Interventions for Occluded Central Venous Catheters: A Meta-analysis

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abstract

CONTEXT: Thrombotic occlusion is 1 of the most frequent complications in catheters implanted in children.

OBJECTIVE: To identify the interventions used to treat thrombotic events in long-term central venous catheters in pediatric patients with cancer.

DATA SOURCES: Electronic searches were performed in the Cumulative Index to Nursing and Allied Health Literature, Cochrane Central Register of Controlled Trials, Latin American and Caribbean Health Sciences Literature, LiVIVO, PubMed, Scopus, Web of Science, Google Scholar, OpenGrey, and ProQuest databases. There were no restrictions on language or publication period.

STUDY SELECTION: This systematic review was performed in 2 phases and included clinical trials and observational studies on drugs used to treat thrombotic catheter events in pediatric patients with cancer. The review was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis checklist, and the protocol was registered at PROSPERO (identifier CRD42018083555).

DATA EXTRACTION: The authors evaluated the quality of included studies using the Methodological Index for Nonrandomized Studies and Grading of Recommendations Assessment, Development and Evaluation methods. The meta-analysis was performed by using Stata software.

RESULTS: Ten studies were included. The drugs used to restore catheter function were alteplase, urokinase, and streptokinase. A meta-analysis of 6 studies revealed an overall restoration rate of 88% for alteplase.

LIMITATIONS: Reference studies were excluded when it was not possible to reliably extract data that met the inclusion criteria of this review. Sampling issues (absence of randomization, blinding, or a control group) were the main methodologic concerns for the included articles.

CONCLUSIONS: On the basis of the evidence obtained, thrombolysis is effective and potentially safe in this population.

Drs Costa and Ferreira conceptualized and designed the study, drafted the initial manuscript, and reviewed the manuscript; Ms Vieira and Dr Guerra designed the data collection instruments, collected data, conducted the initial analyses, and reviewed the manuscript; Drs Vasques and Reis conceptualized and designed the study, coordinated and supervised data collection and critically reviewed the manuscript for important intellectual content, and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

This trial has been registered with PROSPERO (https://www.crd.york.ac.uk/prospero/) (identifier CRD42018083555).

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Central venous catheters (CVCs) have been used for >3 decades in pediatric oncology. These devices are considered appropriate in the care of children with cancer and are commonly used for drug administration, blood sampling, and nutritional support. However, they are also associated with a variety of complications, including catheter occlusion.

CVC occlusion may be due to thrombus formation or nonthrombotic causes, such as catheter malposition or intraluminal drug precipitation. The most frequent causes of catheter dysfunction in pediatric patients are wall thrombi, intraluminal and CVC tip thrombi, or thrombi caused by fibrin sheaths. CVC occlusion may lead to inability to draw blood and/or infuse fluids.

CVC thrombotic occlusion is 1 of the most frequent complications, occurring in 20% to 40% of the catheters implanted in children. This type of CVC occlusion can lead to infection, thromboembolism, catheter dysfunction, or thrombus propagation, resulting in deep venous thrombosis.

Replacement or removal of an occluded CVC in a child who is sick may lead to discontinuation of therapy, need for sedation or general anesthesia, repeated surgical interventions, and significant cost increases associated with prolonged treatment and additional procedures. The treatment of CVC occlusion is less costly and faster than the surgical removal and replacement of the catheter, reducing the risk of adverse events (AEs) to the patient.

Fibrinolytic therapy has been used for >20 years in the treatment of CVC thrombotic occlusion. The fibrinolytic system in children is a dynamic, age-dependent system with unique characteristics that markedly influence the response to thrombolytic agents. In addition, the pathophysiological mechanisms of thrombosis in children are different from those in adults. Despite this, protocols for the administration of thrombolytic agents for restoration of catheter function in children with cancer are generally empirical and are extrapolated from adult guidelines; moreover, thrombolytic therapies differ in the type of drug used, dosing, and the duration of treatment.

A systematic review to evaluate interventions to restore patency of occluded CVCs has been previously published. However, the authors of this review examined a small number of randomized clinical trials that generally addressed the management of thrombotic occlusion, regardless of the type of catheter or the patient age and clinical condition. In addition, new technologies and studies have been developed since its publication, and there is a need to update the findings.

