Time to Appropriate Antibiotic Therapy is an Independent Indicator of Poor Outcome in Children with Nosocomial Klebsiella Pneumoniae Bloodstream Infection

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Research Article

Keywords: Klebsiella pneumoniae, Delayed therapy, Time to appropriate therapy, Nosocomial bloodstream infection, Children

Posted Date: December 31st, 2020

DOI: https://doi.org/10.21203/rs.3.rs-136343/v1

Abstract

Objectives: To evaluate the effects of time to appropriate therapy (TTAT) on outcomes in children with nosocomial *K. pneumoniae* bloodstream infection, and to find an optimal time window for empiric antibiotics administration.

Methods: Children with nosocomial *K. pneumoniae* bloodstream infection hospitalized in Children's Hospital of Chongqing Medical University from April 2014 to December 2019 were enrolled retrospectively. TTAT cutoff point and risk factors were determined and analyzed by Classification and Regression Tree (CART) analysis and Logistic Regression analysis.

Results: Overall, sixty-seven patients were enrolled. The incidence of septic shock and mortality was 17.91% (12/67) and 13.43% (9/67), respectively. The CART-derived TTAT cutoff point was 10.7 hours. The multivariate logistic regression analysis indicated delayed therapy (TTAT ≥ 10.7 h), PRISM III scores ≥ 10, early TTP (TTP ≤ 13 h), and need for invasive mechanical ventilation were independent risk factors of septic shock (OR 9.87, 95% CI 1.46-66.59, P = 0.019; OR 9.69, 95% CI 1.15-81.39, P = 0.036; OR 8.28, 95% CI 1.37-50.10, P = 0.021; OR 6.52, 95% CI 1.08-39.51, P = 0.042; respectively) and in-hospital mortality (OR 22.19, 95% CI 1.25-393.94, P = 0.035; OR 40.06, 95% CI 2.32-691.35, P = 0.011; OR 22.60, 95% CI 1.78-287.27, P = 0.016; OR 12.21, 95% CI 1.06-140.67, P = 0.045; respectively).

Conclusions: TTAT is an independent predictor of poor outcome in children with nosocomial *K. pneumoniae* bloodstream infection. Initial appropriate antibiotic therapy should begin within 10.7 hours from the onset of bloodstream infection.

Introduction

Klebsiella pneumoniae (*K. pneumoniae*) is one of leading gram-negative pathogens of bloodstream infection in hospitalized children [1], also a major worldwide source and shuttle for antibiotic resistance [2], and with high morbidity and mortality. Antibiotic therapy plays a crucial role in the treatment of bloodstream infection, and the time of initiating appropriate antibiotic has significant effects on the prognosis [3–9]. The Surviving Sepsis Campaign in 2020 [10] recommends that the antibiotic should be administrated within 1 hour after the recognition of septic shock, and within 3 hours after the recognition of sepsis-associated organ dysfunction without shock. The 1-hour and 3-hour goals are strongly recommended, while with low quality of evidence and remains controversial [10, 11]. Meanwhile, our previous study showed that the delayed appropriate antibiotic therapy ≥ 13.6 hours, not ≥ 1 or 3 hours, was associated with the highest sepsis-related mortality in children with *Streptococcus pneumoniae* sepsis [7]. Furthermore, the 1-hour and 3-hour goals are sometimes unrealistic to be achieved due to limitations in identification and diagnosis of sepsis-associated organ dysfunction and septic shock [11]. Immediate antibiotic treatment is lifesaving for some patients, while, the overdiagnosis of sepsis and aggressive time-to-antibiotic targets may lead to antibiotic overuse and antibiotic-associated harms [8, 12]. The Infectious Diseases Society of America states the administration time of antibiotic varies with

different pathogens and populations [13]. In adult patients, the optimal appropriate therapy time was 24 hours for *K. pneumoniae* bloodstream infection [3], 48.1 hours for *Enterococci* bloodstream infection [4], 52 hours for *Pseudomonas aeruginosa* bloodstream infection [5] and 44.75 hours for *Staphylococcus aureus* bacteremia [6]. The appropriate antibiotic time may be different in bacteremia patients with different pathogens and it still remains unknown in pediatric patients with *K. pneumoniae* bloodstream infection. Therefore, more studies are needed to explore the appropriate antibiotics administration time in different populations. We aimed to evaluate an optimal time window for appropriate antibiotic administration, to determine the effects of time to appropriate therapy (TTAT) on outcomes in children with nosocomial K. pneumoniae bloodstream infection.

Patients And Methods

Study designs and patients

This was a retrospective, observational cohort study conducted in Children's Hospital of Chongqing Medical University, a 2000-bed tertiary teaching hospital in Chongqing, China, ranked the top two domestic children's hospitals (rank list: http://top100.imicams.ac.cn/home). Patients hospitalized between April 2014 and December 2019 with *K. pneumoniae* bloodstream infection were enrolled. The inclusion criteria were of the following: (i) inpatients, (ii) aged 1 month to 18 years, (iii) diagnosed with monomicrobial *K. pneumoniae* bloodstream infection. The exclusion criteria included any of the following: (i) patients diagnosed with community-acquired *K. pneumoniae* bloodstream infection, (ii) patients with incomplete clinical information and (iii) patients received appropriate antibiotics against *K. pneumoniae* prior to blood culture. This retrospective study was approved by the Ethics Committee of Children's Hospital of Chongqing Medical University. Informed consent was waived from the parents/guardians owing to the retrospective design of this study.

Data collection and definitions

The collected data included demographic characteristics (age and gender), underlying conditions, axillary temperature, serum albumin level, sources of infection, severity of illness, antibiotic susceptibility testing, antibiotic therapy during hospitalization, TTAT, time to positivity (TTP) and clinical outcomes (septic shock and mortality).

