JPPT | Single Center Retrospective Study

Effect of Targeted Single-Dose Antibiotics to Reduce the Occurrence of Pediatric Central Line–Associated Bloodstream Infections Post Alteplase Administration

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OBJECTIVE Previous studies have shown an association between alteplase for line clearance and central line–associated bloodstream infections (CLABSIs). The objective of this study was to evaluate the use of post-alteplase antibiotics as a CLABSI reduction strategy in pediatric intensive care unit (PICU) patients.

METHODS This was a single center, retrospective, observational study evaluating PICU patients from January 1, 2014, through August 1, 2021, conducted at a tertiary academic PICU. Included in this study were critically ill patients who had 1 or more central venous lines (CVLs) requiring alteplase for line clearance. The primary objective was incidence of CLABSI occurrence post alteplase administration for CVL clearance, with or without targeted single-dose antibiotics (piperacillin-tazobactam or vancomycin) post alteplase. Secondary outcomes included evaluation of total alteplase administrations and risk factors associated with CLABSI occurrence.

RESULTS Two hundred fifty patients were included, with 156 receiving alteplase only, 82 piperacillin-tazobactam, and 12 vancomycin, and with median ages of 2.8, 3.8, and 3.8 years, respectively. Seven CLABSIs occurred in the alteplase-only group, with 0 incidences in both the piperacillin-tazobactam (exact OR, 0.12; exact 95% CI, <0.01–0.59; $p < 0.01$) and vancomycin (exact OR, 1.20; exact 95% CI, 0.03–9.80; $p = 1.00$) groups. Patients in the piperacillin-tazobactam group achieved statistical significance for CLABSI risk factors that may benefit by decreasing CLABSI incidence (p values <0.01–0.02).

CONCLUSIONS Alteplase use has been associated with CLABSIs. Providing a single dose of post-alteplase antibiotics targeting the most likely site-specific pathogens may reduce the incidence of CLABSIs.

ABBREVIATIONS CLABSI, central line–associated bloodstream infection; CoNS, coagulase-negative staphylococcus; CVL, central venous line; NHSN, National Healthcare Safety Network; PICU, pediatric intensive care unit; TPN, total parenteral nutrition

KEYWORDS alteplase; central line infections; pediatric intensive care unit; pediatrics; piperacillin-tazobactam; prophylactic antibiotics; vancomycin

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Introduction

Central venous lines (CVLs) are often used in pediatric intensive care units (PICUs) for medication administration, parenteral nutrition, hemodynamic monitoring, oximetric monitoring, and blood sampling.[1] Central line–associated bloodstream infections (CLABSIs) are a risk to pediatric patients for a variety of reasons, including increased morbidity, mortality, cost to patient care, and increased antibiotic use.[1–10] CLABSI prevention typically consists of an evidence-based bundle strategy that includes proper hand hygiene, sterile technique for manipulation and insertion of CVL, and regular dressing changes. Additional prevention techniques include antibiotic-coated catheters, antibiotic locks or flushes, and chlorhexidine application. Common interventions to treat an identified CLABSI include systemic intravenous antibiotics and CVL removal/replacement.[2,3] These strategies put patients at risk of adverse effects associated with the selected antibiotic, *Clostridium difficile* infections, and complications with the removal and reinsertion of central lines in high-risk patients.

Pediatric patients are at an increased risk of CVL occlusion primarily due to their small vessel size in comparison to the large bore size of tubing. This size differentiation may cause trauma to the vessel, activating a clotting cascade that can lead to line occlusion. Alteplase has been used for its fibrinolytic mechanism to clear central lines when occlusion is suspected to

be caused by a thrombus. Current literature has found an association with alteplase and increased CLABSI occurrence in pediatric patients compared with patients not receiving alteplase.[6] The use of alteplase for CVL occlusion also results in increased need for line access and manipulation, introducing further opportunities for line contamination and potential infection. Additional risk factors that have been associated with pediatric CLABSIs include CVL in place for >7 days, ≥2 CVLs in place, total parenteral nutrition (TPN), hematologic/immunologic conditions, malignancies, history of CLABSI, transfusion of blood products, age <1 year, and weight <5 kg.[8,9]