Although alteplase is the only drug approved by the US Food and Drug Administration (FDA) for restoration of catheter function in the United States, urokinase and streptokinase are available in other countries and continents for this purpose, despite established recommendations. Thus, the use of different types of thrombolytic agents for the treatment of CVC thrombotic occlusion around the world justifies the need for such a systematic review and meta-analysis.

In this systematic review, we aimed to identify the interventions used to treat thrombotic events involving long-term use of CVCs in pediatric patients with cancer.

**METHODS**

**Protocol and Registration**

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis checklist. The protocol was registered at the International Prospective Register of Systematic Reviews (PROSPERO) under identifier CRD42018083555.

**Eligibility Criteria**

**Inclusion Criteria**

This review included articles about clinical trials or observational studies involving pediatric patients with cancer (children and adolescents younger than 18 years) with partially or completely occluded long-term CVCs (totally implanted catheters [TICs] and tunneled catheters [TCs]), including all treated lumens and all types of cancer; in addition, this review included articles about interventions to treat thrombotic events by using pharmacologic and nonpharmacologic substances. Restoration of catheter function was defined as the ability to instill 5 mL of saline solution and to aspirate 3 mL of blood in patients weighing ≥10 kg or the ability to infuse 3 mL of saline solution and to aspirate 1 mL of blood in patients weighing <10 kg. There were no restrictions on language or publication period.

**Exclusion Criteria**

The studies were assessed in 2 phases. In phase 1 (title and abstract review), the following exclusion criteria were applied: (1) studies with use of a short-term CVC, hemodialysis catheter, peripherally inserted central catheter, apheresis catheter, umbilical catheter, or arterial catheter or with use of different types of catheters in the same study; (2) studies in adults or in mixed populations in which it was not possible to perform reliable extraction of data referring to children with cancer; (3) studies in which the authors evaluated interventions to prevent thrombotic events; and (4) reviews of the literature, letters, case reports, or protocols.

In phase 2 (full-text reading), the following additional criteria were applied: (5) studies in which authors...
did not investigate treatment of catheter occlusion, (6) duplicated data, (7) studies in which authors did not include patients with cancer, and (8) studies with incomplete data on the treated population or catheter type used.

**Search Methods**

We developed search strategies for each of the following databases: Cumulative Index to Nursing and Allied Health Literature (CINAHL), Cochrane Central Register of Controlled Trials (CENTRAL), Latin American and Caribbean Health Sciences Literature (LILACS), LIVIVO, PubMed, Scopus, and Web of Science. A gray literature search was performed by using Google Scholar, OpenGrey, and ProQuest Theses and Dissertations. The ending search date was February 16, 2018, across all databases. Hand searching of the reference lists of included studies was also performed. In addition, e-mails were sent to experts to inquire about additional studies relevant to the review.

Appropriate truncation and word combinations were selected and adapted for each database search (Supplemental Tables 3 through 12). All references were managed by using reference manager software (EndNote X7; Thomson Reuters, New York), and duplicates were removed.

**Search Outcomes**

The selection was completed in 2 phases. In phase 1, 2 reviewers (A.C.C.d.C. and N.N.P.V.) independently reviewed the titles and abstracts of all citations identified from databases. Articles that did not appear to meet the inclusion criteria were discarded. In phase 2, the same reviewers applied the inclusion criteria to the full text of the articles. The reference lists of selected studies were critically assessed by both examiners. Any disagreement in phase 1 or 2 was resolved by discussion until an agreement between the 2 authors was attained. When consensus was not reached, a third author (C.I.V.) was included for a final decision.

**Data Extraction and Synthesis**

Two reviewers independently collected data from the selected studies. A third reviewer assessed the accuracy of the information collected. For all included studies, the following characteristics were recorded: study characteristics (author, year, country of publication, and study design), sample characteristics (size, catheter type, and number of occluded CVCs), intervention characteristics (drug type, doses, infusion time, and follow-up time), outcome characteristics (efficacy [restoration of catheter patency] and safety), and the main conclusion. If the required data were not complete or the data presented could not be extrapolated, attempts were made by e-mail to contact the authors to retrieve missing information.

The efficacy outcome was expressed as the percentage of catheter function restored from the total sample of included studies.

