A Drug Use Evaluation of Alteplase 2 mg Vials at
Kingston General Hospital

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Abstract

**Background:** Alteplase, a recombinant tissue plasminogen activator, is a high alert medication with many indications. In Fiscal 2015, the expenditure of alteplase 2 mg vials increased by 64% at Kingston General Hospital (KGH), despite formulary restrictions and no change in acquisition cost. Applicable restrictions include: catheter occlusion, transcatheter thrombolysis, provocative mesenteric angiography, and intrapleural fibrinolysis. KGH Pharmacy Services is responsible for the drug budget to ensure expenditures are evidence-based and reflect value for money.

**Objective:** To assess appropriateness of the use of alteplase 2 mg vials at KGH because of the high and increasing expenditure.

**Methods:** A prospective, observational, drug use evaluation of alteplase was conducted over 52 days between October and December 2015, including all adult patients dispensed alteplase 2 mg vials during their hospital or renal unit visit. Patient demographics, adherence to KGH restrictions and evidence-based use, completeness of documentation, and wastage were analyzed.

**Results:** A total of 100 courses of therapy (50 renal unit, 50 non-renal unit) were included. Overall, 48% adhered to restrictions, 4% renal unit and 92% non-renal unit. Ninety-four percent of orders outside restrictions were evidence-based. Occluded central venous catheter (87%) and dialysis lock (88%) were the most common indications in non-renal unit and renal unit patients, respectively. Electronic and written orders were correct 54% of the time (90% renal unit and 12% non-renal unit); the most frequent discrepancies included incorrect route and not following hospital policy or standards. No wastage was identified for 88% of renal unit orders. Wastage was unclear in 32% of non-renal unit patients as documentation was inconsistent, with 16% of orders having no documentation of administration.

**Conclusion:** The results support implementation of additional physician order sets for alteplase, revising KGH restrictions to reflect evidence-based practice, and preparing 10 mg doses of alteplase in the pharmacy to improve medication prescribing, documentation, patient safety, and minimize cost.

**Key words:** alteplase, cost, safety, drug use evaluation, evidence-based

**Word Count:** 306
Background and Rationale

Alteplase is a recombinant tissue plasminogen activator that initiates local fibrinolysis [1,2]. Alteplase is supplied in both 2 mg vials (Cathflo®) and 100 mg vials (Activase®, rt-PA®) with different indications for use; Cathflo®, the 2 mg vial of alteplase, is approved by Health Canada for the restoration of central venous catheter (CVC) function [1]. However, alteplase also has several off-label indications for use with varying levels of evidence, ranging from case reports to randomized controlled trials. A summary of the uses for alteplase 2 mg vials with the most supporting evidence can be seen in Appendix 1.

At Kingston General Hospital (KGH), alteplase is restricted on the Drug Formulary due to cost; the restrictions for use of alteplase at KGH at the time of data collection can be seen in Appendix 2. The restrictions were revised in 2013 to include use for provocative mesenteric angiography after a Drug Use Evaluation (DUE) of alteplase was conducted in Imaging Services (IS). However, an evaluation of alteplase use and a review of the restrictions in other areas of the hospital has not occurred for at least ten years. A query was posted to the DUE Pharmacy Specialty Network through the Canadian Society of Hospital Pharmacists (CSHP), which identified clear restrictions for use of alteplase at 4 of 7 institutions. Of the 7 institutions that responded, six were hemodialysis centers; all 6 institutions have specific policies or protocols in place for the use of alteplase in occluded hemodialysis catheters. At KGH, the Hemodialysis Unit procedure includes the use of alteplase in 3 different methods: as a 4 mg IV infusion, a 2 mg dwell (1 mg in each arterial and venous lumen), and a post-dialysis lock (1 mg in each arterial and venous lumen), which are described in Appendix 1 [3].

Despite the restrictions for use at KGH, alteplase is consistently one of the top 25 drug expenditures on a quarterly basis. In Fiscal 2015 (F2015), the total cost of alteplase, including both the 100 mg and the 2 mg vials was $551 136, compared to $448 979 in Fiscal 2014 (F2014). Although a decrease in use was seen for the 100 mg vials, a significant increase in use was seen for the 2 mg vials. In F2015, $300 036 was spent on alteplase 2 mg vials – a 64% increase from $183 029 in F2014. There was no change in the acquisition cost for the 2 mg vial from F2014 to F2015.
In addition to being a costly medication, alteplase is also a high alert medication associated with several reports of incidents causing potential harm to patients. The Institute for Safe Medication Practices (ISMP) recommends that the purpose of the use of alteplase is communicated with complete orders (dose, route, administration directions) prior to pharmacy dispensing alteplase [4, 5]. A confounding variable to this practice at KGH is the availability of the alteplase 2 mg vials in the Automated Dispensing Cabinets (ADCs) in many patient care areas, including the renal unit. As a result, nurses frequently override one time doses of alteplase before a pharmacist is able to review the physician order, which may increase the potential for medication errors and patient harm. In the renal unit, nurses administer alteplase, but in all other areas of the hospital at this time, alteplase must be administered by a physician for occluded CVCs and pleural effusions. Nurses who have completed an authorization program may administer alteplase for occluded CVCs, however this usually applies to nurses within the Oncology Program.