K.pneumoniae bloodstream infection was defined as at least 1 blood culture positive for *K. pneumoniae* associate with related clinical manifestations of infection [14]. Nosocomial bloodstream infection was defined as positive blood culture obtained > 48 hours after admission, while signs and symptoms of infection were absent at admission [14]. The immunosuppression patients were defined as patients who received immunosuppressive chemotherapy or high dose steroid therapy more than 2 weeks, or with primary immunodeficiency diseases. Hypoalbuminemia was defined as intravascular albumin level < 2.5 g/dL for children younger than 7 months and < 3.4 g/dL for children 7 months or older [15]. Source of

infection was defined according to the CDC /NHSN surveillance guidelines [16]. The severity of illness was assessed by the Pediatric Risk of Mortality (PRISM) III score [17]. TTP was defined as the time span between incubation of blood and detection of bacterial growth. Our previous study demonstrated that TTP ≤ 13 hours and a PRISM III score ≥ 10 indicated poor outcomes in children with *K. pneumoniae* bloodstream infection [18]. Empiric antibiotic treatment was defined as initial antimicrobial therapy for suspected infection without definitive microbiologic pathogen identification [10]. The appropriate antibiotic therapy was defined as the patients received at least one intravenous antibiotic documented in vitro susceptibility according to the breakpoint established according to the Clinical and Laboratory Standards Institute (CLSI) guideline [19]. Multi-drug resistant (MDR) was defined according to the European Centers for Diseases Prevention and Control (ECDC) international expert proposal [20]. The TTAT was defined as the time duration from onset of bloodstream infection to receive initial appropriate antibiotic therapy [3]. The onset of bloodstream infection was identified by no less than two senior infectious disease physicians according to clinical manifestations (e. g. fever, chill and so on) and biomarkers (e. g. C-reactive protein, procalcitonin and so on), and approved by the subsequent positive blood culture result. Sepsis was defined as infection complicated by one or more organ dysfunctions [21]. Organ system dysfunctions are assessed with an increase in the pediatric Sequential Organ Failure Assessment (pSOFA) score by 2 or more points [22]. Septic shock was defined as patients with sepsis and hypotension requiring vasopressor therapy and lactate greater than 2 mmol/L despite adequate fluid resuscitation [21]. Hypotension was diagnosed according to cutoffs of the age-adapted mean arterial blood pressure in pSOFA score system [22].

Clinical outcomes

The primary outcome was in-hospital mortality, the second outcome was incidence of septic shock.

Statistical analysis

Classification and regression tree (CART) analysis [23], which included optimal tree selection based on pruning and 10-fold cross-validation, was used to find the optimal cutoff point of TTAT, and the patients at highest risk for in-hospital mortality. The CART-derived TTAT cutoff point was also assessed by receiver operating characteristic (ROC) curve analysis [24]. Hazard curves were generated by the Kaplan–Meier method, and differences in survival were compared using the log-rank test. The corresponding in-hospital mortality of different cutoff points of TTAT were assessed by the χ^2 test for a linear trend. Categorical variables were compared by χ^2 test or Fisher's exact test, and continuous variables were compared by Student's t test or Mann-Whitney *U* test. Univariate and multivariate logistic regression test were constructed to explore independent risk factors of septic shock and in-hospital mortality. Variables with P-level < 0.10 in univariate analysis were further included in multivariate models, with forward likelihood ratio selection. Odds ratio (OR) and the corresponding 95% confidence interval (CI) were

calculated. All statistical analyses performed using SPSS software for Windows, v.23 (SPSS Inc., Chicago, IL, USA). The level of significance was set at P-value < 0.05 (two-sided).

Results

Study population

One hundred and thirty-two patients were retrospectively enrolled at the beginning. Sixty-five of them were excluded: sixty cases were classified as community-acquired infection, three cases with incomplete clinical information, and two cases received effective antibiotic against *K. pneumoniae* isolates prior to blood culture. Finally, sixty-seven cases were enrolled in this study (Fig. 1).

Clinical characteristic of K. pneumoniae bloodstream infection in children

The median age was 4.33 (IQR 0.76–10.67) years, and the male accounted for 61.69% (42/67). More than half of the patients had hematologic malignancy or immunosuppression (44/67, 65.67%; 41/67, 61.19%, respectively). The most common source of bloodstream infections originated from respiratory tract (55.22%), followed by gastrointestinal tract (20.90%) and unknown source (14.93%). There were 32 (47.76%) extended-spectrum beta-lactamase (ESBL) positive and 6 (8.96%) multidrug resistant (MDR) *K. pneumoniae* isolates. More than half of the *K. pneumoniae* isolates resistant to sulbactam (40/67, 59.70%). The resistant rate of cephalosporin and tazobactam was 22.39% (15/67) and 20.90% (14/67), respectively. There were 28 (41.79%) patients receiving antibiotic therapy prior to blood culture. While, thirty-eight (56.72%) patients were treated with carbapenem empirically before the susceptibility tests. The median TTP and TTAT was 14.12 (IQR 12.72–16.22) hours and 4.52 (IQR 0.97–14.18) hours, respectively. Twenty-two (32.84%) patients had secondary hypoalbuminemia and eleven (16.42%) patients administered with invasive mechanical ventilation during hospitalization. The median length of stay before the onset of bloodstream infection was13.68 (IQR 6.59–17.53) days, the median length of whole hospitalization stay was 28.96 (IQR 20.04–42.75) days. Septic shock occurred in 17.91% (12/67) of patients. The in-hospital mortality was 13.43% (9/67). The detailed characteristics of those patients are presented in Table 1.