After heterogeneity between the studies was assessed, a meta-analysis was performed for the data by using Stata software version 14 (Stata Corp, College Station, TX). Heterogeneity was calculated by using $I^2$, following the appropriate Cochrane guidelines. A value $>50\%$ was considered an indicator of substantial heterogeneity among studies, enabling the use of a random-effects model. When $I^2$ was $\leq50\%$, a fixed-effects model was used. The significance level was set at 5%.

**Quality Appraisal**

Risk of bias of selected studies was evaluated by using the Methodological Index for Nonrandomized Studies (MINORS) for nonrandomized clinical trials and observational studies. Two reviewers independently assessed the quality of each study. For judgment of risk of bias, items were scored as 0 (not reported), 1 (reported but inadequate), or 2 (reported and adequate). The ideal overall score was 16 for noncomparative studies and 24 for comparative studies. Disagreements between both reviewers were resolved by a third reviewer.

A summary of the overall strength of evidence available was performed by using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) method. A summary of findings table was produced by using GRADEpro software (McMaster University, Hamilton, Canada).

**RESULTS**

**Study Selection**

In phase 1, 3601 articles were found across the 7 databases. After duplicates were removed, 26 of the 2936 studies were selected for phase 2. A gray literature search was used to identify 242 articles, but none met the inclusion criteria. The reference lists of included studies were screened, and 23 articles were included. After 3 consecutive attempts in a period of 1 month, we did not obtain answers from the experts, and articles were not included through this type of search. Subsequently, 49 articles were obtained for full-text reading, and 39 articles were excluded (Supplemental Table 13). Therefore, only 10 studies fulfilled the eligibility criteria and were included in the qualitative synthesis. Of these, 6 matched the criteria used for the meta-analysis. A flow diagram of the process of identification, inclusion, and exclusion of studies is shown in Fig 1.

**Study Characteristics**

Of the 10 selected studies, 6 were clinical trials; of 4 observational studies, 3 were
based on evaluation of patient charts, and 1 was a prospective cohort study. CVC sample sizes ranged from 4 to 160 among a total of 447 long-term CVCs studied in 747 patients. Among the long-term CVCs used, 218 (48.3%) were TCs and 233 (51.7%) were TICs. Partial occlusion was evaluated in 4 studies (40%), and partial or total occlusion was evaluated in 6 studies (60%).

Partial occlusion was defined as the inability to withdraw 3 mL of blood, with a retained ability to infuse 5 mL of saline through the catheter. Complete occlusion was defined as the inability to withdraw 3 mL of blood and the inability to infuse 5 mL of saline through the catheter.

The drugs used for restoration of catheter patency were alteplase (n = 6), urokinase (n = 3), and streptokinase (n = 1). In all trials, investigators evaluated the efficacy of

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**FIGURE 1**
drugs without using a control group. In only 1 study was the same drug (urokinase) used in 3 different groups with 2 infusion regimens. The aim of the studies was to evaluate the efficacy and safety of the drugs in restoring catheter patency by using different doses and different infusion times. The restoration rate ranged from 50% to 97.5%, and the administration time ranged from 30 minutes to 48 hours. The authors of 2 studies reported AEs related to alteplase, including sepsis, catheter rupture, and blood dyscrasia (characterized as an abnormality of either prothrombin or partial thromboplastin time, or of fibrinogen, with increased bleeding events within 48 hours). There were no AEs reported in the other articles. The descriptive characteristics of the included articles are summarized in Table 1.

Results of Individual Studies
The Atkinson et al study included the smallest number of catheters, and alteplase was used at the standard 2-mg dose, achieving a success rate of 75%. It should be noted that the CVC used had already been treated with a urokinase bolus (10 000 IU) without success. The Blaney et al study included the largest number of catheters, with the same 2-mg dose of alteplase, and achieved a restoration rate of 83.1%.

Chesler and Feusner achieved a high success rate (88.1%) despite using a minimum dose of alteplase (0.5 mg). Fisher et al also used a lower dose of alteplase (1 mg) but achieved an even higher rate of restoration (92.8%). Iqbal et al used alteplase doses between 0.5 and 1 mg, depending on patient weight, and had the highest success rate among the included studies (97.5%). Peng et al used alteplase in doses ranging from 0.5 to 2 mg, achieving a restoration rate of 75.8%. Bagnall et al used urokinase at a dose of 200 IU/kg per hour in a prolonged infusion, achieving a success rate of 91.7%. The catheters used in this study had already undergone unsuccessful thrombolysis with consecutive alteplase boluses at 5000 and 10 000 IU.