Pharmacy Services at KGH is responsible for the monitoring and management of the hospital drug budget, and a desired outcome for Pharmacy Services is to ensure that drug expenditures are a result of evidence-based practices to maximize value for money. Additionally, the 2015-2016 KGH corporate plan identifies Pharmacy Services as being responsible for the implementation of safeguards for prescribing, dispensing, and administration of high-alert medications, such as alteplase. A review of the use of alteplase 2 mg vials at KGH may identify quality and safety improvements in the drug distribution and administration process as well as potential cost-saving measures.
Purpose

To assess appropriateness of the use of 2 mg vials of alteplase at KGH because of the high and increasing expenditure.
Objectives

Research Question

1. How are alteplase 2 mg vials being utilized at KGH?

Objectives

Primary Objective:

1. To assess if the use of the 2 mg vials of alteplase at KGH complies with the current restrictions for use.

Secondary Objectives:

1. To assess the drug distribution and administration process for the 2 mg vials of alteplase to ensure it is safe and cost effective.
2. To assess if the use of alteplase at KGH follows evidence-based practice when not compliant with the current restrictions for use.
3. To assess if the KGH restrictions for use of the 2 mg vials of alteplase need to be revised to reflect current and evidence-based practice.
4. To compare compliance with restrictions and evidence-based practice between the renal unit and other areas of the hospital.
Methodology

A prospective, observational, cross-sectional, drug use evaluation of 2 mg vials of alteplase was conducted, with no direct intervention to therapy. Approval was obtained by the Queen’s University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board prior to study commencement.

Sample Size

A priori sample size calculations were not undertaken, as this was an observational study that did not involve an intervention or effect size. As per the World Health Organization Introduction to Drug Utilization Research, for meaningful results to be obtained from a drug use evaluation, a minimum of 50 to 75 records per health care facility is considered adequate; therefore, a convenience sample consisting of 100 patient records was utilized [6]. Since renal unit patients obtain a new visit number for each dialysis session, visit number was used to identify patients, and individual patients could be included in the study multiple times. Patients were assigned a study identification number; study numbers were matched up with patient visit number in a password protected Excel® spreadsheet. As the renal unit has incurred approximately 50% of the cost of the 2 mg vials annually, half of the study was conducted (N=50) using renal unit patient records and the remainder, (N=50), patient records were obtained from all other areas of the hospital.

Population

Inclusion Criteria

☐ All adult patients (greater than 18 years old) dispensed alteplase 2 mg vials during their hospital or renal unit visit.
**Exclusion Criteria**

The exclusion criteria were determined as follows:

- Pediatric patients (less than 18 years old)
  - The use of alteplase in pediatric patients is extremely infrequent. In F2015, the total drug expenditure for alteplase in pediatrics was limited to use for a single patient.

- Use of alteplase in IS
  - A review of the use of alteplase in IS was completed in 2013, and restrictions were updated at that time. Alteplase use in IS remains consistent.

- Patients dispensed alteplase 100 mg vials
  - The drug expenditure for alteplase 100 mg vials remained relatively stable since F2011, and decreased in the last fiscal year.

**Data Collection**

A convenience sample of 100 courses of therapy seen over a 52 day period was utilized. To ensure that both vials issued from the KGH dispensary and vials removed from the ADC were accounted for in the study, both the Pharmacy Information System (PIS) and ADC reports were used to identify patients dispensed alteplase 2 mg vials. Data collection forms were created in accordance with the KGH Template for Drug Utilization Review and the CSHP Drug Use Evaluation Guidelines [7]. Since the potential indications for use and the documentation systems were different for the renal unit compared to the remainder of the hospital, a separate data collection form was created for the renal unit; forms for renal unit and non-renal unit can be seen in Appendix 3 and 4, respectively. One data collection form was used for each course of therapy.

The pharmacy resident collected data for renal unit patients over two, one week periods of October 26, 2015 – October 31, 2015 and December 14, 2015 – December 19, 2015, or 50 alteplase courses of therapy, whichever came first; data collection was completed for the renal unit on December 17, 2015. Patient demographics, alteplase order, indication for use, adherence to restrictions for use, blood flow (QB), and documentation of administration were obtained from
NephroCare®, the sole source of documentation for hemodialysis patients. Data regarding drug distribution and wastage were obtained from the daily ADC report and from the PIS.

The pharmacy resident collected data from patients outside of the renal unit starting October 26, 2015 for a maximum of 90 days, or 50 alteplase courses of therapy, whichever came first; data collection was completed on December 11, 2015. Patient demographics, alteplase order, indication for use, adherence to KGH restrictions, and documentation of administration and removal were obtained from the PIS as well as a chart review of the patient’s Medication Administration Record (MAR), orders, and interprofessional progress notes. Data regarding drug distribution and wastage were obtained from the daily ADC report and from the PIS.