Table 1
Clinical characteristics of 67 children with nosocomial *K. pneumoniae* bloodstream infection

Characteristics	Number/median	Percent/IQR
Demographic characteristics		
Male (n, %)	42	61.69
Age (years) (median, IQR)	4.33	0.76–10.67
Underlying conditions		
Hematologic malignancy (n, %)	44	65.67
Immunosuppression (n, %)	41	61.19
Congenital heart disease (n, %)	14	20.90
Sources of infection		
Respiratory tract (n, %)	37	55.22
Gastrointestinal tract (n, %)	14	20.90
Unknown source (n, %)	10	14.93
Invasive operation (n, %)	5	7.46
Urinary tract (n, %)	1	1.49
Drug resistant bacteria phenotypes		
Sulbactam resistant (n, %)	40	59.70
Extended spectrum beta-lactamase (n, %)	32	47.76
Cephalosporin resistant (n, %)	15	22.39
Tazobactam resistant (n, %)	14	20.90
Carbapenem resistant (n, %)	7	10.45
Multidrug resistant (n, %)	6	8.96
Aminoglycoside resistant (n, %)	4	5.97
Empiric antibiotic treatment		
Carbapenem (n, %)	38	56.72
Fourth-generation cephalosporin (n, %)	9	13.43
Third-generation cephalosporin (n, %)	8	11.94

Abbreviations: IQR, inter-quartile range; PRISM, pediatric risk of mortality; TTAT, time to appropriate therapy; TTP, time to positivity.

Characteristics	Number/median	Percent/IQR
Tazobactam (n, %)	7	10.45
Second-generation cephalosporin (n, %)	3	4.48
Sulbactam (n, %)	2	2.99
Length of stay before the onset of bloodstream infection (days) (median, IQR)	13.68	6.59–17.53
Length of hospitalization stay (days) (median, IQR)	28.96	20.04–42.75
The peak of temperature (centigrade) (median, IQR)	39.8	39.3–40.1
Antibiotics administration prior to blood culture (n, %)	28	41.79
With secondary hypoalbuminemia during hospitalization (n, %)	22	32.84
PRISM III score (median, IQR)	8	3–9
TTP (h) (median, IQR)	14.12	12.72–16.22
TTAT (h) (median, IQR)	4.52	0.97–14.18
Need for invasive mechanical ventilation (n, %)	11	16.42
Septic shock (n, %)	12	17.91
In-hospital mortality (n, %)	9	13.43

Abbreviations: IQR, inter-quartile range; PRISM, pediatric risk of mortality; TTAT, time to appropriate therapy; TTP, time to positivity.

TTAT of K. pneumoniae bloodstream infection in children

The TTAT cutoff point derived by CART to delineate the risk of in-hospital mortality was 10.7 hours. Patients were classified into early (TTAT < 10.7 h) and delayed therapy group (TTAT ≥ 10.7 h) according to TTAT cutoff point. Twenty-three (34.33%) patients received delayed therapy. The in-hospital mortality in delayed therapy group was significantly higher than that in early therapy group (29.17% *vs* 4.65%, P = 0.028). In the subgroup of patients with early therapy, the in-hospital mortality was significantly higher in patients with PRISM III scores ≥ 10 than those with PRISM III scores < 10 (33.33% *vs* 2.50%, P = 0.008). In the subgroup of patients with early therapy and PRISM III scores < 10, patients with TTP ≤ 13 h had remarkably higher in-hospital mortality than those with TTP > 13 h (10.00% *vs* 0.00%, P = 0.002) (Fig. 2). In ROC curve analysis, the CART-derived TTAT cutoff point had the best predict value of in-hospital mortality (AUC [95% confidence interval (CI)], 0.721 [0.564–0.879], 77.78% sensitivity and 70.69% specificity), with moderate predictive efficacy [25]. The Kaplan–Meier survival curve of these patients is shown in Fig. 3. In χ^2 test for a linear trend, patients in TTAT ≥ 10.7 h group had the highest in-hospital

mortality when compared to those in TTAT < 3 h and 3 h ≤ TTAT < 10.7 h periods groups. (P = 0.008) (Fig. 4).

Comparisons of clinical characteristics between the early and delayed therapy groups

Characteristics of two TTAT groups were shown in Table 2. When compared with the delay therapy group (TTAT ≥ 10.7 h), more patients in early therapy (TTAT < 10.7 h) group had hematologic malignancy (84.09% *vs* 30.43%, P < 0.001) and immunosuppression (72.73% *vs* 39.13%, P = 0.007). There were prominently more early therapy patients administrated with carbapenem empirically before the susceptibility tests than delayed therapy patients (68.18% *vs* 34.78%, P = 0.009). Meanwhile, patients received delayed therapy may attribute to the notably higher proportion of empirical third-generation cephalosporin therapy (26.09% *vs* 4.55%, P = 0.029) and cephalosporin resistant isolates (39.13% *vs* 13.64%, P = 0.017) than those received early therapy. Accordingly, the delayed therapy patients had significantly higher incidence of secondary hypoalbuminemia (56.52% *vs* 20.45%, P = 0.002) and septic shock (39.13% *vs* 6.82%, P = 0.003), higher proportion of requiring invasive mechanical ventilation (34.78% *vs* 6.82%, P = 0.010), higher in-hospital mortality (30.43% *vs* 4.55%, P = 0.010) than those early therapy patients. While, the PRISM III scores, the length of stay before the onset of bloodstream infection and length of the whole hospitalization stay were with no differences between the two groups.

Table 2
Comparison of clinical characteristics in early and delayed therapy groups in 67 nosocomial *K. pneumoniae* bloodstream infection children

Characteristics	TTAT ≥ 10.7 h (n = 23)	TTAT < 10.7 h (n = 44)	P
Demographic characteristics			
Male (n, %)	13 (56.52%)	29 (65.91%)	0.451
Age (median, IQR)	0.85 (0.52–9.75)	5.75 (2.50-11.05)	0.070
Underlying conditions			
Hematologic malignancy (n, %)	7 (30.43%)	37 (84.09%)	0.000*
Immunosuppression (n, %)	9 (39.13%)	32 (72.73%)	0.007*
Congenital heart disease (n, %)	8 (34.78%)	6 (13.64%)	0.088
Sources of infection			
Respiratory tract (n, %)	11 (47.83%)	26 (59.09%)	0.379
Gastrointestinal tract (n, %)	5 (21.74%)	9 (20.45%)	1.000
Unknown source (n, %)	5 (21.74%)	5 (11.36%)	0.441
Invasive operation (n, %)	2 (8.70%)	3 (6.82%)	1.000
Urinary tract (n, %)	0 (0.00%)	1 (2.27%)	1.000
Drug resistant bacteria phenotypes			
Sulbactam resistant (n, %)	16 (69.57%)	24 (54.55%)	0.234
Extended spectrum beta-lactamase (n, %)	14 (60.87%)	18 (40.91%)	0.120
Cephalosporin resistant (n, %)	9 (39.13%)	6 (13.64%)	0.017*
Tazobactam resistant (n, %)	6 (26.09%)	8 (18.18%)	0.660
Carbapenem resistant (n, %)	3 (13.04%)	4 (9.09%)	0.935
Multidrug resistant (n, %)	2 (8.70%)	4 (9.09%)	1.000
Aminoglycoside resistant (n, %)	2 (8.70%)	2 (4.55%)	0.890
Empiric antibiotic treatment (n, %)			
Carbapenem (n, %)	8 (34.78%)	30 (68.18%)	0.009*