Molinari et al used urokinase in 3 different doses and in 2 infusion protocols. Partially occluded CVCs were divided into 2 groups: 1 by using urokinase bolus administration of 5000 IU and another by using urokinase bolus administration of 25 000 IU. Fully occluded CVCs, or those refractory to the previously described treatments, received low-dose systemic urokinase at a dose of 1000 IU/kg per hour in a prolonged infusion that varied from 1 to 3 hours because low-dose systemic urokinase could be administered up to 4 times. Restoration rates in these 3 groups were 89.4%, 97%, and 77.8%, respectively.

The Winthrop and Wesson study had the earliest publication date, and the authors used a urokinase dose of 5000 IU, achieving a success rate of 66.7%. Tobiansky et al alone used streptokinase for CVC thrombolysis, in a dose of 5000 IU, and showed the lowest rate of restoration among the included studies (50%).

Synthesis of Results
Six of the 10 studies included were used in the meta-analysis. One study was excluded as unique in using streptokinase, and another was excluded because the catheters were treated with multiples doses of urokinase, making it impossible to identify the dose received through each catheter. In addition, 2 studies were excluded because the authors addressed the use of urokinase in totally different doses and infusion regimens, with considerable heterogeneity among them, not allowing for a reliable comparison. Because the heterogeneity among the studies was significant (59.22%; confidence interval 1.41–83.65), the random-effects model was chosen for the statistical analysis. After consideration of the alteplase intervention, the results revealed an overall CVC function restoration rate of 88% (total sample = 322 catheters) (Fig 2).

Risk of Bias of Individual Studies
Three studies were classified as having a high risk of bias because they scored ≤8 points (50% of the total score), and 3 other studies were classified as having a low risk of bias because they scored between 13 and 18 points. The other 4 studies were classified as having an unclear risk of bias because they scored between 9 and 11 points. More information about the MINORS scores is provided in Fig 3.

Risk of Bias Within Studies
Although the studies had different designs, the main methodologic problem concerned the sample. In most of the studies, including the clinical trials, convenience samples were used, without randomization of participants and without use of a control group.

Confidence in Cumulative Evidence
Using the GRADE summary of findings table, we found that the quality of evidence ranged from very low to low. This variation was directly related to the risk of bias as well as to heterogeneity among the studies (Table 2).