Data were imported into an Excel® spreadsheet designed for data collection.
Analysis

Data were entered into an Excel® file designed for the project and imported into SPSS® for Statistical Analysis. The analysis was primarily descriptive in nature, using frequencies and percentages for patient demographics such as clinical service, gender, prescribing service, adherence to KGH restrictions for use, adherence to evidence-based indication, documentation of administration, correctly written orders and reasons for incorrect orders [Appendix 5], improvement in blood flow, and wastage identified. The amount of alteplase used for each course of therapy and the number of vials charged by pharmacy was used to determine wastage quantity. Wastage was labeled as unclear if there was missing documentation and therefore administration could not be confirmed. Means, standard deviations, and medians were calculated for continuous data, such as age and weight. Chi-square tests were used to compare categorical data between the renal unit and the remainder of the hospital. In renal unit patients, blood flow (QB) prior to administration and after administration of alteplase was analyzed using paired sample t-tests.
Results

A total of 100 courses of therapy (50 renal unit and 50 non-renal unit) for alteplase 2 mg vials were identified between October 26, 2015 and December 17, 2015, and included in the study. As several patients received alteplase more than once throughout the study duration, there were a total of 68 patients included, 28 renal unit patients and 40 non-renal unit patients [Table 1]. The average age of the renal unit patients was 68.1 (range: 43-90) with 39% female; the average age of the non-renal unit patients was 62.0 (range: 32-91) with 58% female. Twenty-four (86%) of renal unit patients had a CVC and were more likely to have multiple dialysis access attempts—the average number of dialysis access attempts was 3.57, with 18 (65%) patients having “dialysis access” listed as a “problem” in their chart. All renal unit orders were prescribed by the nephrology service; for non-renal unit patients, the majority of orders came from the internal medicine service or surgical services at 19% and 12%, respectively [Figure 1].

Of interest, 12 of 28 renal unit patients had “standing physician orders” for alteplase locks, with 4 patients having a “standing order” for an alteplase lock more than once per week, accounting for 17 of 50 (34%) renal unit courses of therapy; 8 patients had a “standing order” for a once weekly alteplase lock, accounting for 9 of 50 courses of therapy (18%) [Figure 2].

Overall, 48 of 100 courses of therapy adhered to KGH restrictions for use whereas 47 did not; indication for use was unable to be confirmed in 5 of 100 courses of therapy. Two (4%) and 46 (92%) courses of therapy from the renal unit and the rest of the hospital complied with KGH restrictions, respectively [Figure 3]. The indication for use for those that met the restrictions for non-renal unit patients were: 40 (87%) for occluded central venous catheter, 3 (6%) for transcatheter thrombolysis for peripheral vascular occlusive disease, and 3 (7%) for patients with loculated pleural effusions [Figure 4]. The breakdown of indication for alteplase as per renal unit procedure was: 42 (88%) lock, 2 (4%) dwell, and 4 (8%) infusion [Figure 5].

For courses of therapy that did not comply with KGH restrictions, the indication was evidence-based for 44 of 47 (94%). For the 3 courses of therapy that were not evidence-based, the indications were: alteplase infusion (blood flow (QB) <200 mL/min) in renal unit patients (N=2), and pleural effusion for 1 dose only in non-renal unit patients (N=1).
Of the 100 courses of therapy included in the study, it was found that 91 orders were written, either electronically or by hand. Of the 91 orders, only 49 (54%) were written correctly; 44 (90%) from the renal unit and 5 (12%) for the non-renal unit patients. The most common reasons for incorrect orders were incorrect route and not following hospital policy or standards. For non-renal unit patients, 33 (77%) orders contained incorrect routes, with the most common errors being no route specified or “IV” administration specified as opposed to intracatheter (IC) [Figure 6]. Additionally, 39 (91%) orders for non-renal unit patients did not comply with KGH Patient Care Orders Administration Policy 11-040; the most common reasons for deviation were the use of unapproved or dangerous abbreviations, such as TPA, and missing information, such as, no route, no frequency, no dose, or no duration.

In terms of the drug distribution process, all 50 orders from the renal unit were overridden by a nurse from the ADC, as expected, as orders from NephroCare® are not profiled in the PIS. There was no wastage identified for 44 (88%) orders from the renal unit; in one instance, there was an extra alteplase vial removed and not accounted for via documentation or return to ADC stock. For 5 (10%) orders, it was not possible to determine wastage due to lack of documentation; all other orders had administration “signed off” by the nurse in the computerized medication administration record (cMAR) in NephroCare®.