*Statistical significance, P < 0.05. Abbreviations: IQR, inter-quartile range; PRISM, pediatric risk of mortality; TTAT, time to appropriate therapy; TTP, time to positivity.

Characteristics	TTAT ≥ 10.7 h (n = 23)	TTAT < 10.7 h (n = 44)	P
Fourth-generation cephalosporin (n, %)	3 (13.04%)	6 (13.64%)	1.000
Third-generation cephalosporin (n, %)	6 (26.09%)	2 (4.55%)	0.029*
Tazobactam (n, %)	4 (17.39%)	3 (6.82%)	0.356
Second-generation cephalosporin (n, %)	0 (0.00%)	3 (6.82%)	0.510
Sulbactam (n, %)	2 (8.70%)	0 (0.00%)	0.114
Length of stay before the onset of bloodstream infection (median, IQR)	11.75 (7.14–23.13)	14.42 (10.50-17.19)	0.561
Length of hospitalization stay (median, IQR)	24.00 (12.92–38.88)	30.90 (22.98–46.93)	0.080
The peak of temperature (median, IQR)	39.6 (39.1–40.0)	39.9 (39.3–40.4)	0.135
Antibiotics administration prior to blood culture (n, %)	14 (60.87%)	14 (31.82%)	0.022*
With secondary hypoalbuminemia during hospitalization (n, %)	13 (56.52%)	9 (20.45%)	0.002*
PRISM score ≥ 10 (n, %)	3 (13.04%)	3 (6.82%)	0.692
TTP ≤ 13 h (n, %)	7 (30.43%)	12 (27.27%)	0.785
Need for invasive mechanical ventilation (n, %)	8 (34.78%)	3 (6.82%)	0.010*
Septic shock (n, %)	9 (39.13%)	3 (6.82%)	0.003*
In-hospital mortality (n, %)	7 (30.43%)	2 (4.55%)	0.010*

*Statistical significance, P < 0.05. Abbreviations: IQR, inter-quartile range; PRISM, pediatric risk of mortality; TTAT, time to appropriate therapy; TTP, time to positivity.

Comparisons of clinical characteristics between the survival and non-survival groups

The clinical characteristics of the survival and non-survival patients were compared in the Table 3. The non-survival patients had significantly higher proportion of cephalosporin resistant and extended spectrum beta-lactamase (ESBL) positive isolates, higher proportion of PRISM III scores ≥ 10, TTP ≤ 13 h and TTAT ≥ 10.7 h, higher incidence of requiring invasive mechanical ventilation and septic shock when compared to those in survival group. (P < 0.05). The length of stay before the onset of bloodstream infection and length of the whole hospitalization stay were with no significant differences between two groups.

Table 3
Comparison of clinical characteristics in survival and non-survival groups in 67 nosocomial *K. pneumoniae* bloodstream infection children

Characteristics	Non-survival (n = 9)	Survival (n = 58)	P
Demographic characteristics			
Male (n, %)	4 (44.44%)	38 (65.52%)	0.398
Age (median, IQR)	9.75 (1.72–12.13)	4.29 (0.73–9.69)	0.316
Underlying conditions			
Hematologic malignancy (n, %)	5 (55.56%)	39 (67.24%)	0.757
Immunosuppression (n, %)	5 (55.56%)	36 (62.07%)	0.996
Congenital heart disease (n, %)	1 (11.11%)	13 (22.41%)	0.737
Sources of infection			
Respiratory tract (n, %)	5 (55.56%)	32 (55.17%)	1.000
Gastrointestinal tract (n, %)	2 (22.22%)	12 (20.69%)	1.000
Unknown source (n, %)	2 (22.22%)	8 (13.79%)	0.875
Invasive operation (n, %)	0 (0.00%)	5 (8.62%)	1.000
Urinary tract (n, %)	0 (0.00%)	1 (1.72%)	1.000
Drug resistant bacteria phenotypes			
Sulbactam resistant (n, %)	8 (88.89%)	32 (55.17%)	0.120
Extended spectrum beta-lactamase (n, %)	8 (88.89%)	24 (41.38%)	0.022*
Cephalosporin resistant (n, %)	5 (55.56%)	10 (17.24%)	0.033*
Tazobactam resistant (n, %)	3 (33.33%)	11 (18.97%)	0.585
Carbapenem resistant (n, %)	2 (22.22%)	5 (8.62%)	0.235
Multidrug resistant (n, %)	2 (22.22%)	4 (6.90%)	0.181
Aminoglycoside resistant (n, %)	2 (22.22%)	2 (3.45%)	0.084
Empiric antibiotic treatment			
Carbapenem (n, %)	6 (66.67%)	32 (55.17%)	0.775

*Statistical significance, P < 0.05. Abbreviations: IQR, inter-quartile range; PRISM, pediatric risk of mortality; TTAT, time to appropriate therapy; TTP, time to positivity.