Blood clots are theorized to be a rich environment for pathogens to grow and replicate in; when alteplase is used, clots with infectious growth have the potential to be released and cause bloodstream infections.[4,6,7] The use of alteplase for CVL clearance is associated with increased CLABSI rates within 5 days post alteplase administration.[6] While alteplase may increase the risk of CLABSI development, a CVL with blood clots harboring infectious pathogens remains a possible source of infection for patients unable to clear the clot. Common pathogens associated with CLABSIs include coagulase-negative staphylococcus (CoNS), *Staphylococcus aureus*, *Enterococcus* spp, *Escherichia coli*, and *Klebsiella* spp.[11,12] Within our institution, the PICU found the following pathogens to be prevalent post alteplase administration: *Enterococcus faecalis*, *Klebsiella oxytoca*, *Pseudomonas aeruginosa*, and *Staphylococcus epidermidis* (Figure 1).

Recognizing the potential CLABSI risk associated with alteplase, our PICU implemented a targeted strategy to reduce the occurrence of CLABSIs by selecting a single dose of empiric antibiotics to cover our most common pathogens post alteplase.

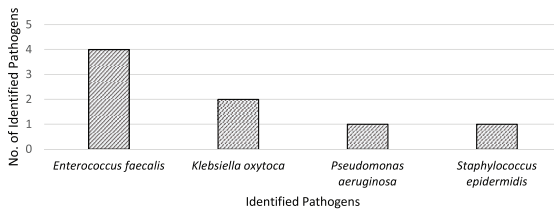
Materials and Methods

This retrospective observational study was conducted in a single center tertiary academic PICU. The study included all patients admitted to the PICU with a CVL who had suspected occlusion of a CVL catheter port and received alteplase for CVL clearance between January 2014 and August 2021. Subjects were excluded if they received study antibiotic within 24 hours prior to alteplase administration, if they received concurrent duplicative antibiotic coverage respective to study antibiotic (vancomycin: *S aureus*, *Enterococcus* spp; and piperacillin-tazobactam: *Enterococcus* spp, *Klebsiella* spp, and *P aeruginosa*), if the study antibiotic was administered >6 hours post alteplase administration, and if they had only a positive fungal blood culture result. Subjects were divided into 2 groups: patients who received alteplase for CVL clearance (January 2014–December 2018) or patients who received alteplase for CVL clearance plus empiric single-dose post-alteplase antibiotic (vancomycin: December 2018–May 2019; piperacillin-tazobactam: May 2019–August 2021), regardless of concurrent antibiotic therapy (see supplemental material, Supplemental Figure S4). See Supplemental Table S4 for full CVL alteplase and antibiotic protocol.

The primary objective was CLABSI occurrence after alteplase administration for CVL clearance. We hypothesized the addition of single-dose antibiotics post alteplase administration does not decrease the incidence of CLABSI occurrence. Alteplase 1-mg/mL dose was dependent on patient weight and line type (<5 kg: 0.1–0.3 mL, 5–30 kg: 0.5 mL, >30 kg: 1–2 mL). Study antibiotics included vancomycin (15 mg/kg/dose) from December 2018 through May 2019 and piperacillin-tazobactam (100 mg/kg/dose) from May 2019 through August 1, 2021. A CLABSI associated with alteplase administration was defined as a positive bacterial blood culture drawn from CVL within 5 days post alteplase administration.

Data collection was conducted via REDCap secure software (Research Electronic Data Capture; Vanderbilt University, Nashville, TN). Statistical analysis was conducted by a statistician within Penn State Health College of Medicine, with use of exact logistic regression for evaluation of the primary endpoint and risk-factor associations with a 95% CI for statistical significance.

Figure 1. CLABSI pathogens isolated in PICU from 2014–2018 post alteplase.



CLABSI, central line–associated bloodstream infection; PICU, pediatric intensive care unit.