The distribution process for the remainder of the hospital is more challenging to describe, as it is different for every patient care area at KGH. For the 50 non-renal unit orders identified, there were a total of 63 separate alteplase administrations, as some courses of therapy required more than one dose. Fifty-four alteplase doses were in patient care areas that had alteplase available in the ADC; 43 (80%) doses were overridden by the nurses, 8 (15%) doses were entered in the PIS and appropriately removed under the patient’s profile, and 3 (6%) doses had missing information regarding distribution as alteplase retrieval was not linked to a patient identifier or it was unclear if the patient received the dose due to absence of documentation. The remaining nine doses were from areas that did not have alteplase available in the ADC, and were thus sent from KGH Pharmacy prior to administration.

Despite a well-defined process for documentation of medications administered by a regulated health care professional at KGH, documentation of administration varied greatly between patient
care areas. Only 34 (54%) administrations were documented in the MAR, 43 (68%) administrations were documented in the progress notes, and 9 (14%) administrations were documented in the patient care orders section of the chart. Of note, 10 (16%) administrations had no associated documentation. As a result, determination of waste was challenging; only 34 of 50 (68%) courses of therapy were used as intended with no wastage identified, whereas wastage was unclear for the remainder.
Discussion

Three primary recommendations were identified to improve the quality and safety and reduce the cost associated with utilization of alteplase at KGH: 1) Revise the KGH restrictions for use for alteplase to reflect current practice and evidence-based medicine or make alteplase unrestricted at KGH, 2) Implement order sets for intrapleural instillation of alteplase and for occluded CVCs to standardize procedure, improve documentation, and minimize risk for medication errors, and 3) Prepare alteplase 10 mg doses for intrapleural administration in pharmacy as a means of cost savings. A secondary recommendation is to continue to explore options for increasing the number of areas in the hospital with computerized physician order entry (CPOE) and cMAR to minimize medication prescribing, transcribing, and administration errors.

Effective January 18, 2016, the restrictions for use of alteplase were revised to include: alteplase administered as a 4 mg IV infusion via a hemodialysis CVC as per renal unit procedures. Since data collection was completed in December 2015, this new restriction was not included in data analysis. Including the new restriction in analysis would increase compliance with KGH restrictions in the renal unit from 2 (4%) orders to 6 (12%) orders; however, this restriction revision does not address the alteplase lock procedure, which is the indication for the majority of use in the renal unit. It is recommended that if alteplase is to remain restricted at KGH, all renal unit procedures be added to KGH restrictions for use to reflect current practice of alteplase use. New restrictions should include: alteplase lock post-dialysis for patients with ongoing dialysis access issues, alteplase dwell for blood flow (QB) less than or equal to 200 mL/min, and alteplase infusion for QB greater than 200 mL/min but less than 300 mL/min as per renal unit procedures [Appendix 6]. It is also recommended that active physician orders for alteplase, particularly alteplase lock orders, should be reevaluated at predefined intervals, such as once weekly or biweekly, to ensure that use is still appropriate; Pharmacy Services could work with the Renal Program to determine the most feasible way to implement this change.

While most orders for non-renal unit patients (92%) complied with current restrictions at KGH, alteplase has been used at KGH in the last year for indications that were not captured during the study period, such as, retained hemothorax and intraabdominal abscesses. Although the data for these indications is weak, there is supportive evidence in the literature [Appendix 1].
recommended that if alteplase is to remain restricted at KGH, restrictions for alteplase use are revised to account for use in retained hemothorax and intraabdominal abscesses [Appendix 6].

An alternative option would be to remove restrictions for the 2 mg vials of alteplase since the current use was found to be appropriate and evidence-based, and growing bodies of evidence for continually evolving off-label indications for alteplase could make the list of restrictions quite cumbersome and difficult to enforce.

Accreditation Canada’s Medication Management Standard guidelines for high-alert medications, such as alteplase, suggest several strategies for safe use, including “standardizing the ordering, storage, preparation, administration, and dispensing of these products through the use of protocols, guidelines, dosing charts, and orders sets (pre-printed or electronic) [8].” Alteplase order sets already exist at KGH for acute stroke and for catheter directed alteplase infusion for arterial and venous thrombosis. As the majority of orders for alteplase in non-renal unit patients were for occluded catheters, and were written incorrectly, it would be beneficial to have a standard order set for the use of alteplase for occluded catheters. Through Treatment Connects®, several order sets for occluded CVCs were identified; a sample order set that may be revised to meet our needs at KGH can be seen in Appendix 7.

Additionally, the results of this study support the notion CPOE minimizes the risk of prescribing errors and cMAR enhances safety by improving documentation of administration. The renal unit, which has CPOE and cMAR, had fewer incorrect orders (90% versus 12%) and had a higher compliance with documentation of administration as well as a more standardized approach to documentation. This finding supports implementation of hospital wide CPOE and cMAR as a long term measure to improve medication safety.

