

# Preliminary experience of tigecycline treatment in critically ill children with ventilator-associated pneumonia

Shupeng Lin<sup>1</sup> , Lingfang Liang<sup>2</sup>,  
Chenmei Zhang<sup>2</sup> and Sheng Ye<sup>2</sup>

## Abstract

**Objective:** Ventilator-associated pneumonia (VAP) is a life-threatening complication for children who are treated in a paediatric intensive care unit. Tigecycline treatment of children with VAP has not been well studied. This study aimed to describe tigecycline use in children with VAP in a tertiary care hospital.

**Methods:** We conducted a retrospective chart review in a tertiary hospital from May 1, 2012 to May 1, 2017.

**Results:** Twenty-four children (20 girls) with median age of 8 months (range, 27 days to 6 years and 9 months) were treated with tigecycline. In-hospital mortality was 41.7% (10/24). The primary diagnosis was congenital heart disease (15/24). A total of 70.8% (17/24) of patients received a loading dose (1.5 mg/kg), followed by 1 mg/kg every 12 hours. The median duration of tigecycline therapy was 10.75 days (range, 3–21.5 days). Sulperazone was the most frequently used concomitant antibiotic. Eighteen pathogens were isolated in 16 cases. Tigecycline therapy failed in 41.6% (10/24) of patients and 20.8% (5/24) died. The pathogen was eradicated in 37.5% (6/16) of patients. No serious adverse effects were detected.

**Conclusion:** Tigecycline combined with other agents as salvage therapy in children with VAP is well tolerated. Our preliminary results show a positive clinical response.

<sup>1</sup>Zhejiang University School of Medicine Children's Hospital, Division of Hematology- Oncology, No. 57 Zhugan Road, Hangzhou, CN 310052

<sup>2</sup>Zhejiang University School of Medicine Children's Hospital, Pediatric Intensive Care Unit, No. 3333 Binsheng Road, Hangzhou, CN 310003

## Corresponding author:

Sheng Ye, Pediatric Intensive Care Unit, Zhejiang University School of Medicine Children's Hospital, No. 3333 Binsheng Road, Hangzhou, CN 310003.  
Email: [yeshengchina@zju.edu.cn](mailto:yeshengchina@zju.edu.cn)



## Keywords

Tigecycline, ventilator-associated pneumonia, children, *Acinetobacter baumannii*, congenital heart disease, pathogen

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## Introduction

Ventilator-associated pneumonia (VAP) is defined as pneumonia occurring in mechanically ventilated patients that develops at least 48 hours after introduction of mechanical ventilation. VAP is the most common cause of device-associated health-care-associated infections in the paediatric intensive care unit in developing areas, with an incidence from 9.0 to 30.8 per 1000 ventilator-days. VAP is associated with an increased risk of death and prolonged duration of mechanical ventilation.<sup>1–3</sup> Antibiotics are important in VAP treatment, but it is currently challenged by multidrug-resistant (MDR) bacteria. Gram-negative bacteria, such as *Acinetobacter baumannii*, are the main pathogens in children with VAP, and they are resistant to many broad-spectrum antibiotics, such as carbapenems.<sup>1</sup>

Tigecycline is a tetracycline class antibacterial that is indicated for patients aged 18 years and older. Tigecycline is prescribed for complicated skin, skin structure, and intra-abdominal infections and community-acquired bacterial pneumonia, especially in those infected by MDR bacteria.<sup>4</sup> A phase III, multicentre, randomized, double-blind study that included 945 adults showed that tigecycline was not superior to imipenem/cilastatin in patients with VAP regarding clinical response.<sup>5</sup> However, tigecycline is still a choice in critically ill children when alternatives are unavailable because of its wide antibacterial spectrum.

Since tigecycline was approved by the state food and drug administration in

early 2012, it may be prescribed in consideration of the risk-benefit ratio when no alternative antibacterial drugs are available in critically ill children in our hospital. In this study, we retrospectively reviewed tigecycline therapy in children with VAP in the past 5 years in our hospital, and investigated its efficacy and safety.