Results

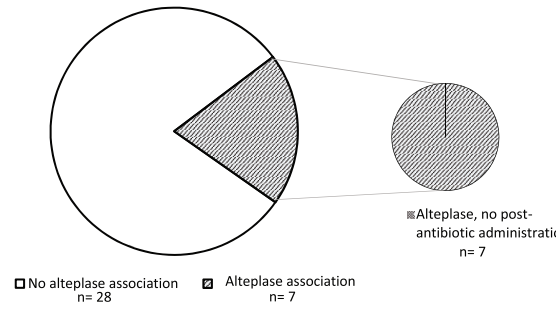
Overall, subject groups were similar despite the retrospective design and no randomization. Table 1 summarizes notable patient characteristics and assessed risk factors for CLABSI occurrence. The alteplase-only group had the most subjects (n = 156), followed by the piperacillin-tazobactam group (n = 82) and vancomycin group (n = 12). There was variability between the groups in terms of body weight, with the piperacillin-tazobactam group having the highest-weighing patients. Most patients in all 3 groups had diagnosed cardiac and/or pulmonary conditions. In the latter half of Table 1, the CLABSI risk factors show similarities between all 3 groups. Most patients had CVL for greater than 7 days, were younger than 1 year, were receiving TPN at the time of alteplase administration, and 30% to 40% of patients weighed less than 5 kg at the time of alteplase administration.

Table 1. Patient Characteristics

	Alteplase Only (n = 156)	Piperacillin-Tazobactam (n = 82)	Vancomycin (n = 12)
Male, n (%)	85 (55)	46 (56)	6 (50)
Weight, median (IQR), kg	12.4 (8.9–15.8)	18.6 (14.7–22.5)	14.8 (10.5–19.1)
Age, median (IQR), yr	2.8 (2.8–2.9)	3.8 (3.7–3.9)	3.8 (3.7–3.9)
Other antibiotics, n (%)	88 (56)	38 (46)	4 (33)
Medical condition, n (%)			
Cardiac	92 (59)	60 (73)	6 (50)
Pulmonary	93 (60)	56 (68)	8 (67)
CLABSI risk factors, n (%)			
CLABSI history	2 (1)	1 (1)	0
Packed red blood cells	118 (76)	59 (72)	9 (75)
CL duration >7 days	125 (80)	65 (79)	11 (92)
Multiple CLs	43 (28)	17 (21)	4 (33)
<1 yr old	88 (56)	44 (54)	7 (58)
TPN	104 (67)	35 (43)	6 (50)
<5 kg	65 (42)	30 (37)	4 (33)

CL, central line; CLABSI, central line–associated bloodstream infection; TPN, total parenteral nutrition

Figure 2. Total PICU CLABSIs from 2014–2021 and associated alteplase administrations.



CLABSI, central line–associated bloodstream infection; PICU, pediatric intensive care unit.

Table 2. CLABSI Incidence Comparison in Antibiotic Groups vs Alteplase-Only Group

Comparison	Exact OR (95% Exact CI)	p value
Alteplase and piperacillin-tazobactam vs alteplase only	0.12 (<0.01–0.59)	<0.01
Alteplase and vancomycin vs alteplase only	1.20 (0.03–9.80)	1.00

During the study period, 7 CLABSIs were identified within 5 days post alteplase administration (Figure 2). All 7 CLABSIs were in the alteplase-only group vs 0 in the piperacillin-tazobactam group (exact OR, 0.12; exact 95% CI, <0.01–0.59; p < 0.01) and 0 in the vancomycin group (exact OR, 1.20; exact 95% CI, 0.03–9.80; p = 1.00) (Table 2). Based on the OR and absolute risk reduction of 4.5% in the piperacillin-tazobactam group, the number needed to treat was 22 patients to prevent a CLABSI post alteplase administration.

Within the entirety of the study period, 1186 total doses of alteplase were administered for CVL clearance. Of these total administrations, 10 were associated with a CLABSI in 7 subjects within 5 days post alteplase administration, all of which occurred in the alteplase-only group. Regarding the 10 alteplase administrations associated with a CLABSI, 3 patients received 2 doses of alteplase associated with CLABSI diagnosis.