The final recommendation relates to the potential cost savings for alternative methods of alteplase supply. The alteplase 2 mg vials cost an additional $5.05 per milligram compared to the 100 mg vials. Although it would be cost-effective to use the 100 mg vials to make 2 mg doses, Accreditation Canada recommends the use of commercially available formats wherever possible, and it would be impractical in terms of pharmacy technician workload due to the high volume of use. Reconstituted alteplase must be stored in the freezer; it is stable in the freezer for up to 6 months, and can be supplied on a daily basis with a 24 hour expiry date to be kept in the
refrigerator [9, 10]. Preparing 10 mg alteplase syringes to be stored in the freezer can be explored as an option for pleural effusions to minimize cost—this would save $50.50 per dose and $303 for each course of therapy. Over the course of the study period, there were 3 pleural effusions, extrapolated to approximately 22 pleural effusion cases annually—a potential cost savings of $6666. In order to facilitate this change, an order set for intrapleural instillation of alteplase stipulating that 10 mg doses of alteplase must be supplied by pharmacy would be beneficial. Additionally, minimizing the floor stock quantity of alteplase so doses of 10 mg cannot be prepared on patient care areas would also facilitate this change. An order set would also standardize ordering and administration of intrapleural alteplase to improve safety by improving documentation and reducing risk for medication errors.

A number of limitations to this study have been identified, most importantly, the lack of documentation regarding administration of alteplase in patient charts made it challenging to collect all data required, resulting in missing information in many cases. This challenge was mainly seen in the non-renal unit patients who did not have electronic documentation.

An additional limitation is the availability of alteplase in the ADC in many patient care areas. Since alteplase is stored in the refrigerator, it can be accessed any time that the fridge is opened, thereby not linking it to a specific patient identifier, and thus potentially leading to missing dispensed alteplase during data collection. As confirmation of the accuracy of the number of vials of alteplase was not included in the original project protocol, it was not always assessed, and pharmacy technicians may have resolved the discrepancy prior to investigator review. On a similar token, it is possible for nurses to return unused alteplase vials to the fridge without issuing a credit in the ADC, again leading to incorrect counts and inaccurate assumptions of medication wastage.

Finally, as the majority of the use of alteplase in non-renal unit patients was for occluded CVCs, it would be prudent to assess the potential cause of the occluded CVC prior to alteplase administration, as there is evidence that drug precipitation may also result in occluded CVCs and use of alteplase would not be helpful. It was outside the scope of this project to assess for potential causes of occlusions and for resolution of the occlusion post alteplase use and may be considered as a future investigation. An order set or flow chart for the management of a CVC
occlusion would facilitate further investigation and may also minimize inappropriate use of alteplase by reminding the health care team to explore all possible causes of catheter occlusion and methods for management depending on the most likely cause.
Conclusion

Alteplase 2 mg vial use at KGH appears to be appropriate and evidence-based. The study findings support consideration of: implementing additional order sets for intrapleural administration of alteplase and for occluded CVCs, revising restrictions for use of alteplase at KGH to reflect both current and evidence-based practice or removing restrictions, preparing 10 mg doses of alteplase in the pharmacy instead of on patient care areas, and increasing the number of areas in the hospital with CPOE and cMAR. This would result in improved medication prescribing, documentation, patient safety, and decrease cost.
References

## Tables

### Table 1: Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Renal (%)</th>
<th>Non-Renal (%)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=28</td>
<td>N=40</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>11 (39.3)</td>
<td>23 (57.5)</td>
<td>0.139</td>
</tr>
<tr>
<td>Male</td>
<td>17 (60.7)</td>
<td>17 (42.5)</td>
<td>-</td>
</tr>
<tr>
<td>Age (SD)</td>
<td>68.1 (13.4)</td>
<td>62.0 (13.5)</td>
<td>0.071</td>
</tr>
<tr>
<td>Weight (SD)</td>
<td>93.6 (26.5) (N=27)</td>
<td>81.7 (28.0) (N=24)</td>
<td>0.124</td>
</tr>
<tr>
<td>CVC</td>
<td>24 (85.7)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>AVF</td>
<td>3 (10.7)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Dialysis access problem</td>
<td>18 (64.3)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Number of dialysis access attempts (SD)</td>
<td>3.57 (2.53)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

SD=standard deviation  
CVC= central venous catheter  
AVF= arteriovenous fistula
Figures

Figure 1: Alteplase orders by prescribing service.
Figure 2: Renal unit patient comparison of “standing” versus no “standing” order.
Figure 3: Adherence to KGH restrictions.
Figure 4: Non-renal unit alteplase indication
Figure 5: Renal unit alteplase indication
Figure 6: Reasons for incorrect alteplase orders.
Appendices

Appendix 1: Evidence-Based Indications for Alteplase

(Excluding Acute Stoke/ Myocardial Infarction/ Pulmonary Embolism/ Use in Interventional Radiology)