## Methods

This was a retrospective review study that was conducted in a children's hospital affiliated to Zhejiang University, School of Medicine in China between May 1, 2012 and May 1, 2017. This hospital consists of 1900 beds and only admits patients aged younger than 18 years. This retrospective study was approved by the Medical Ethics Committee of Zhejiang University School of Medicine Children's Hospital (approval number: 2017-IRB-038). Data collection of the patients was verbally approved by the patients' parents.

### *Selection of patients and study design*

All patients who received tigecycline for VAP were identified by the hospital information system and were enrolled if patients received at least 2 days (4 doses) of administration of tigecycline. A custom made MS excel database (Microsoft Excel 2007) of patients was created to record demographic and medical data. Demographic data included age, sex, and weight, and medical data included the following characteristics: medical history (underlying disease), dose

and duration of tigecycline therapy, information of other antimicrobial agents (prior or concomitant to tigecycline treatment), invasive procedures (i.e., deep venous catheterization), and laboratory tests. Laboratory tests comprised counts of leukocytes and neutrophilic granulocytes, C-reactive protein levels, procalcitonin levels, microorganisms (results of blood/bronchial or other cultures and antimicrobial susceptibility testing), biochemistry (aspartate transaminase, alanine aminotransferase, bilirubin, creatinine, and amylase levels), and coagulation (activated partial thromboplastin time and fibrinogen). All of these data were collected at the time of starting and ending tigecycline therapy.

### *Tigecycline administration*

Tigecycline (Pfizer Inc., New York, NY, USA) vials were used, each containing 50 mg of dry powder. Tigecycline was administered intravenously after being dissolved in normal saline and infused over 1 hour (according to its instruction).

**Definitions.** According to the Centers for Disease Control and Prevention, VAP was diagnosed by the presence of new or progressive radiographic evidence of a pulmonary infiltrate for longer than 48 hours after initiation of mechanical ventilation, and the presence of clinical signs and symptoms of pneumonia (fever, purulent sputum, leukocytosis, oxygen desaturation).<sup>6</sup> The purpose of tigecycline treatment was considered empiric or targeted. The term empiric indicated that administration was started based on surveillance data or no response to other antimicrobials, while targeted indicated that the patient was treated according an antimicrobial susceptibility report. The course of intravenous tigecycline administration was defined as a period of continuous tigecycline administration in the same patient. Bacteria resistant to at least three

antimicrobial agents of different antimicrobial categories were considered to be MDR. Antimicrobial susceptibility testing of bacteria was performed based on the clinical laboratory standards institute guidelines and the break points for tigecycline as defined by the American Food and Drug Administration. The tigecycline minimum inhibitory concentrations (MICs) for *Acinetobacter* in our hospital are susceptible (MIC = 2 µg/mL), intermediate (MIC = 4 µg/mL), and resistance (MIC ≥ 8 µg/mL).

### *Evaluation of outcome and adverse events.*

Resolution of clinical manifestation and microbial eradication were the primary outcomes that were evaluated to determine tigecycline efficacy. "Cured" was considered when clinical and microbiological results returned to normal and no other antibiotics were required. If patients improved and required antimicrobial degradation, they were considered as "improved". Patients who died and who had persistent clinical signs and symptoms of VAP were considered as failure of treatment. The in-hospital mortality and tigecycline toxicity were recorded in all of the patients. Occurrence of teeth discoloration (yellow-grey-brown) was confirmed by a telephone survey for survivors.

### *Statistical analysis*

All statistical analysis was performed using IBM SPSS Statistics, version 22.0 (IBM Corp., Armonk, NY, USA). The chi-square test or Fisher's exact test for small samples was used for categorical variables when necessary. The Student's t-test was used for comparison of continuous variables.<sup>7</sup> A p value less than 0.05 was considered to be statistically significant.