DISCUSSION
Thrombotic events are increasingly common and cause significant problems in children with cancer and those requiring a CVC. Despite this, guidelines for the management of long-term CVC occlusion are unavailable for the pediatric population. However, thrombolytic agents with established roles in the management of thrombotic CVC complications are adopted as the first
<table>
<thead>
<tr>
<th>Study Characteristics</th>
<th>Sample Characteristics</th>
<th>Intervention Characteristics</th>
<th>Outcome Characteristics</th>
<th>Main Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Author, Year; Country</strong></td>
<td><strong>Study Design</strong></td>
<td><strong>Sample Size, n (No. LT-CVCs occluded)</strong></td>
<td><strong>Catheter Type (n)</strong></td>
<td><strong>Drug Type (Dose)</strong></td>
</tr>
<tr>
<td>Bagnall et al, 1989; United States</td>
<td>Quasi-randomized study</td>
<td>58 (12)</td>
<td>TIC (2) and TC (10); did not clear after 2 boluses of urokinase (5000 IU/mL and 10 000 IU/2 mL)</td>
<td>Urokinase continuous infusion (200 IU/kg per lumen per h); up to 2 infusions</td>
</tr>
<tr>
<td>Molinari et al, 2004; Italy</td>
<td>Quasi-randomized study</td>
<td>84 (84)</td>
<td>TC (84)</td>
<td>IL-UK (5000 IU/mL or 25 000 IU/mL) in bolus; low-dose S-UK (1000 IU/kg per h); up to 4 infusions</td>
</tr>
<tr>
<td>Winthrop et al, 1984; Canada</td>
<td>Quasi-randomized study</td>
<td>14 (21)</td>
<td>TC (21)</td>
<td>Urokinase (5000 IU/2 mL)</td>
</tr>
<tr>
<td>Atkinson et al, 1990; United States</td>
<td>Quasi-randomized study</td>
<td>25 (4)</td>
<td>TIC (1) and TC (3); remained occluded after an initial bolus of 10 000 IU of urokinase</td>
<td>Alteplase (2 mg/2 mL); up to 2 doses</td>
</tr>
<tr>
<td>Blaney et al, 2006; United States</td>
<td>Open-label, quasi-randomized study</td>
<td>310 (180)</td>
<td>TIC (180)</td>
<td>Alteplase (2 mg/2 mL for wt (\geq 30) kg or 110% of the estimated internal volume of CVC for wt (&lt; 30) kg; not to</td>
</tr>
<tr>
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<tr>
<td><strong>Study Design</strong></td>
<td><strong>Sample Size, n</strong></td>
<td><strong>Drug Type (Dose)</strong></td>
<td><strong>Follow-up</strong></td>
<td><strong>Efficacy</strong></td>
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<tr>
<td><strong>Country</strong></td>
<td></td>
<td><strong>Infusion Time, h</strong></td>
<td><strong>Time</strong></td>
<td><strong>with alteplase. Serious AEs included major hemorrhage (defined as severe blood loss [&gt;5 mL/kg] or blood loss resulting in hypotension or requiring transfusion), thrombosis, embolic events (defined as any serious embolic event, including pulmonary or arterial events [eg, stroke, peripheral or major organ] or cholesterol plaque), sepsis, catheter-related complications, or any other serious adverse event. In total, 9 serious AEs were reported in 8 patients, 2 of which were assessed by the investigator as related to alteplase administration (1 case of sepsis and 1 case of a ruptured catheter lumen). No patients experienced ICH.</strong></td>
</tr>
<tr>
<td>Retrospective observational study (review of patient medical records)</td>
<td>42 (42) TC (40) and TIC (2)</td>
<td>Alteplase (0.5 mg/1 mL); up to 2 doses</td>
<td>0.5 and 1 mL</td>
<td>0.5 and 1 mL</td>
</tr>
<tr>
<td>United States</td>
<td></td>
<td></td>
<td>30 d</td>
<td>with alteplase. Serious AEs included major hemorrhage (defined as severe blood loss [&gt;5 mL/kg] or blood loss resulting in hypotension or requiring transfusion), thrombosis, embolic events (defined as any serious embolic event, including pulmonary or arterial events [eg, stroke, peripheral or major organ] or cholesterol plaque), sepsis, catheter-related complications, or any other serious adverse event. In total, 9 serious AEs were reported in 8 patients, 2 of which were assessed by the investigator as related to alteplase administration (1 case of sepsis and 1 case of a ruptured catheter lumen). No patients experienced ICH.**</td>
</tr>
<tr>
<td>Retrospective observational study (review of patient medical records)</td>
<td>22 (14) TC (9) and TIC (5)</td>
<td>Alteplase (1 mg/1 mL); up to 2 doses</td>
<td>0.5–3 mL</td>
<td>0.5–3 mL</td>
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<tr>
<td>United States</td>
<td></td>
<td></td>
<td>24 h</td>
<td>Alteplase was safe and effective in restoring patency of occluded CVCs in infants and children.</td>
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<tr>
<td>Study Characteristics</td>
<td>Sample Characteristics</td>
<td>Intervention Characteristics</td>
<td>Outcome Characteristics</td>
<td>Main Conclusion</td>
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<tr>
<td><strong>Author, Year; Country</strong></td>
<td><strong>Study Design</strong></td>
<td><strong>Catheter Type</strong></td>
<td><strong>Drug Type (Dose)</strong></td>
<td><strong>Infusion Time, h</strong></td>
</tr>
<tr>
<td>Iqbal et al, 2002; Saudi Arabia</td>
<td>Quasi-randomized study</td>
<td>40 (40) TC (3) and TIC (37)</td>
<td>Alteplase (1 mg/mL for wt &gt; 10 kg and 0.5 mg/0.5 mL for wt &lt; 10 kg); up to 2 doses</td>
<td>1–2</td>
</tr>
<tr>
<td>Peng et al, 2011; Australia</td>
<td>Retrospective observational study (review of patient charts)</td>
<td>89 (62) TC (36) and TIC (26)</td>
<td>Alteplase (0.5 mg/2 mL, 0.5 mg/2 mL, 2 mg/2 mL, or 2 mg/3 mL, according to the clinical practice guideline); up to 2 doses</td>
<td>&lt;2, 2–4, and &gt;4</td>
</tr>
<tr>
<td>Tobiansky et al, 1997; Australia</td>
<td>Observational study, cohort study</td>
<td>63 (8) TC and TIC (8)</td>
<td>Streptokinase (5000 IU/mL)</td>
<td>6</td>
</tr>
</tbody>
</table>
approach to restore catheter patency.\(^5\)