<table>
<thead>
<tr>
<th>Indications</th>
<th>Guidelines/Evidence for use</th>
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| Restoration of central venous catheter (CVC) function (Health Canada Approved) | - Alteplase is the only Health Canada approved thrombolytic proven to be safe, effective, and appropriate for restoring catheter patency in the adult and pediatric (older than 2 years) population[1,2]  
- Safety and efficacy of alteplase has been demonstrated in the pediatric population, including children younger than 2. [2]  
- Overall quality of studies is low; inadequate evidence to draw strong conclusions on efficacy/safety of alteplase [3]  
- Alteplase 2 mg/2 mL may be effective in treating withdrawal or total occlusion of CVC lumens caused by thrombosis [3]  
- Very low quality evidence suggests no difference with alteplase 1 mg with alteplase 2 mg after 1st or 2nd instillation [3] |
| Retained Hemothorax (Off-Label)                 | - Literature limited to small observational studies, retrospective chart reviews and case series; optimal dose (doses of 2 to 100 mg have been used in literature), frequency, and duration of therapy is unknown [4-11]  
- Unable to draw conclusions of efficacy/safety from available evidence; however, intrapleural fibrinolysis appears to be an effective option for achieving successful resolution of retained hemothorax and may decrease the need for thoracotomy, without increasing risk for bleeding [4-11]  
- There is a need for adequately powered and long term RCTs to support the results and guide dosing, duration, and place in therapy, |
| Intraabdominal abscesses (Off-Label)            | - Single center prospective open-label randomized trial (N=20) comparing alteplase 2 mg (in up to 50 mL) or 4 mg (in 51 to 100 mL) twice daily for 3 days versus normal saline for treatment of loculated abdominopelvic abscesses requiring percutaneous drainage. Volume administered equal to half the residual volume of the abscess. Alteplase superior to normal saline with respect to primary outcome of abscess resolution without the need for repeat intervention or surgery within 30 days of initiation of infusion therapy. [12]  
- Single center retrospective review of intracavitary alteplase (4 to 6 mg in 25 mL of normal saline twice daily for 3 days) instilled into 46 abdominal or pelvic abscesses refractory to simple catheter drainage showed efficacy in complete evacuation of abscess in 89% with no increased bleeding complications (4 patients fully anticoagulated, 24 patients prophylactic anticoagulation) [13] |
<p>| Pleural Effusions / Empyema                     | - Intrapleural tPA-Dornase alfa therapy at a dose of 10 mg                                                                                                                                                                                                                                                                                                  |</p>
<table>
<thead>
<tr>
<th>(Off-Label)</th>
<th>(alteplase) and 5 mg (dornase alfa) twice daily for 3 days improved fluid drainage in patients with pleural infection and reduced the frequency of surgical referral and the duration of hospital stay; treatment with placebo only, dornase alfa alone, or tPA alone was ineffective. [14]</th>
</tr>
</thead>
</table>
| **Alteplase dwell in hemodialysis (HD)** | - Alteplase is the thrombolytic of choice when treating occluded CVCs but there is little published evidence on the most effective method of administration in HD, but the most common methods are: push/pause, dwell (short and long) and infusion[15]
- Recommended in the BC Renal Agency Guidelines if blood pump speed is less than 200 mL/min [15]
- Little is known about the optimal dose of tPA to restore HD catheter patency and doses of 1-2 mg have been used with no obvious correlation between dosage and success [15, 16]
- A retrospective, single centre cohort study comparing 2 mg per lumen versus 1 mg per lumen found that 2 mg dose of tPA was superior to 1 mg dose with regard to resolving occlusion and prolonging catheter days (longer duration until catheter replacement); however, results need to be confirmed by an RCT [16] |
| (Off-Label) |  |
| **Alteplase infusion in HD** | - The infusion method has been used successfully for thrombolytic occlusion management of HD catheters in adult and pediatric patients [2]
- Low-dose infusion methods have been shown to be effective in studies with protocols ranging from 1-4 mg of alteplase in 0.9% NaCl over 30-60 minutes; there is also literature to support low-dose infusion over 180 minutes [2]
- Single lumen infusion method is recommended in the BC Renal Agency Guidelines if blood pump speed is 200 mL/min or greater and less than 300 mL/min [15]
  - Instill 2 mg or 4 mg in 100mL 0.9% NaCl via the HD catheter over 60 minutes according to protocol [15] |
| (Off-Label) |  |
| **Alteplase lock in HD** | - Most studies do not support the use of rTPA in preventing thrombosis and alteplase is not for use on an ongoing basis unless as a last resort (no other catheter sites, maturing fistula, etc) [15]
- Chronic alteplase use is strongly discouraged other than exceptional circumstances (ie resistant CVCs) AND: CVC is the last option for HD access AND the patient is unable to tolerate further CVC replacements; OR a maturing AV fistula or AV graft is imminent [15]
- The Pre-Clot study compared alteplase 1 mg per lumen once per week and heparin 5000 units/ml as a catheter locking solution for remaining 2 sessions versus the control of heparin 5000 units/ml every dialysis and showed a lower risk of catheter malfunction and catheter related bacteremia versus the control with no significant differences in bleeding events. [15, 17, 18]
- It is proposed that using alteplase as a locking solution in accordance to the Pre-Clot study protocol will cost similar to heparin alone as lower risk of hospitalization and catheter related |
bacteremia may partially offset the increased cost [19]
- There is a need for adequately powered and long term RCTs to support the results [15, 17, 18]