## Results

### Characteristics of patients

Twenty-four children (20 girls) with a median age of 8 months (range, 27 days to 6 years and 9 months) were treated with tigecycline for VAP between May 1, 2012 and May 1, 2017. All of the patients received tigecycline treatment for at least 2 days (4 doses) and no patients were excluded. The median time of mechanical ventilation and intensive care unit (ICU) length of stay were 21.5 days (range, 5–86 days) and 45 days (range, 6–86 days), respectively. In-hospital mortality was 41.7% (10/24). Two of the 24 (8.3%) patients had all medical support withdrawn in consideration of disease severity and financial problems. Three deaths were attributable to severe infection. Congenital heart disease comprised over half (15/24) of the primary disease. Locations of infection comprised blood and catheters. A total of 19 patients received cardiopulmonary bypass surgery (15/24), closed thoracic drainage (1/24), pelvic drainage (1/24), oesophagogastrotomy (1/24), and skin debridement (1/24). The characteristics of the patients are shown in Table 1.

### Use of tigecycline, prior drugs, and concomitant drugs

Use of tigecycline, previous drugs, and concomitant drugs is shown in Table 2. A total of 70.8% (17/24) of patients received a loading dose of 1.5 mg/kg, followed by 1 mg/kg every 12 hours. A total of 25% (6/24) of patients were provided a loading dose of 2 mg/kg and there was no loading dose in one patient. Most (16/24) prescriptions were targeted, according to spectrum culture results, and others (8/24) were empirically used in consideration of the clinical condition. Prior drugs, such as sulperazone, piperacillin/tazobactam, and

meropenem, before tigecycline administration were administered and failed to lead to any improvement. The median duration of previous drugs was 7.5 days (range, 2–26 days). Sulperazone (13/22) was the most frequently used concomitant drug, followed by piperacillin/tazobactam (5/22). The median duration of tigecycline therapy was 10.75 days (range, 3–21.5 days). The remaining two patients received tigecycline alone.

### Isolated pathogen

Table 2 shows that there were 18 pathogens isolated in 16 patients and all were gram-negative bacteria. *A. baumannii* was the predominant microbiology and comprised 87.5% (14/16). Most of the *A. baumannii* (11) pathogens were susceptible to tigecycline. Only one strain of *A. baumannii* was resistant to tigecycline and two strains behaved with intermediate susceptibility to tigecycline. However, *A. baumannii* in case 5 developed resistance after 7 days of tigecycline administration.

### Tigecycline efficacy

A total of 41.6% (10/24) of patients showed failure of tigecycline therapy, 20.8% (5/24) of patients died, and one patient abandoned this therapy because of critical illness. Eight patients achieved clinical improvement in total. In targeted therapy cases, 37.5% (6/16) of patients were pathogen-negative at the end of treatment. These results are shown in Table 2.

### Adverse events

Because all of the patients were ventilated, data on nausea or vomiting were not available. There were no reports of diarrhoea, increased levels of aspartate transaminase or bilirubin, or a decrease in fibrinogen concentrations. No survivors developed teeth discoloration when talked to by telephone.