In this systematic review, we investigated the available evidence for the interventions used in the treatment of thrombotic events in long-term CVCs in pediatric patients with cancer. Among interventions used to restore catheter function, alteplase was the most frequent, followed by urokinase. No nonpharmacologic intervention was identified.

Alteplase is a recombinant tissue plasminogen activator and is considered the first option in the noninvasive treatment of CVC thrombotic occlusion. The benefit of alteplase is its high specificity for fibrin, low immunogenicity, and short systemic half-life (5 minutes). This protease converts plasminogen to plasmin when in contact with fibrinous material, promoting thrombolysis.\(^27\)

The use of alteplase in the restoration of catheter function was approved in September 2001 by the FDA after 2 clinical trials,\(^28,29\) but the population used in these studies consisted predominantly of adult patients, prompting the need for a phase IV study to clarify the safety and efficacy of the drug in the general pediatric population. The results of this research\(^8\) corroborated the results of previous studies regarding the safety and efficacy of alteplase in restoring CVC function in children, regardless of age, weight, or type of catheter used.

The alteplase dose for restoration of catheter patency depends on patient weight and the filling volume of the occluded lumen. The FDA,\(^28,29\) the manufacturer,\(^30\) and the American College of Chest Physicians\(^31\) recommended administration of up to 2 doses of 2 mg (2 mL) for patients weighing $\geq 30$ kg and up to 2 doses of 1 mg/1 mL for patients weighing $< 30$ kg; the dose should be up to 110% of the volume of the occluded catheter, not exceeding 2 mL. However, in this systematic review, large dose variations were observed, ranging from 0.5 mg/0.5 mL to 2 mg/3 mL.

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FIGURE 2
Meta-analysis of restoration of catheter function with alteplase (sample = 322). Results are from the random-effects model meta-analysis. ES, effect size.
with different dose standardizations in relation to the child’s weight, differing from the recommendations described previously.

There are some differences in the literature related to the drug infusion time; however, the FDA and the manufacturer recommend that alteplase remain within the catheter for 30 minutes and that if function is not restored within that time, 90 minutes be added for a total time of 120 minutes for the first dose. If the CVC remains occluded, a second intraluminal dose should be administered for an equal period of time, extending the infusion time to 240 minutes.32 With some slight variations, in this review, most studies in which alteplase was used followed the recommended treatment times.

Alteplase was generally well tolerated in clinical trials in pediatric populations, with a reported low incidence of AEs such as sepsis, minor bleeding (gastrointestinal bleeding, hematomas), fever, and venous thrombosis.32 The studies included in this review reported AEs considered serious and related to the drug, including 1 case of sepsis and 1 case of catheter rupture. Particular attention should be paid to sepsis because a positive correlation was observed between the use of alteplase for treatment of occluded catheters and the development of CVC-associated bloodstream infection. This correlation probably reflects the potential of the thrombus to contain biofilm, making alteplase a vehicle for bacterial dissemination when infused into the catheter.33

Although variations in doses and infusion times were found, the authors of the studies considered alteplase to be safe and effective in restoration of CVC patency. However, one should always consider the risk of bleeding associated with thrombolytic therapy, especially when the drug is used in children younger than 2 years and those weighing <10 kg because there are few studies in this population. The risk of catheter thrombosis and associated complications was significantly higher in young children and those with low weight. Higher risk was associated with the relatively greater size of the catheter compared with that of the small vessel lumen, reduced plasma levels of plasminogen and antithrombin III, and low catheter flow when compared with that in older children.26 In addition, there was a risk of systemic infusion of alteplase because of reduced priming of pediatric catheters.