Table 3.1, Table 3.2, and Supplemental Table S3.3 show assessed risk factors and the association with CLABSI occurrence. Within the piperacillin-tazobactam group (Table 3.1), the evaluated risk factors showed exact ORs that were statistically significant to benefit from receiving piperacillin-tazobactam and preventing a CLABSI occurrence. When evaluating these same risk factors in the vancomycin group (Table 3.2), no risk factors showed statistical significance

Discussion

These data suggest that targeted single-dose antibiotics may be an effective method to reduce the occurrence of CLABSIs if administered within 6 hours of alteplase administration. Our PICU specifically chose empiric antibiotics with sufficient coverage against the most commonly identified CLABSI pathogens at our institution, with vancomycin targeting initially identified *Enterococcus* and *Staphylococcus* spp infections from December 2018 to May 2019. Beginning in May 2019, we transitioned to piperacillin-tazobactam for post-alteplase coverage, after re-evaluation of CLABSI pathogens revealed a lack of *Staphylococcus* spp infections and to add additional coverage for *P aeruginosa* and *Klebsiella* spp (see supplemental material, Supplemental Figure S3 for total CLABSI pathogens occurring between 2014-2021 and Figure S5 for number of CLABSI occurrences per year) While these agents are often selected for specific bacterial resistance or empirically for broad-spectrum coverage, the use of a single therapeutic dose may decrease antibiotic usage later in hospitalization by preventing

Table 3.1 Risk Factor Comparison in Piperacillin-Tazobactam Group vs Alteplase-Only Group

Piperacillin-Tazobactam	Exact OR (95% Exact CI)	p value
Hematologic/ immunologic conditions	0.12 (<0.01–0.60)	0.01
Malignancies	0.12 (<0.01–0.58)	<0.01
History of CLABSI	0.12 (<0.01–0.59)	<0.01
Transfusion of blood products	0.11 (<0.01–0.54)	<0.01
Duration of CVL >7 days	0.12 (<0.01–0.60)	0.01
Multiple CLs	0.13 (<0.01–0.66)	0.01
Age <1 yr	0.12 (<0.01–0.61)	0.01
TPN	0.15 (<0.01–0.77)	0.02
Weight <5 kg	0.13 (<0.01–0.62)	0.01

CL, central line; CLABSI, central line–associated bloodstream infection; CVL, central venous line; TPN, total parenteral nutrition

Table 3.2 Risk Factor Comparison in Vancomycin Group vs Alteplase-Only Group

	Exact OR (95% Exact CI)	p value
Hematologic/ immunologic conditions	1.20 (0.03–9.98)	1.00
Malignancies	1.28 (0.03–10.66)	1.00
History of CLABSI	1.18 (0.03–9.67)	1.00
Transfusion of blood products	1.14 (0.02–9.57)	1.00
Duration of CVL >7 days	1.10 (0.02–9.06)	1.00
Multiple CLs	1.12 (0.02–9.41)	1.00
Age <1 yr	1.17 (0.02–10.04)	1.00
TPN	1.40 (0.03–12.08)	1.00
Weight <5 kg	1.28 (0.03–10.69)	1.00

CL, central line; CLABSI, central line–associated bloodstream infection; CVL, central venous line; TPN, total parenteral nutrition

a CLABSI occurrence. Notably, 56% of alteplase-only, 46% of piperacillin-tazobactam, and 33% of vancomycin subjects were receiving additional antibiotic treatment for previously identified or presumed infection, unrelated to CLABSI.