Characteristics	Non-survival (n = 9)	Survival (n = 58)	P
Fourth-generation cephalosporin (n, %)	0 (0.00%)	9 (15.52%)	0.456
Third-generation cephalosporin (n, %)	1 (11.11%)	7 (12.07%)	1.000
Tazobactam (n, %)	1 (11.11%)	6 (10.34%)	1.000
Second-generation cephalosporin (n, %)	0 (0.00%)	3 (5.17%)	1.000
Sulbactam (n, %)	1 (11.11%)	1 (1.72%)	0.252
Length of stay before the onset of bloodstream infection (median, IQR)	16.76 (8.88-33.00)	13.23 (8.47–17.28)	0.211
Length of hospitalization stay (median, IQR)	24.00 (10.63–52.65)	29.46 (22.59–43.74)	0.594
The peak of temperature (median, IQR)	39.6 (39.0–40.0)	39.8 (39.3–40.2)	0.407
Antibiotics administration prior to blood culture (n, %)	8 (88.89%)	20 (34.48%)	0.007*
With secondary hypoalbuminemia during hospitalization (n, %)	6 (66.67%)	16 (27.59%)	0.052
PRISM score ≥ 10 (n, %)	3 (33.33%)	3 (5.17%)	0.028*
TTP ≤ 13 h (n, %)	6 (66.67%)	13 (22.41%)	0.019*
TTAT ≥ 10.7 h (n, %)	7 (77.78%)	16 (27.59%)	0.010*
Need for invasive mechanical ventilation (n, %)	5 (55.56%)	6 (10.34%)	0.003*
Septic shock (n, %)	9 (100.00%)	3 (5.17%)	0.000*

*Statistical significance, P < 0.05. Abbreviations: IQR, inter-quartile range; PRISM, pediatric risk of mortality; TTAT, time to appropriate therapy; TTP, time to positivity.

Risk factors of in-hospital mortality

Univariate and multivariate analyses were conducted to find independent risk factors of in-hospital mortality, and the results were presented in Table 4. In univariate analysis, patients with PRISM III scores ≥ 10, early TTP (TTP ≤ 13 h), delayed therapy (TTAT ≥ 10.7 h), need for invasive mechanical ventilation, with secondary hypoalbuminemia during hospitalization, ESBL positive isolates, and cephalosporin resistant isolates were related to in-hospital mortality. According to the multivariate analysis, PRISM III scores ≥ 10 (OR 40.06, 95% CI 2.32-691.35, P = 0.011), early TTP (OR 22.60, 95% CI 1.78-287.27, P = 0.016), delayed therapy (OR 22.19, 95% CI 1.25-393.94, P = 0.035), and need for invasive mechanical

ventilation(OR 12.21, 95% CI 1.06-140.67, P = 0.045) were independent risk factors of in-hospital mortality.

Table 4
Logistic regression analysis of risk factors of in-hospital mortality among 67 *K. pneumoniae* bloodstream infection children.

Variables	Univariate analysis			Multivariate analysis		
	OR	95%CI	P	OR	95%CI	P
PRISM III scores ≥ 10	9.17	1.50-55.93	0.016*	40.06	2.32-691.35	0.011*
TTP ≤ 13 h	6.92	1.52–31.56	0.012*	22.60	1.78-287.27	0.016*
TTAT ≥ 10.7 h	9.19	1.72–48.98	0.009*	22.19	1.25-393.94	0.035*
Need for invasive mechanical ventilation	10.83	2.27–51.71	0.003*	12.21	1.06-140.67	0.045*
Extended spectrum beta-lactamase bacteria	11.33	1.33–96.67	0.026*			
Cephalosporin resistant bacteria	6.00	1.37–26.38	0.018*			
With secondary hypoalbuminemia during hospitalization	3.73	1.03–13.59	0.046*			

* indicates statistical significance, P < 0.05. Abbreviations: PRISM, pediatric risk of mortality; TTAT, time to appropriate therapy; TTP, time to positivity.

Risk factors of septic shock

The univariate and multivariate logistic regression analysis of risk factors of septic shock were shown in Table 5. In univariate analysis, patients with PRISM III scores ≥ 10, early TTP (TTP ≤ 13 h), delayed therapy (TTAT ≥ 10.7 h), need for invasive mechanical ventilation, with secondary hypoalbuminemia during hospitalization and ESBL positive isolates were related to septic shock. Multivariate analysis demonstrated that delayed therapy (OR 9.87, 95% CI 1.46–66.59, P = 0.019), PRISM III scores ≥ 10 (OR 9.69, 95% CI 1.15–81.39, P = 0.036), early TTP (OR 8.28, 95% CI 1.37–50.10, P = 0.021) and need for invasive mechanical ventilation (OR 6.52, 95% CI 1.08–39.51, P = 0.042) were independent risk factors of septic shock.

Table 5
Logistic regression analysis of risk factors of septic shock among 67 nosocomial *K. pneumoniae* bloodstream infection children.

Variables	Univariate analysis			Multivariate analysis		
	OR	95%CI	P	OR	95%CI	P
TTAT ≥ 10.7 h	8.79	2.08–37.11	0.003*	9.87	1.46–66.59	0.019*
PRISM III scores ≥ 10	5.78	1.00-33.24	0.049*	9.69	1.15–81.39	0.036*
TTP ≤ 13 h	5.02	1.35–18.67	0.016*	8.28	1.37–50.10	0.021*
Need for invasive mechanical ventilation	10.00	2.33–42.97	0.002*	6.52	1.08–39.51	0.042*
With secondary hypoalbuminemia during hospitalization	5.25	1.17–23.55	0.030*			
Extended spectrum beta-lactamase bacteria	4.17	1.02–17.13	0.047*			
Cephalosporin resistant bacteria	3.21	0.84–12.23	0.087			

* indicates statistical significance, P < 0.05. Abbreviations: PRISM, pediatric risk of mortality; TTAT, time to appropriate therapy; TTP, time to positivity.