Until 1999, urokinase was used worldwide in pediatric centers for treatment of CVC occlusion. However, in January 1999, the FDA withdrew

### TABLE 2 GRADE’s Summary of Findings Table

<table>
<thead>
<tr>
<th>Certainty Assessment</th>
<th>Study Design</th>
<th>Risk of Bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other Considerations</th>
<th>Certainty</th>
</tr>
</thead>
<tbody>
<tr>
<td>Restoration of catheter function with thrombolytic therapy</td>
<td>Clinical trials and observational studies</td>
<td>Serious&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Serious&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Not serious</td>
<td>Serious&lt;sup&gt;c&lt;/sup&gt;</td>
<td>None</td>
<td>☎️⭐️⭐️⭐️very low</td>
</tr>
<tr>
<td>Restoration of catheter function with alteplase</td>
<td>Clinical trials and observational studies</td>
<td>Serious&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Serious&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Not serious</td>
<td>Not serious</td>
<td>None</td>
<td>☎️⭐️⭐️⭐️low</td>
</tr>
<tr>
<td>Restoration of catheter function with urokinase</td>
<td>Clinical trials and observational studies</td>
<td>Serious&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Serious&lt;sup&gt;e&lt;/sup&gt;</td>
<td>Not serious</td>
<td>Not serious</td>
<td>None</td>
<td>☎️⭐️⭐️⭐️low</td>
</tr>
</tbody>
</table>

Question: What is the efficacy of interventions used to treat thrombotic catheter occlusion in pediatric patients with cancer?

<sup>a</sup> All included studies are nonrandomized with the absence of blinding and a control group.
<sup>b</sup> $I^2 = 62.86\%$.
<sup>c</sup> Use of different doses and different infusion times.
<sup>d</sup> $I^2 = 59.86\%$.
<sup>e</sup> $I^2 = 61.32\%$.
urokinase from the market because of suspected transmission of infectious agents associated with its use.\textsuperscript{34}

Urokinase is a type of plasminogen activator that also converts plasminogen to plasmin and has a half-life of \(\sim 12\) minutes. Although urokinase derived from human cells was withdrawn from the market in the late 1990s, this form is still available for use in Europe, having been replaced by the recombinant form derived from nonhuman cells in North America on the basis of FDA recommendations.\textsuperscript{10}

Studies have reported the use of urokinase in different doses, both for intraluminal bolus administration and for extended systemic infusion, with varying infusion times.\textsuperscript{5} The Italian Association of Pediatric Hematology and Oncology recommends use of urokinase for treatment of CVC occlusion at a bolus dose of 5000 IU/mL, with an infusion time of 15 to 60 minutes (recommendation IIB). In the case of persistent CVC occlusion that is resistant to intraluminal thrombolysis, and in the absence of catheter-related thrombosis, systemic urokinase infusion is indicated at 1000 IU/kg per hour for 3 hours, and may be repeated for a maximum of 12 hours, or at a dose of 200 IU/kg per hour for up to 24 hours (recommendation IIB).\textsuperscript{5} In most of the studies in this systematic review, doses were used in accordance with the literature.

A study\textsuperscript{34} conducted in several pediatric oncology and hematology centers revealed a low incidence of complications with use of urokinase (9%). Allergic reactions, fever and tremors, generation of microemboli, and minor hemorrhagic events were reported. According to the manufacturer, urokinase is contraindicated in patients with central nervous system neoplasms because of the risk of intracranial bleeding.\textsuperscript{34} However, no reports of this restriction of use or of severe bleeding events were found in the studies included in this review. In addition, no drug-related AEs were reported in the studies.

Studies conducted in the 1990s revealed that some catheters might have undergone multiple treatments with urokinase. This partial treatment of occlusion might have led to inadequate lysis of the thrombus and formation of a nidus for infection, thus increasing the risk of CVC-associated bloodstream infection and associated complications.\textsuperscript{34} Infectious complications related to the use of urokinase were not reported in the studies in this systematic review.

