resistant *S. aureus*	14 (4.29%)	10 (10.87%)	12 (16.22%)	12 (24.49%)	<0.001*
Multidrug-resistant GNB	9 (2.76%)	4 (4.35%)	11 (14.86%)	3 (6.12%)	0.001*
Vancomycin-resistant enterococci	1 (0.31%)	4 (4.35%)	7 (9.46%)	3 (6.12%)	<0.001*

*P<0.05, represents significant differences among TDFAA groups; GNB, gram-negative bacteria.

Definition of parameters potentially influencing outcomes

Severity was evaluated using APACHE II and sequential organ failure assessment (SOFA) scores upon ICU admission.

Patient data were recorded and defined as follows. Sepsis was defined as acquiring sepsis at home or acquiring in a healthcare facility/nursing home, during a recent hospitalization within 90 days, or while undergoing chemotherapy or intravenous injections at a hospital, large wound care, or recent hemodialysis within 30 days.

"Time between diagnosis of sepsis and first appropriate antibiotic" was recorded in hours and appropriate antibiotics were administered within hours. Otherwise, reevaluation regarding appropriate antibiotics was performed after the culture results were available 2-5 days later.

Polymicrobial infections were defined as culture results indicating the presence of more than one bacterial species. MDR organisms included MDR gram-negative bacteria (MDR-GNB), vancomycin-resistant enterococci (VRE), and methicillin-resistant *Staphylococcus aureus* (MRSA). MDR-GNB were defined as acquired non-susceptibility to at least one of three or more antimicrobial GNB categories [17].

"Previous antibiotics exposure" was defined as at least one 7-dayantibiotic treatment within 90 days before sepsis admission.

Table 2. Comparison of TDFAA groups regarding previous antibiotic exposure and types of infection

	TDFAA				*P*-value
	≤1 h (N=326)	1-24 h (N=92)	24-48 h (N=74)	>48 h (N=49)	
Previous antibiotic exposure (90 days)					<0.001*
No	237 (72.7%)	43 (46.74%)	49 (66.22%)	28 (57.14%)	
Yes	89 (27.3%)	49 (53.26%)	25 (33.78%)	21 (42.86%)	
Durations of previous antibiotic use (days)	2.4 ± 4.41	6.08 ± 6.57†	4.74 ± 7.3†	8.39 ± 11.53†,‡	<0.001*
Previous antibiotics exposure (groups)					<0.001*
No previous antibiotics	237 (72.7%)	43 (46.74%)	49 (66.22%)	28 (57.14%)	
Narrower spectrum	61 (18.71%)	24 (26.09%)	11 (14.86%)	8 (16.33%)	
Broad spectrum	28 (8.59%)	25 (27.17%)	14 (18.92%)	13 (26.53%)	
Types of infection					<0.001*
Non-iatrogenic infection	132 (40.49%)	19 (20.65%)	23 (31.08%)	7 (14.29%)	
Iatrogenic infection	194 (59.51%)	73 (79.35%)	51 (68.92%)	42 (85.71%)	

*P<0.05, represents significant differences among TDFAA groups; †P<0.05, represents significant differences with TDFAA ≤1 h group; ‡P<0.05, represents significant differences with TDFAA 24-48 h group.

"Duration of previous antibiotic use" was defined and recorded as the total number of days that a patient had been administered antibiotics within 90 days before sepsis admission.

Previous antibiotics exposure and antibiotic categories were classified as follows: narrower-spectrum antibiotics (penicillin G, penicillin V, cephalexin, cephazoline, ampicillin/sulbactam, cefmetazole, cefaclor, cefuroxime, amoxicillin/clavulanate, ampicillin, amoxicillin, and ciprofloxacin) and broad-spectrum antibiotics (ceftriaxone, ceftazidime, carbenicillin, ticarcillin, levofloxacin, piperacillin/tazobactam, carbapenem, cefepime, cefpirome, and moxifloxacin) [18].