References:

Appendix 2: Alteplase restrictions for use at Kingston General Hospital
(Prior to January 2016)

2 mg Vials

1. Use as a 1 mg/mL solution in occluded central venous catheters or dialysis catheters
2. Transcatheter thrombolysis for the following indications:
   - Peripheral vascular occlusive disease
   - Venous thrombosis (upper and lower extremity, pulmonary embolism)
   - Dialysis fistulae and graft occlusions
3. Use in Interventional Radiology for provocative mesenteric angiography
4. Use for intrapleural fibrinolysis in the treatment of empyema and parapneumonic effusion in children admitted to Pediatrics,
5. Use in adult patients with radiographic evidence of loculated pleural effusion that cannot be drained despite the placement of chest tube, AND
   - Clinical and laboratory evidence of infection in pleural space (empyema), AND
   - For intrapleural instillation at a maximum dose of 10 mg BID X 6 doses (given with dornase alfa), AND
   - Must be approved by an attending physician from Respirology, Thoracic Surgery, or Critical Care Medicine for this indication

100 mg Vials

1. For intravenous or intra-arterial treatment of acute cerebral infarction according to protocol
2. Treatment of pulmonary embolism in hemodynamically unstable patients requiring pressor support
3. Treatment of pulmonary embolism in hemodynamically stable patients, in consultation with Respirology
Appendix 3: Renal Unit Data Collection Form

Alteplase 2mg vial Data Collection Form – Renal Unit

Date:

Assigned Study ID Number:

Location:

Age (years):
Weight (kg):

Gender:  M / F

Type of Dialysis access

1. CVC
2. AVG
3. AVF

Total number of dialysis access (current and failed)

Dialysis access listed as a problem for patient  Y / N

Physician name:

Order written as:

____________________________________________________________________________________

Is the order written correctly:  Y / N

If no, reason for incorrect order (select all that apply)

<table>
<thead>
<tr>
<th>Incorrect name</th>
<th>Yes</th>
<th>No</th>
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<tr>
<td>Incorrect Route</td>
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<td></td>
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<tr>
<td>Incorrect Frequency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incorrect Duration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not following hospital policy/standards</td>
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</tr>
</tbody>
</table>

Indication for use as per NephroCare®:

<table>
<thead>
<tr>
<th>Dwell (Pre)</th>
<th>Dwell (Post)</th>
<th>Lock</th>
<th>Infusion (Pre)</th>
<th>Infusion (Post)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood flow (QB) (mL/min):</td>
<td>Blood flow (QB) (mL/min):</td>
<td>Blood flow (QB) (mL/min):</td>
<td>Blood flow (QB) (mL/min):</td>
<td></td>
</tr>
</tbody>
</table>

Adherence to KGH Restrictions for use:  Y / N

If yes, select restriction below:

☐ 1. Use as a 1 mg/mL solution in occluded central venous catheters or dialysis catheters

☐ Transcatheter thrombolysis for the following indications:

☐ 2. Peripheral vascular occlusive disease
☐ 3. Venous thrombosis (upper and lower extremity, pulmonary embolism)
☐ 4. Dialysis fistulae and graft occlusions

If no, indication:

Is this indication evidence-based?

Y / N
| Administration documented in patient in Medication List (in Nephrocare®) | Yes | No | n/a |
| Administration documented in patient Progress Notes (in Nephrocare®) | | | |
| Dose given same as dose ordered | | | |
| Documentation of alteplase removal (if used for catheter occlusion) | | | |

**Distribution Issues**

<table>
<thead>
<tr>
<th>Vials taken from OmniCell:</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vials used:</td>
<td>Overridden</td>
</tr>
</tbody>
</table>

Wastage identified: Y / N  
If yes, please describe source of wastage:
## Appendix 4: Non-Renal Unit Data Collection Form

**Alteplase 2mg vial Data Collection Form – Kingston General Hospital (Excluding Renal Unit)**

**Date:**

**Assigned Study ID Number:**

**Location:**

**Age (years):**  
**Weight (kg):**  
**Gender:** M / F

**Ordering Service:**

**Order written as:** 
___________________________________________________________________________

**Is the order written correctly:** Y / N

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<tr>
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<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incorrect name</td>
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<td></td>
</tr>
<tr>
<td>Incorrect Dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incorrect Route</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incorrect Frequency</td>
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<td>Incorrect Duration</td>
<td></td>
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</tr>
<tr>
<td>Not following hospital policy/standards</td>
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**Adherence to KGH Restrictions for use:** Y / N