Currently, limited data exist that evaluate the utility of prophylactic antibiotics to reduce CLABSI occurrence, with notable evidence gaps in PICU patients. Furthermore, studies evaluating prophylactic antibiotics to prevent CLABSIs associated with alteplase administration are not available. In adult autologous stem cell transplant patients, Ziegler and colleagues[13] evaluated the use of levofloxacin to prevent CLABSI occurrence in high-risk patients. Patients included in this study received prophylactic levofloxacin from the day of autologous stem cell transplant until one of the following occurred: day 13, absolute neutrophil count >500/mm^3 or neutropenic fever. A total of 324 patients were included in the study, 150 of whom received daily prophylactic levofloxacin. The levofloxacin group had reduced CLABSI incidence from 18.4% to 6.0% and reduced incidence of neutropenic fever.

Harms and colleagues[14] evaluated prophylactic amoxicillin in newborn infants to prevent CLABSIs. A total of 147 subjects were included in the randomized, placebo-controlled trial, 75 of whom received amoxicillin. The study found that patients receiving amoxicillin had bacterial contamination of catheter tip occurrence at 13.3% when compared with patients receiving no prophylactic amoxicillin, at 28.8% ($p < 0.05$). In comparison, a reduction in bacteremia was not significant (0% vs 2.7%). This study suggests that prophylactic amoxicillin may reduce the occurrence of bacterial contamination, a factor that contributes to bloodstream infections.[14]

Spafford and colleagues[15] evaluated the addition of vancomycin to parenteral nutrition to reduce catheter-related coagulase-negative staphylococcal sepsis in neonates. The study included 70 infants, 35 of whom received parenteral nutrition with vancomycin. Compared with the placebo group, the addition of vancomycin reduced CoNS infection from 40% to 22% ($p = 0.03$), reduced catheter-related sepsis from 15% to 0% ($p = 0.004$), and decreased the number of infants needing reinsertion of a central venous catheter ($p = 0.014$). This study concluded that the addition of vancomycin to parenteral nutrition might decrease multiple complications associated with an infected central venous catheter.[15]

Our study included a few prominent limitations. One key limitation that we were unable to assess was line care and access frequency. Our electronic health record system does not currently track the number of

times a line is accessed, which previous studies have confirmed increase the risk of CLABSI occurrence.[6] Nursing staff also received multiple line-care education sessions to improve and enhance central line care to reduce CLABSI occurrence. This study spanned more than 7 years, introducing many potential confounders for CLABSI occurrence. During the study period, the National Healthcare Safety Network (NHSN) modified the definition of a CLABSI, which likely affected the number of diagnosed CLABSIs post definition change.[16] In an adult intensive care unit, the CLABSI rate was found to increase by 27.1% (p = 0.027) after the NHSN definition change, although this increase in CLABSI was not reflected in our patients receiving alteplase. Finally, a cumulative total of 52% of patients across all 3 groups were receiving additional antibiotics, which likely provided substantial protection against potential CLABSI pathogens, including the most prevalent CLABSI pathogen, CoNS. The widespread use of additional antibiotics across the study makes identified institutional CLABSI pathogens difficult to interpret and extrapolate to various patient populations. Owing to study constraints, we were unable to isolate patients to further delineate which risk factors may have led to a CLABSI vs the true effect of vancomycin/piperacillin-tazobactam in preventing a CLABSI in a patient with no additional antibiotic coverage and protection

While limited by the above reasons, this study suggests targeted single-dose antibiotics may provide protection against CLABSI occurrence after alteplase administration for line clearance. Knowledge of institution-specific pathogens helped guide antibiotic selection, leading to our use of piperacillin-tazobactam; however, widespread use of any broad-spectrum antibiotic may lead to antibiotic resistance and piperacillin-tazobactam may not be appropriate for every institution, based on identified common CLABSI pathogens. Future investigations should consider delineation of patient-specific CLABSI risk factors, which may allow for a more targeted approach and surveillance for changing patterns of antibiotic resistance associated with this single-dose strategy.

Conclusion

Single-dose post-alteplase antibiotic administration may be a viable strategy to reduce the incidence of CLABSIs by targeting the most likely patient- or institution-specific pathogens. Further studies should give significant consideration to patient and antibiotic selection strategies in an effort to reduce CLABSI occurrence associated with alteplase administration.

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Ethical Approval and Informed Consent. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation and have been approved by the appropriate committees at our institution.

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