Statistical analysis

Continuous variables are presented as mean/standard deviation. One-way ANOVA was performed to compare differences among different TDFAAs. TDFAAs were divided into four groups: TDFAA, ≤1 hour, TDFAA, 1-24 hours, TDFAA, 24-48 hours, and TDFAA, >48 hours. Categorical variables are presented as counts and percentages, with Chi-squared or Fisher's exact tests for group comparisons, as appropriate. Multivariate linear regression analysis with stepwise model selection was performed to investigate factors associated with TDFAA. Factors with significant TDFAA association were included in the multivariable models and identified using stepwise model selection methods for the final model. Statistical analyses were performed using at least two statistical analysis tools. Two-tailed P<0.05 indicates statistical significance.

Results

Comparison of pathogens and resistance phenotypes

Table 1 shows comparison of TDFAAs for pathogens and resistance phenotypes for the 541 total patients.

Acinetobacter species, *Enterococcus faecium*, *E. coli*, and PA demonstrated significant differences among TDFAA groups. Percentages of *Acinetobacter* species and *E. faecium* were higher for TDFAA of 24-48 hours than any other TDFAA. Percentages of *E. coli* and PA were higher with TDFAA of 1-24 hours than other TDFAAs.

Polymicrobial infection was higher with TDFAA of 1-24 hours than any other TDFAA. A higher distribution of patients with polymicrobial infections and MDR organisms existed in the delayed TDFAA groups, especially 24-48 hours. As for resistance phenotypes, significant differences existed among TDFAA groups with carbapenem resistance (GNB bacteria, cefepime-resistant GNB, ESBL-resistant GNB, MRSA, MDR-GNB, and VRE). Patients with TDFAA of 24-48 hours had higher percentages of carbapenem-resistant GNB. Percentages of ESBL-resistant GNB were lower with TDFAA of ≤1 hour than any other TDFAA. MRSA gradually increased as TDFAA increased. Patients with TDFAA of 24-48

Table 3. Comparison of TDFAA groups regarding comorbidity, organ dysfunction, and severity of disease

	TDFAA				*P*-value
	≤1 h (N=326)	1-24 h (N=92)	24-48 h (N=74)	>48 h (N=49)	
Charlson comorbidity score	3.32 ± 2.22	3.75 ± 2.81	4.04 ± 2.33	5.61 ± 2.91†,‡,§	<0.001*
Multiorgan dysfunction					0.033*
No organ failure	39 (11.96%)	8 (8.7%)	6 (8.11%)	2 (4.08%)	
One organ failure	117 (35.89%)	31 (33.7%)	21 (28.38%)	10 (20.41%)	
Two organ failures	101 (30.98%)	29 (31.52%)	29 (39.19%)	15 (30.61%)	
More than three organ failures	69 (21.17%)	24 (26.09%)	18 (24.32%)	22 (44.9%)	
Disease severity					
APACHE II	24.53 ± 6.58	26.85 ± 7.04†	26.12 ± 6.05	29.73 ± 6.23†,§	<0.001*
SOFA Score	6.74 ± 3.19	6.96 ± 2.77	7.03 ± 3.04	8.55 ± 3.81†,‡	0.003*
Quick SOFA					0.457
0	27 (8.28%)	8 (8.7%)	3 (4.05%)	0 (0%)	
1	115 (35.28%)	30 (32.61%)	26 (35.14%)	14 (28.57%)	
2	130 (39.88%)	36 (39.13%)	29 (39.19%)	23 (46.94%)	
3	54 (16.56%)	18 (19.57%)	16 (21.62%)	12 (24.49%)	
Lactate (mmol/L)	2.57 ± 2.6	2.25 ± 2.17	2.25 ± 2.29	3.56 ± 4.35‡	0.032*
Septic shock (included lactate)					0.043*
No	235 (72.09%)	68 (73.91%)	53 (71.62%)	26 (53.06%)	
Yes	91 (27.91%)	24 (26.09%)	21 (28.38%)	23 (46.94%)	
Mechanical ventilation					<0.001*
No	157 (48.16%)	35 (38.04%)	22 (29.73%)	8 (16.33%)	
Yes	169 (51.84%)	57 (61.96%)	52 (70.27%)	41 (83.67%)	

*P<0.05, represents significant differences among TDFAA groups; †P<0.05, represents significant differences with TDFAA ≤1 h group; ‡P<0.05, represents significant differences with TDFAA 1-24 h group; §P<0.05, represents significant differences with TDFAA 24-48 h group; -: Not available, estimated; SOFA, sequential organ failure assessment.

hours had higher percentages of MDR-GNB and VRE (**Table 1**).