Discussion

In this study, we demonstrated that patients with PRISM III scores ≥ 10, early TTP (TTP ≤ 13 h), requiring for invasive mechanical ventilation were independent factors associated with poor outcomes, which were in accordance with our previous study [18, 26]. Furthermore, we also showed that delayed therapy (TTAT ≥ 10.7 h) was risk factor of septic shock and in-hospital mortality, which was consistent with the results of previous studies indicating delayed appropriate antibiotic therapy was associated with poor outcomes [6, 5, 4, 3, 27–29]. Falcone et al. [3] indicated that appropriate antibiotic therapy should begin within 24 h from the collection of blood culture in adult carbapenemase-producing *K. pneumoniae* bloodstream infection patients. In this study, we found TTAT ≥ 10.7 h increased 22.19-fold risk of in-hospital mortality and 9.87-fold risk of septic shock in nosocomial *K. pneumoniae* bloodstream infection children. The difference of TTAT thresholds between our and Falcone et al. [3] may be as follows. First, we used different definition of the start point of TTAT. It is more accurate to define the start point of TTAT as onset of bloodstream infection. To obtain the accurate TTAT for community-acquired infection patients may be difficult, while it`s feasible to gain the data of onset of bloodstream infection and accurate TTAT for nosocomial infection patients. Second, the optimal TTAT cutoff point (10.7 h) in our study was derived by CART analysis and demonstrated by using ROC curve analysis and χ^2 test for a linear trend. While, Falcone et al. [3] didn't explore the optimal TTAT cutoff point. Third, although we both enrolled patients

with *K. pneumoniae* bloodstream infection, the patients enrolled in our study were children rather than adult. Two studies [8, 9] stated that TTAT > 3 h was related to higher mortality, which was much shorter than that in our study. The explanations may as the following. First, patients with septic shock should administrate appropriate antibiotic more aggressively than those with sepsis-associated organ dysfunction but without shock [10]. There were 17.91% (12/67) patients with septic shock in our study. While, there were 78.13% (125/160) and 79.23% (103/130) patients with septic shock in Han's [8] study and Weiss's [9] study, respectively. The lower proportion of septic shock patients in our study may explain the longer TTAT cutoff point. Second, the methods of defining TTAT cutoff points were different. We used the CART analysis while the other two studies used multivariate analysis.

We found that the secondary hypoalbuminemia during hospitalization may be associated with delayed appropriate antibiotic therapy. The delayed antibiotic therapy may lead to persistent bloodstream infection, which resulted in increased capillary permeability, escape of serum albumin, and shorten the half-time of albumin [30]. Low albumin levels may indicate severe condition and poor outcomes [31]. Moreover, our results indicated that patients in delayed therapy group had significantly higher proportion of empiric third-generation cephalosporin administration prior to blood culture than that in early therapy groups. The explanation may as the following. The third-generation cephalosporin is one of the most recommended empiric broad-spectrum antibiotic therapies for patients with nosocomial infection [32]. However, with increased of third-generation resistant *K. pneumoniae* isolates [2], empirical third-generation cephalosporin administration may result in delaying appropriate antibiotic therapy. *K. pneumoniae* is a major worldwide source and shuttle for antibiotic resistance [2], and the nosocomial gram-negative bacteria bloodstream infection patients had higher proportion of inappropriate antibiotic therapy [33]. Therefore, it is very important for clinicians to evaluate whether the empiric antibiotic therapy is appropriate or not. More than half (38/67, 56.72%) of patients in our study had been empirically treated with carbapenem. And the prevalence of carbapenem-resistant *K. pneumoniae* in this study (7/67, 10.45%) was higher than that in many European countries according to the data from the European Centre for Disease Prevention and Control (website: http://atlas.ecdc.europa.eu/public/index.aspx?Instance=GeneralAtlas). We consumed that frequently using carbapenem may contribute to carbapenem-resistant *K. pneumoniae* isolate.

Appropriate antibiotic therapy can improve the clinical outcomes in children with severe bloodstream infection. However, to avoid the overuse or misuse of antibiotic, it is very important for clinician to recognize the bloodstream infection and identify the correct pathogen. In high-income countries, some rapid diagnostic testing technologies can help the clinician to identify *K. pneumoniae* quickly. However, in some low-income countries, the clinical experiences and education level of recognizing *K. pneumoniae* bloodstream infection may be more important. Furthermore, building susceptibility databases of *K. pneumoniae* isolates may help guiding clinicians to choose more appropriate and timely empiric antibiotic therapy.

This study has some limitations. Firstly, this is a single-center, retrospective study with relatively small sample size, and multi-center, larger sample size, prospective study is expected to strength the results of

this study. Secondly, we only enrolled patients with nosocomial *K. pneumoniae* bloodstream infection, and this may influence the extrapolation of our data to other populations. Thirdly, when applied our results to clinical practice, we should pay attention to the difference of definitions of the start point of TTAT between us and other studies.

Conclusions

Our study demonstrated that TTAT may serve as an independent risk factor of septic shock and in-hospital mortality in children with nosocomial *K. pneumoniae* bloodstream infection. The clinicians should initiate appropriate antibiotic within 10.7 hours of the onset of the *K. pneumoniae* bloodstream infection.

Declarations

Funding:

This study was supported by the Science and Technology Department of Chongqing (cstc2018jscx-msybX0021).

Conflict of Interest:

All authors declare that they have no conflict of interest, and they have no financial relationship with the organization that sponsored the research.

Ethical approval:

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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Figures