**Table 1.** Patients' characteristics.

No.	Age (y/mo/d)	Sex (M/F)	Underlying disease	Infection	Invasive procedure	Mechanical ventilation time (d)	ICU stay (d)	Hospital outcome	Cause of death (yes/no)
1	8 mo, 17 d	M	CHD	VAP	Open heart surgery with CPB	38	62	Cured	No
2	10 mo, 5 d	F	CHD	VAP+catheter	Open heart surgery with CPB	12	33	Cured	No
3	2 mo, 28 d	M	CHD	VAP	Open heart surgery with CPB	43	56	Cured	No
4	8 mo, 17 d	M	CHD	VAP	Open heart surgery with CPB	20	55	Cured	No
5	3 y, 7 mo	M	CHD	VAP	Open heart surgery with CPB	40	60	Died	No
6	3 y, 8 mo	M	CHD	VAP	Open heart surgery with CPB	40	60	Died	No
7	6 mo, 17 d	F	CHD	VAP	Open heart surgery with CPB	41	52	Cured	No
8	1 y, 9 mo	M	Drowning	VAP	None	11	14	Died	No
9	1 y, 8 mo	M	CHD	VAP+blood	Open heart surgery with CPB	40	56	Improved	No
10	5 y, 4 mo	F	CHD	VAP+blood	Open heart surgery with CPB	11	57	Cured	No
11	6 y, 9 mo	M	CAP	VAP	Closed thoracic drainage	22	23	Died	Yes
12	8 mo, 18 d	M	CHD	VAP	Open heart surgery with CPB	15	22	Died	No
13	4 mo, 16 d	M	BPD	VAP+urinary tract	Pelvic drainage	16	38	Cured	No
14	1 mo, 22 d	M	CHD	VAP	Open heart surgery with CPB	12	19	Cured	No
15	27 d	M	CEA	VAP	Oesophagostomy	15	24	Died	No
16	4 mo, 28 d	F	CHD	VAP+blood	Open heart surgery with CPB	86	86	Improved	No
17	1 mo, 24 d	M	CHD	VAP+blood	Open heart surgery with CPB	36	36	Died	No
18	7 mo, 11 d	M	CHD	VAP+blood+catheter	Open heart surgery with CPB	44	44	Abandoned	No
19	4 y, 6 mo	F	Burn	VAP+blood	Skin debridement	11	73	Improved	No
20	4 y, 4 mo	F	CHD	VAP+catheter	Open heart surgery with CPB	32	47	Cured	No
21	2 y, 3 mo	M	HPS	VAP+blood	None	21	24	Died	No
22	2 mo, 11 d	F	Sepsis	VAP+blood	None	6	6	Abandoned	No
23	4 mo, 14 d	F	Cerebral dysplasia	VAP+blood	None	27	46	Died	Yes
24	1 mo	M	HPS	VAP+blood	None	5	9	Died	Yes

y: years; mo: month; d: days; M: male; F: female; VAP: ventilator-associated pneumonia; ICU: intensive care unit; CHD: congenital heart disease; CAP: community-associated pneumonia; BPD: bronchopulmonary dysplasia; CPB: cardiopulmonary bypass; CEA: congenital oesophageal atresia; HPS: haemophagocytic syndrome. Cause of death refers to whether infection is the leading cause of death.

**Table 2.** Use of tigecycline, concomitant drugs, prior drugs, isolated pathogens, and efficacy.

No.	L dose	M dose	Type of therapy	Prior drug	Duration of prior drug (days)	Concomitant drug	LOT (days)	Isolate (tigecycline susceptibility)	MO	CO
1	1.5	I	Targeted	SPZ	15	No	20.5	<i>Acinetobacter baumannii</i> (NA)	P	Improved
2	1.5	I	Targeted	MEM	7	VMC+SPZ	7.5	<i>A. baumannii</i> (NA)	P	Failed
3	1.5	I	Empirical	LFX	12	PRC/TZB	21.5	Negative	P	Improved
4	1.5	I	Empirical	SPZ	6	PRC/TZB	21.5	<i>Burkholderia cepacia</i> (NA), <i>Pseudomonas aeruginosa</i> (NA)	P	Improved
5	1.5	I	Targeted	PRC/TZB	4	SPZ	10	<i>A. baumannii</i> (S)	P	Failed
6	1.5	I	Targeted	SPZ	26	LFX	8	<i>A. baumannii</i> (S)	P	Failed
7	1.5	I	Targeted	SPZ	6	SPZ	19.5	<i>A. baumannii</i> (S)	E	Failed
8	2	I	Targeted	MEM	3	SPZ	6.5	<i>Klebsiella pneumoniae</i> (I), <i>Proteus mirabilis</i> (R)	P	Failed
9	1.5	I	Empirical	SPZ	8	PRC/TZB	8.5	<i>B. cepacia</i> (R)	P	Failed
10	1.5	I	Empirical	LFX	16	PRC/TZB	16	Negative	P	Improved
11	2	I	Empirical	PRC/TZB	2	SPZ	14.5	Negative	P	Failed
12	1.5	I	Targeted	SPZ	6	PRC/TZB	3.5	<i>A. baumannii</i> (S)	E	Died
13	2	I	Empirical	MEM	13	MEM	11.5	Negative	P	Improved
14	1.5	I	Targeted	SPZ	3	SPZ	13.5	<i>A. baumannii</i> (I)	E	Improved
15	1.5	I	Targeted	SPZ	15	SPZ	4.5	<i>A. baumannii</i> (I)	E	Died
16	1.5	I	Empirical	SPZ	12	SPZ	17.5	<i>A. baumannii</i> (S)	P	Improved
17	1.5	I	Targeted	PRC/TZB	3	SPZ	8.5	<i>A. baumannii</i> (S)	E	Failed
18	1.5	I	Targeted	PRC/TZB+LFX	5	SPZ+AMK	17.5	<i>A. baumannii</i> (S)	P	Failed
19	1.5	I	Targeted	PRC/TZB	11	SPZ	18.5	<i>A. baumannii</i> (I)	P	Improved
20	1.5	I	Targeted	MEM	12	SPZ	20.5	<i>A. baumannii</i> (R)	P	Failed
21	2	I	Targeted	MEM	26	SPZ+LZD	6.5	<i>A. baumannii</i> (S)	E	Died
22	0	I	Targeted	TIN	4	ETM	3	<i>Stenotrophomonas maltophilia</i> (S)	P	Abandoned
23	2	I	Targeted	LFX	20	no	4.5	<i>Chryseobacterium meningosepticum</i> (I)	P	Died
24	2	I	Empirical	MEM	4	MEM	5	<i>K. oxytoca</i> (S)	P	Died