Previous antibiotics exposure and types of infection

Comparison of TDFAAs with previous antibiotics exposure and types of infection are presented in **Table 2**.

Mean duration of previous antibiotics use was significantly higher with TDFAA of 1-24, 24-48, and >48 hours than that of ≤1 hour and was significantly higher with TDFAA of >48 hours than that of 24-48 hours.

Previous antibiotics exposure and infection types were significant among TDFAA groups. Patients that had TDFAA of 1-24 hours had higher percentages of narrower- (26.09%) and broad-spectrum antibiotics (27.17%). Patients that had TDFAA of ≤1 hour had higher percentages of non-iatrogenic infections (40.49%) and patients that had TDFAA of >48 hours had higher percentages of iatrogenic infections (85.71%) (**Table 2**).

Comorbidities, organ dysfunction, and disease severity

Mean Charlson comorbidity scores were significantly higher with TDFAA of >48 hours than with TDFAAs of ≤1, 1-24, and 24-48 hours (5.61, 3.32, 3.75, and 4.04, respectively; P≤0.003). Mean APACHE II scores were significantly higher at 1-24 and >48 hours than ≤1 hour (26.85, 29.73, and 24.53, respectively; P≤0.017) and significantly higher at >48 hours than 24-48 hours (29.73 vs. 26.12, respectively; P=0.017). Mean SOFA scores were significantly higher at >48 hours than ≤1 and 1-24 hours (8.55, 6.74, and 6.96, respectively; P≤0.027). Quick SOFA was insignificant (P>0.05). Mean lactate was significantly higher at >48 hours than 1-24 hours (3.56 vs. 2.25, respectively, P=0.038). Higher percentages of

Table 4. Comparison of TDFAA groups regarding mortality, ICU, and hospital stay

	TDFAA				*P*-value
	≤1 h (N=326)	1-24 h (N=92)	24-48 h (N=74)	>48 h (N=49)	
ICU stay (days)	11.76 ± 11.44	14.05 ± 12.05	16.38 ± 13†	14.96 ± 13.27	0.010*
Hospital stay (days)	24.65 ± 20.4	26.75 ± 24.07	29.92 ± 25.71	18.53 ± 17.2§	0.032*
ICU mortality					<0.001*
No	288 (88.34%)	72 (78.26%)	60 (81.08%)	9 (18.37%)	
Yes	38 (11.66%)	20 (21.74%)	14 (18.92%)	40 (81.63%)	
Hospital mortality					<0.001*
No	275 (84.36%)	70 (76.09%)	52 (70.27%)	7 (14.29%)	
Yes	51 (15.64%)	22 (23.91%)	22 (29.73%)	42 (85.71%)	
Duration of vasopressor use (days)	0.37 ± 0.46	0.54 ± 0.76	0.68 ± 1.07†	1.34 ± 1.32†,‡,§	<0.001*

*P<0.05, represents significant differences among TDFAA groups; †P<0.05, represents significant differences with TDFAA ≤1 h group; ‡P<0.05, represents significant differences with TDFAA 1-24 h group; §P<0.05, represents significant differences withTDFAA 24-48 h group.

subjects had more than three organ failures, septic shock, and mechanical ventilation at >48 hours than other times (**Table 3**).

Mortality, ICU, and hospital stay

Mean ICU stay was significantly higher with TDFAA of 24-48 hours than that of ≤1 hour (16.38 vs. 11.76 days, respectively; P=0.017). Mean hospital stay was significantly lower at >48 hours than 24-48 hours (18.53 vs. 29.92 days, respectively; P=0.026). Mean vasopressor duration was significantly higher at >48 hours than ≤1, 1-24, and 24-48 hours (1.34, 0.37, 0.54, and 0.68, respectively; all P<0.001) and was significantly higher at 24-48 hours than ≤1 hour (0.68 vs. 0.37, respectively; P= 0.008) (**Table 4**).