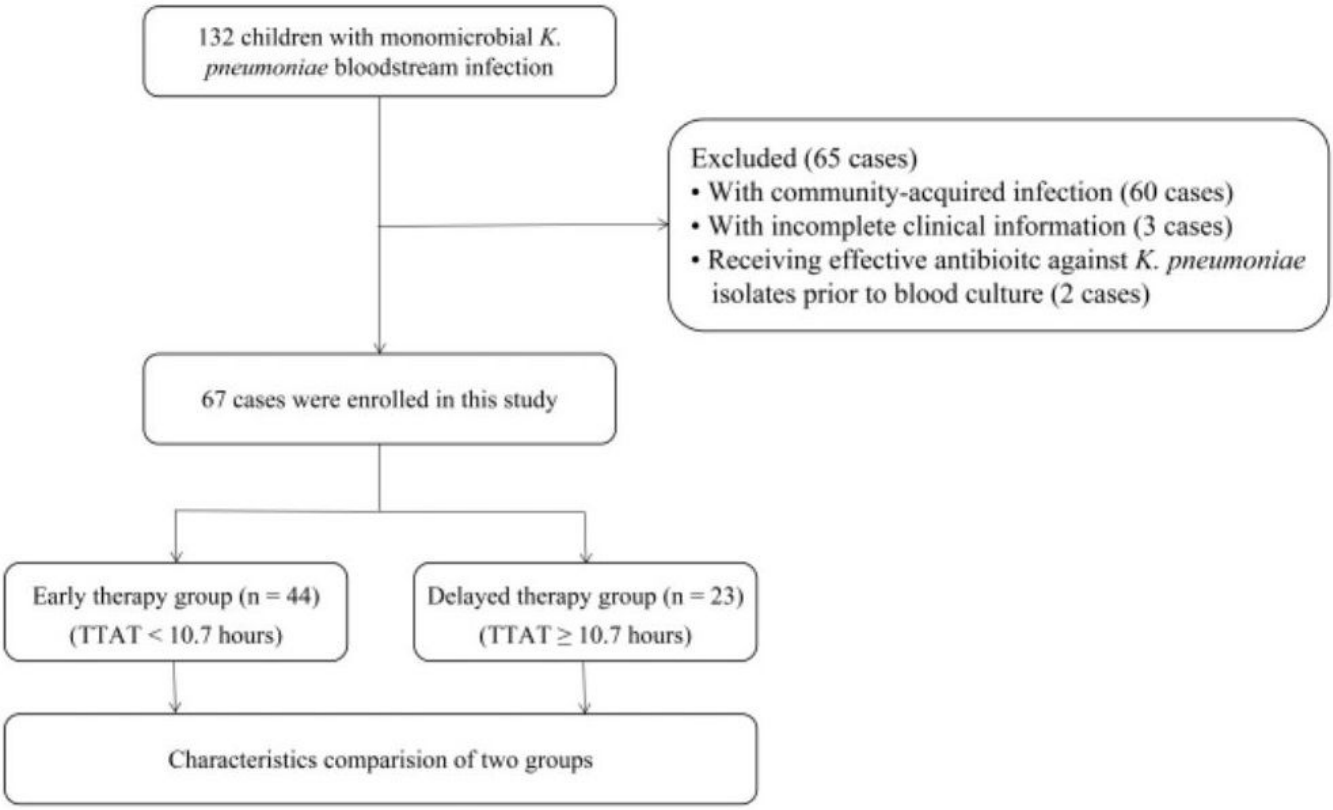

Figure 1

Flow diagram of the population. Abbreviation: TTAT, time to appropriate therapy.

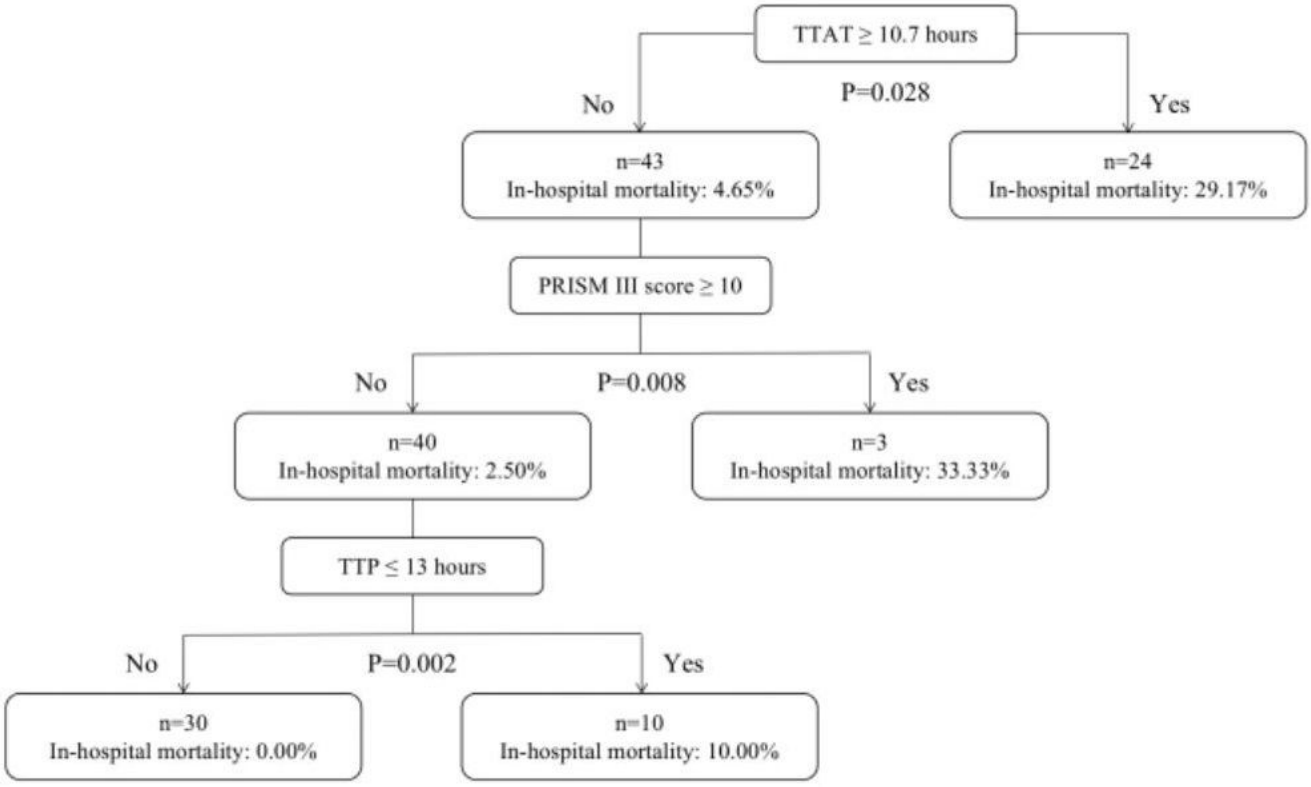

Figure 2

Classification and regression tree analysis of predictors of in-hospital mortality in children with K. pneumoniae bloodstream infection. Abbreviations: PRISM, pediatric risk of mortality; TTAT, time to appropriate therapy; TTP, time to positivity.