Streptokinase, a thrombolytic agent produced by \(\beta\)-hemolytic group C streptococci, is a single-chain polypeptide that reacts with circulating plasminogen, converting it to plasmin and forming streptokinase-plasmin complexes. The streptokinase-plasmin complex has increased thrombolytic activity compared with that of plasmin because it is not inactivated by \(\alpha_2\)-antiplasmin and \(\alpha_2\)-macroglobulin. Streptokinase has a half-life of 18 to 30 minutes, with an associated lytic effect ranging from 82 to 184 minutes.\textsuperscript{10} Streptokinase was widely used in the 1970s and 1980s; however, it induced the formation of antibodies, which led to resistance to treatment, as well as allergic reactions, such as fever, hypotension, urticaria, and bronchospasm, after repeated infusions.\textsuperscript{10} Thus, streptokinase is not considered to be a good alternative for treatment of CVC occlusion because of FDA warnings about the serious risk of anaphylaxis and the possibility of death.\textsuperscript{26}

A qualitative data analysis revealed that similar restoration rates were observed between studies in which alteplase and urokinase were used, with a marked decrease in efficacy with use of streptokinase. However, when the data were evaluated in a meta-analysis, alteplase appeared to be superior to other interventions.

Because of high heterogeneity in the doses of the thrombolitics studied, the duration of infusion of these drugs should be considered in clinical practice because a shorter infusion time optimizes the use of medical resources and avoids delays in treatment, increased costs, and associated complications.

Moreover, the safety factor is fundamental, especially in the pediatric population. Although the authors of the studies included in this review considered thrombolytic therapy as safe for restoration of CVC patency, more vigilance and follow-up protocols should be instituted when these drugs are used in children. The lack of well-established clinical protocols, the use of varied concentrations of drugs (often with no adequate correlation with child weight or occluded CVC intraluminal volume), and the paucity of studies in more vulnerable pediatric populations (low weight and young) induces an increased risk of AEs (especially hemorrhagic events) associated with therapy.

Another important factor to be taken into account in the use of thrombolitics in clinical practice is cost-effectiveness. Despite the efficacy and safety demonstrated in this population, the cost of drugs may be an impediment to their use in some centers. In the case of alteplase, despite the high cost, 1 study\textsuperscript{35} revealed that its use in clearing long-term CVCs was significantly less costly than catheter removal and replacement. This study revealed the cost/benefit in the use of alteplase not only in reducing hospitalization time but also in reducing the use of other services, such as radiology, laboratory, and nursing care, and material resources in general. In the case of urokinase, the authors of 1 study\textsuperscript{36} showed that its use in the pediatric population was cost-
effective, finding a high success rate in restoration of CVC patency (98%), with the estimated cost for catheter replacement >20 times greater than that for use of the drug.

As a methodologic limitation of this review, we highlight the exclusion of reference studies with representative samples and the use of other thrombolytics not described here that met the main outcome of this review (restoration of CVC function). However, some of these studies had a mixed population, and others had different types of catheters, and it was not possible to reliably extract the necessary data for the analysis; even after attempting to contact the authors by e-mail, it was not possible to aggregate this data for the review.

All included studies had a risk of bias related to the study population and the high heterogeneity between the doses used and infusion times; moreover, the quality of the evidence generated was not substantial. Although the evidence that was found tends to reiterate the success of thrombolytic therapy in the pediatric population, there are insufficient data for use in the preparation of robust drug protocols, including concentration and infusion time, to standardize and guide clinical practice for restoration of catheter function.

The authors of only 2 studies\(^8,22\) reported AEs related to thrombolytic therapy; this is an important item to consider in designing future studies.

**CONCLUSIONS**

In view of the evidence obtained, the most common interventions used for treatment of thrombotic catheter occlusion in pediatric patients with cancer were alteplase and urokinase. The studies included in this systematic review revealed that thrombolysis is effective and potentially safe in this population, with slight superiority of alteplase when compared with other interventions.

Although thrombolytic therapy is considered safe for restoration of patency in occluded catheters, more vigilance and follow-up protocols should be instituted when these drugs are used in children, especially in more vulnerable populations (low weight and very young). The impact of our results may affect catheter management, safety, and quality of life in pediatric patients with cancer.

**ABBREVIATIONS**

AE: adverse event
CENTRAL: Central Register of Controlled Trials
CINAHL: Cumulative Index to Nursing and Allied Health Literature
CVC: central venous catheter
FDA: US Food and Drug Administration
GRADE: Grading of Recommendations Assessment Development and Evaluation
LILACS: Latin American and Caribbean Health Sciences Literature
MINORS: Methodological Index for Nonrandomized Studies
TC: tunneled catheter
TIC: totally implanted catheter

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Interventions for Occluded Central Venous Catheters: A Meta-analysis
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