Multivariate analysis results concerning TDFAA-associated factors

The following factors had significant association with TDFAA in the final model: MDR organisms, Charlson comorbidity scores, mechanical ventilation, and septic shock. TDFAA was significantly increased with MDR organisms (β= 21.61, P<0.001), increased Charlson comorbidity scores (β=1.31, P<0.001), mechanical ventilation (β=3.26, P=0.046), and septic shock (β=4.35, P=0.013) (**Table 4**).

Discussion

Timing of antibiotic administration is important in treating severe infections. If patients do not obtain appropriate antibiotic treatment, patient outcomes, such as hospital mortality and length of stay, could significantly worsen [7]. This present study assessed TDFAA and aimed to determine possible factors that affect TDFAA in patients admitted to an ICU because of sepsis diagnoses. This study demonstrated that different pathogens might have different drug resistances increasing TDFAA. Some pathogens delayed or hastened TDFAA. For example, polymicrobial infections and MDR organisms increased TDFAA. Initial empiric antibiotic treatment with ceftriaxone would be problematic if ceftriaxone were not indicated as an appropriate antibiotic treatment when culture results became available.

The following pathogens were observed in a significant percentage of patients in all groups: *Acinetobacter species* (P=0.002), *E. faecium* (P<0.001), *E. coli* (P<0.017), and PA (P=0.048). Percentages of patients with carbapenem-resistant GNB (P=0.001), ESBL-resistant GNB (P<0.001), MRSA (P<0.001), MDR-GNB (P= 0.001), and VRE (P<0.001) were higher with TDFAA of 24-48 hours than that of <24 hours. Percentages of polymicrobial infections and MDR organisms were higher with TDFAA of 24-48 hours than that of shorter durations (both P<0.001).

As with previous studies, immediate treatment of sepsis with an appropriate antibiotic could help determine patient outcomes, particularly those admitted to the ICU within 90 days of prior antibiotic exposure. Improved survival has been demonstrated with early and appropriate

antibiotic treatment, along with timely fluid administration in patients with severe sepsis and septic shock [19].

Recent communication has provided an update on the definition of sepsis, indicating that sepsis should be considered a life-threatening condition with organ dysfunction secondary to a disorganized host response to infection [14]. Induced drug-resistant bacterial growth might be correlated with subsequent septic episodes and increased mortality because of inappropriate antibiotic use [20, 21]. This study found that MDR was significant and the greatest percentage of MDR-GNB was with TDFAA of 24-48 hours (14.86%), more than that of ≤1, 1-24, and >48 hours (2.76%, 4.35%, and 6.12%, respectively; P<0.001). This point agrees with Zilberberg et al. who found that MDR was an important determinant of initially inappropriate antibiotic use and associated with a three-fold increase in hospital mortality rate [22]. Therefore, careful determination and selection of antibiotics are necessary to prevent MDR.

According to bacterial species and TDFAA correlation, TDFAA would be later when infected with MRSA, i.e., the 24-48 hours group. PA distribution would increase TDFAA to 1-24 hours. Bacterial drug-resistance could decrease or increase TDFAA. Therefore, ICU physicians should consider the prevalence of drug-resistant PA and MRSA in their hospital while selecting broad-spectrum antibiotics or combination therapy [23]. However, a retrospective review of 2,700 Canadian patients, admitted with septic shock from 1989-2004, found that only 50% were administered effective antibiotics within 6 hours of onset of hypotension [24]. Each hour of delay in administering antibiotics after shock onset was associated with a nearly 12% reduction in survival [25]. For the present study, all patients were admitted from the Emergency Department. The initial encounter with a physician is important in deciding the first administration of antibiotics within 1 hour, but this is not enough time to screen for MDR risk. TDFAA may be delayed for 24 to 48 hours while ICU physicians recheck and reselect appropriate antibiotics. Further investigation of *E. coli* and drug-resistant *Acinetobacter* prevalence would be helpful in providing information on choosing combination therapy to shorten TDFAA [26].

Previous studies have examined the impact that broad-spectrum antibiotic administration timing after sepsis diagnosis has on in-hospital mortality. Bernhard et al. conducted a literature review and found a large dataset assessed by Ferrer and colleagues comprising 28,150 patients with severe sepsis and septic shock: 17,990 patients were administered antibiotics after sepsis was identified, with an in-hospital mortality rate of 29.7% [4]. Bernhard et al. discussed a prospective, observational, and multicenter cohort study conducted in 44 German ICUs, comprising 1,011 patients with severe sepsis and septic shock. They found no linear association between antibiotic timing and 28-day mortality. However, despite timing, the 28-day mortality rate was lower in patients administered adequate antibiotic therapy than those not administered adequate antibiotic therapy (30% vs. 41%, respectively, P<0.001) [4]. Another study found that the estimated risk for a patient having a culture test positive for a resistant organism after recent antibiotic use was 3.0 (P=0.09) [9].