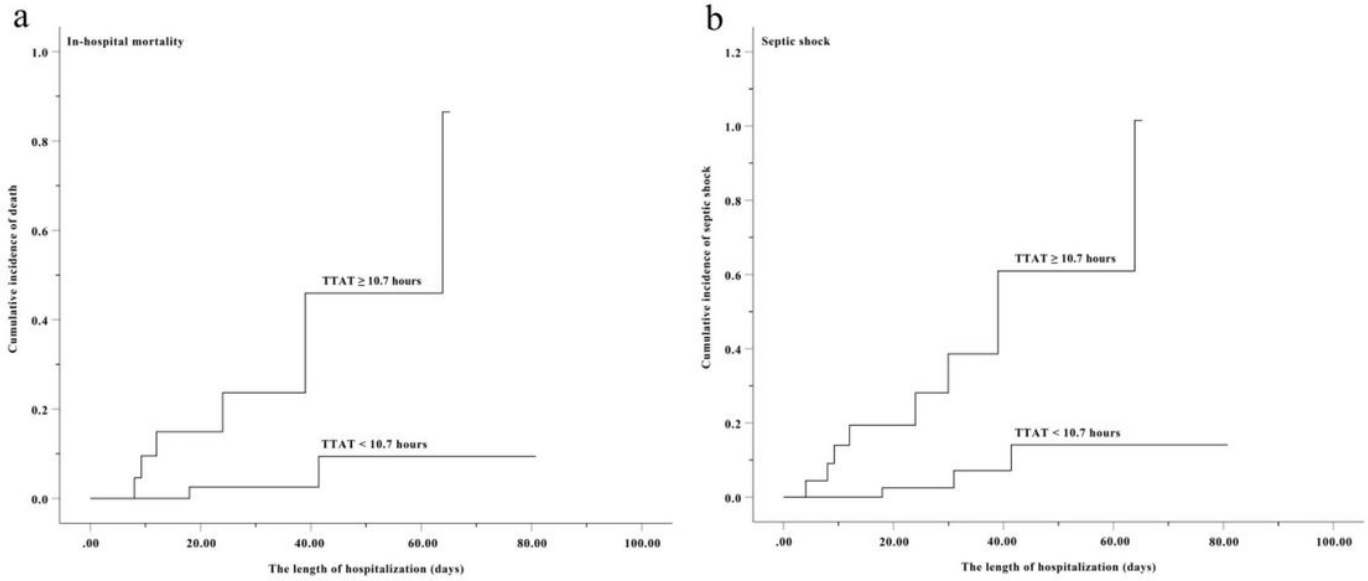

Figure 3

The comparison of patients in different TTAT groups according to in-hospital mortality (a) and septic shock (b). Abbreviation: TTAT, time to appropriate therapy.

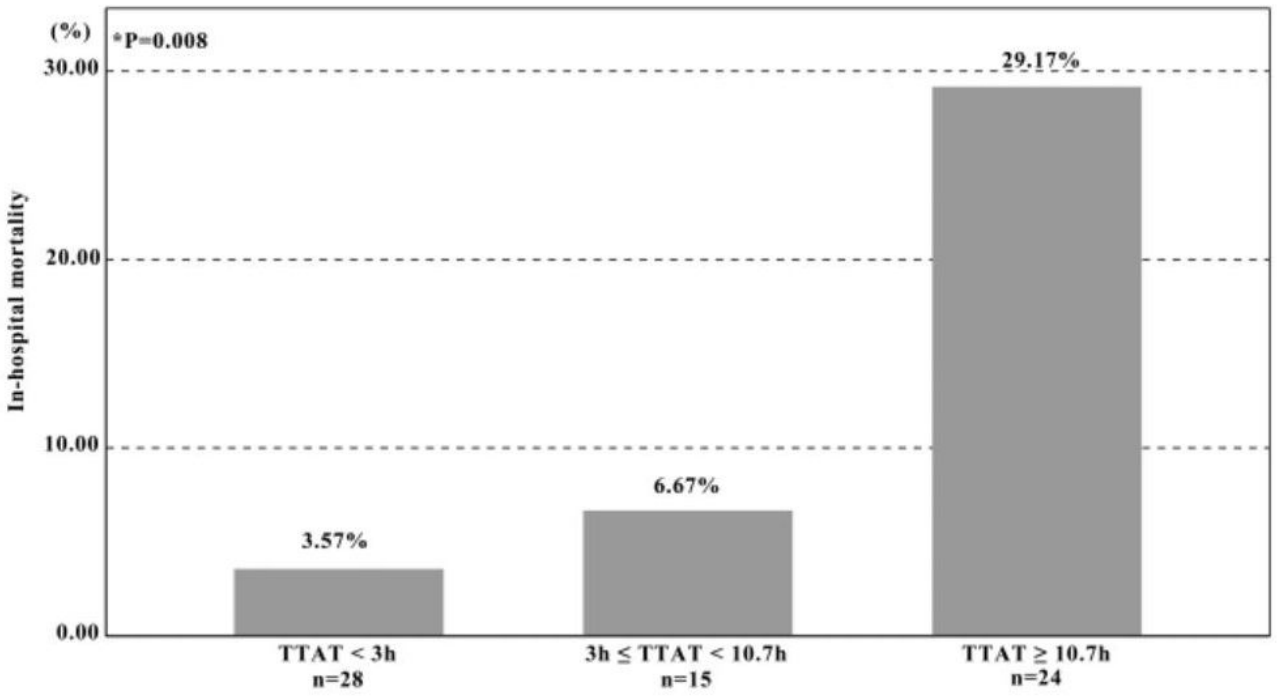

Figure 4

In-hospital mortality stratified by the length of delay in receiving appropriate therapy. *, P level for χ2 test for linear trend. Abbreviation: TTAT, time to appropriate therapy.