L dose: loading dose (mg/kg); M dose: maintenance dose (mg/kg every 12 hours); LOT: length of treatment; S: susceptible; I: intermediate; R: resistance; NA: not applicable; MO: microbiological outcome; CO: clinical outcome; P: persistence; E: eradication; VMC: vancomycin; TIN: tienam; SPZ: sulperazone; PRC/TZB: piperacillin/tazobactam; LFX: levofloxacin; MEM: meropenem; LZD: linezolid; ETM: erythromycin; AMK: amikacin

## Discussion

To the best of our knowledge, this is the first report of tigecycline use in children with VAP. Although tigecycline has a broad antibacterial spectrum, it is not recommended for VAP according to its instructions.<sup>4</sup> There is no reference about the use of tigecycline in VAP children and the efficacy and dosage of tigecycline in VAP adults is still controversial.<sup>5,8</sup>

The results of our study were not encouraging. The overall improvement rate was 33% (8/24), the mortality rate was 20.8% (5/24), and the microbiological eradication rate was 30% (6/20). According to a cohort study in Pakistan, the overall mortality of children with VAP was 23%.<sup>9</sup> Another study on tigecycline that was conducted in an adult population reported an improvement rate of 37.1% and a mortality rate of 13.1%.<sup>5</sup> Therefore, our patients did not appear to benefit from tigecycline administration, which might be explained from two aspects.

One reason for this lack of benefit is that tigecycline was off-label in children with VAP. Tigecycline was prescribed only in severe infections as a salvage therapy and initiation of tigecycline was later than that in adults, as reported in other studies.<sup>8</sup> In fact, only a small portion of deaths were directly attributable to severe infection in our study, and other causes included multi-organ dysfunction or irreversible brain damage due to drowning. A similar result was concluded in a study that included 13 patients with severe infection who had tigecycline treatment.<sup>10</sup> Furthermore, many patients had other severe infections, such as blood stream infection and catheter-related infection. McGovern et al found that tigecycline had no advantage in treating patients with VAP combined with sepsis, and that it even might increase mortality.<sup>11</sup> In the real clinical situation, a patient with multiple severe infections usually has greater severity

and a higher propensity to organ dysfunction, treatment failure, and death.