The present study demonstrated that ICU stay, hospital stay, ICU mortality, hospital mortality, and vasopressor duration were significantly increased based on TDFAA. Hospital mortality was highest with TDFAA of 48 hours (P<0.001). TDFAA of >48 hours was associated with higher APACHE II, Charlson comorbidity, and SOFA scores. Disease severity was correlated with TDFAA and higher mortality rates. Moreover, 319 patients were admitted to the medical ICU for acute respiratory failure requiring mechanical ventilation. Another 159 patients were admitted for septic shock. Patients with acute respiratory failure necessitating mechanical ventilation may have higher APACHE II (high A-a gradient or low PaO_2) and SOFA scores (P/F ratio) and a disease severity that could influence TDFAA. Septic shock patients may have higher APACHE II (low MAP) and SOFA scores (shock requiring vasopressors) that could influence TDFAA. Mechanical ventilation and septic shock were independent predictors, even after adjusting for other parameters (**Table 5**), and perhaps intrinsically associated with a higher probability of resistant isolates because of failure to respond to previously administered antimicrobials. Additional prospective studies are necessary to clarify how mechanical ventilation and septic shock may delay TDFAAs.

Table 5. Results of multivariate analyses investigating factors associated with TDFAA

	β ± SE	*P*-value
Multidrug-resistant organisms (ref = no)	21.61 ± 1.69	<0.001*
Iatrogenic infection (ref = non-iatrogenic infection)	-1.12 ± 1.9	0.556
Previous antibiotics exposure at 90 days (ref = no)	-1.54 ± 1.81	0.398
Charlson comorbidity score	1.31 ± 0.32	<0.001*
Mechanical ventilation (ref = no)	3.26 ± 1.63	0.046*
SOFA score	0.03 ± 0.29	0.918
APACHE II score	0.16 ± 0.13	0.233
Pathogens		
Escherichia coli (ref = no)	-1.90 ± 1.73	0.271
Septic shock (included lactate)	4.35 ± 1.75	0.013*

*P<0.05, represents significantly associated with TDFAA.

While this study elaborated on experiences with TDFAAs of ≤1, 1-24, 24-48, and >48 hours, some limitations existed. First, this study did not consider gram-negative versus gram-positive bacteria, as few studies in medical literature have focused on gram-positive bacteria. In a previous study, recent antibiotic exposure was associated with increased hospital mortality in patients with gram-negative bacteremia, complicated by severe sepsis or septic shock [20]. Another factor this study did not examine was antibiotic dosage. Pea et al. [21] conducted a literature review regarding antibiotic dosing and determined several factors related to under-dosing, including hypoalbuminemia, particularly if high-protein-bound antibiotics are used in critically ill patients. Therefore, dosing regimens could be a topic for future examination. While accounting for multiorgan dysfunction, it could have an impact on drug exposure. Thus, monitoring dosing regimens is necessary for critically ill patients [22].

Conclusion

A higher duration of previous antibiotic use at 90 days was observed with TDFAA of >48 hours than any other TDFAA. Charlson comorbidity, APACHE II, and SOFA scores were significantly higher with TDFAA of >48 hours than any other TDFAA.

ICU stay was significantly longer with TDFAA of 24-48 hours than that of ≤1 hour. ICU mortality was also significantly higher with TDFAA of >48 hours. After adjusting for other factors identified in the stepwise model selection, TDFAA was increased with MDR organisms and increased Charlson comorbidity scores. TDFAA was longer with septic shock and mechanical ventilation. Therefore, careful administration, determination, and selection of antibiotic therapy are warranted based on patient comorbidities, ventilator use, and septic shock. Different pathogens might have different drug resistance that could delay TDFAA. MDR organisms increased TDFAA.

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Disclosure of conflict of interest

None.

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