Currently, there is no consensus on the use of tigecycline for children with VAP, and the appropriate dosage of tigecycline remains unclear.<sup>12</sup> The only available reference for tigecycline use in children recommended 1.2 mg/kg every 12 hours in children aged 8 to 11 years with complicated intra-abdominal infection, complicated skin and skin structure infections, and community-acquired pneumonia.<sup>13</sup> Studies that involved the adult population with VAP showed that a regular dosage may not have an effect and a higher dosage (150–200 mg/d) was usually recommended to achieve better clinical outcomes and microbiological eradication.<sup>5,14</sup> All patients in our study were younger than 8 years, with the youngest child was aged only 27 days. For these patients, tigecycline is not indicated according to drug instructions. Additionally, a conservative dosage (loading dosage of 1.5–2 mg/kg, maintenance dosage of 1.0 mg/kg every 12 hours) was used in consideration of any conceivable adverse events, such as liver or kidney function damage. Therefore, future studies are required to determine an appropriate dosage for children with VAP.

All pathogens that were isolated were gram-negative bacteria and *A. baumannii* was the predominant pathogen in our study. This finding is in line with recent research showing that *A. baumannii* is one of the major pathogens in VAP.<sup>1,15</sup> As an opportunistic pathogen, *A. baumannii* often infects those who are seriously ill, those compromised by surgical procedures, those with severe immunosuppression, or those with invasive life support instruments, such as mechanical ventilation and surgical drainage.<sup>16</sup> MDR is easily developed because of its unique mechanisms. In our patients, there were at least two of the following risk factors: mechanical ventilation, surgical procedures, severe immunosuppression,

and surgical drainage. The MIC confirmed that all documented cases of *A. baumannii* were MDR with resistance to carbapenems, and one patient developed resistance to tigecycline during therapy. One report from Turkey showed that the rate of tigecycline-resistant *A. baumannii* could be as high as 25.8% in patients with VAP.<sup>17</sup> Therefore, tigecycline prescription should be carried out with more caution to abate drug resistance, and microbiology results may be necessary.

In most paediatric cases in our study, tigecycline was combined with other antimicrobial regimens and sulperazone was a common choice. This finding is in line with recent reports on tigecycline use in children with serious infection.<sup>10,18</sup> A total of 14 multinational, randomized (open-label or double-blind), and active-controlled (except for one) phase III and IV studies suggested that with appropriate monitoring, tigecycline may be useful for *Acinetobacter* infections alone or in combination with other anti-infective agents when other therapies are not suitable.<sup>19</sup> Moreover, a drug-sensitive test demonstrated that tigecycline in combination with cefoperazone-sulbactam appeared to be an ideal option in MDR *A. baumannii* treatment.<sup>20</sup>

Possible adverse events associated with tigecycline in children include nausea, vomiting, diarrhoea,<sup>13</sup> delay of neutrophil engraftment,<sup>21</sup> and acute pancreatitis.<sup>22</sup> All of the patients in our study were ventilated and critically ill, and assessing nausea and vomiting was difficult. However, there was no discontinuation or dose reduction of tigecycline due to adverse events in our case series, such as diarrhoea, elevated aspartate transaminase or bilirubin levels, and a decrease in fibrinogen levels. In a previous study, adverse events in adults with VAP who received a higher dosage of tigecycline than recommended (150 or 200 mg as a loading dose followed by 75 or 100 mg,

respectively) were mild to moderate and were tolerable in general.<sup>14</sup>

Definite conclusions on the efficacy and safety of tigecycline cannot be drawn based on our observational case series study. Our study was subject to selection bias and the clinical outcome may have been attributable to a temporal trend (e.g., not the effect of tigecycline). Furthermore, the concomitant use of other antibiotics makes interpretation of the results more challenging.<sup>23-26</sup> However, this observational study provides preliminary experience on salvage therapy with tigecycline in children with VAP.

In conclusion, tigecycline combined with other agents as salvage therapy in children with VAP is feasible and tolerable. However, until more data from randomized, controlled trials are available, tigecycline should be used in children with VAP when alternatives are limited, and the microbiological results should be considered.

### Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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### ORCID iD

Shupeng Lin  <http://orcid.org/0000-0002-9347-3098>

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