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<tr>
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<th>If no, indication:</th>
</tr>
</thead>
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<tr>
<td>1. Use as a 1 mg/mL solution in occluded central venous catheters</td>
<td></td>
</tr>
<tr>
<td>Transcatheter thrombolysis for the following indications:</td>
<td></td>
</tr>
<tr>
<td>2. Peripheral vascular occlusive disease</td>
<td></td>
</tr>
<tr>
<td>3. Venous thrombosis (upper and lower extremity, pulmonary embolism)</td>
<td></td>
</tr>
<tr>
<td>4. Dialysis fistulae and graft occlusions</td>
<td></td>
</tr>
<tr>
<td>5. Use in adult patients with radiographic evidence of loculated pleural effusion that can not be drained despite the placement of chest tube, <strong>AND</strong> Is this indication evidence-based?</td>
<td></td>
</tr>
<tr>
<td>Clinical and laboratory evidence of infection in pleural space (empyema), <strong>AND</strong></td>
<td></td>
</tr>
<tr>
<td>For intrapleural instillation at a maximum dose of 10 mg BID X 6 doses (given with dornase alfa), <strong>AND</strong></td>
<td></td>
</tr>
<tr>
<td>Must be approved by an attending physician from Respirology, Thoracic Surgery, or Critical Care Medicine for this indication</td>
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<tr>
<td>Attending physician:</td>
<td>Y / N</td>
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<td>Dose 1</td>
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</tr>
<tr>
<td>--------</td>
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<td></td>
</tr>
<tr>
<td>Administration documented in patient Progress Notes</td>
<td></td>
</tr>
<tr>
<td>Administration documented in Orders</td>
<td></td>
</tr>
<tr>
<td>Dose given same as dose ordered</td>
<td></td>
</tr>
<tr>
<td>Documentation of alteplase removal (if used for catheter occlusion)</td>
<td></td>
</tr>
<tr>
<td>Documentation of improvement in blood flow</td>
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<td>Vials used:</td>
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<td>Documentation of improvement in blood flow</td>
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<table>
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<td>Documentation of alteplase removal (if used for catheter occlusion)</td>
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<td>Documentation of alteplase removal (if used for catheter occlusion)</td>
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| Administration documented in patient MAR | Yes | No | n/a |
| Administration documented in patient Progress Notes | |
| Administration documented in Orders | |
| Dose given same as dose ordered | |
| Documentation of alteplase removal (if used for catheter occlusion) | |
| Documentation of improvement in blood flow | |

<table>
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<th>Quantity</th>
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<td>Vials sent from KGH pharmacy:</td>
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<tr>
<td>Vials used:</td>
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<p>| Wastage identified: | Y / N |
| If yes, please describe source of wastage: | |</p>
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<td>“For chest tube”</td>
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<td></td>
<td>“Into PICC port”</td>
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<td>Into chest tube</td>
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<tr>
<td>Frequency</td>
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<td></td>
<td>X2 if for occluded catheter</td>
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<tr>
<td>Duration</td>
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<td>Once</td>
<td></td>
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<td></td>
<td>___ days</td>
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<tr>
<td>Not following hospital policy</td>
<td>As per KGH administrative policy 11-040</td>
<td>Not following KGH</td>
</tr>
<tr>
<td>or standards</td>
<td></td>
<td>administrative policy 11-040</td>
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<td></td>
<td></td>
<td>ie. Do not use abbreviations/symbols,</td>
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<td></td>
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<td>brand name only, missing any</td>
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<tr>
<td></td>
<td></td>
<td>information above</td>
</tr>
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Appendix 6: Proposed alteplase restrictions for use at Kingston General Hospital

2 mg Vials

1. Use as a 1 mg/mL solution in occluded central venous catheters or dialysis catheters
2. Transcatheter thrombolysis for the following indications:
   - Peripheral vascular occlusive disease
   - Venous thrombosis (upper and lower extremity, pulmonary embolism)
   - Dialysis fistulae and graft occlusions
3. Use in Interventional Radiology for provocative mesenteric angiography
4. Use for intrapleural fibrinolysis in the treatment of empyema and parapneumonic effusion in children admitted to Pediatrics,
5. Use in adult patients with radiographic evidence of loculated pleural effusion that cannot be drained despite the placement of chest tube, AND
   - Clinical and laboratory evidence of infection in pleural space (empyema), AND
   - For intrapleural instillation at a maximum dose of 10 mg BID X 6 doses (given with dornase alfa), AND
   - Must be approved by an attending physician from Respirology, Thoracic Surgery, or Critical Care Medicine for this indication
6. Use in adult patients with radiographic evidence of retained hemothorax that cannot be drained despite the placement of a chest tube, AND
   - For intrapleural instillation at a maximum dose of 16 mg daily x 3 days, AND
   - Must be approved by an attending physician from Respirology, Thoracic Surgery, or Critical Care Medicine for this indication
7. Use in adult patients with radiographic evidence of loculated intraabdominal abscesses that cannot be drained despite the placement of percutaneous drain, AND
   - For percutaneous instillation at a maximum dose of 4 mg BID X 6 doses, AND
   - Must be approved by an attending physician from Internal medicine or Critical Care Medicine for this indication
8. Use in the Renal Unit for the following indications:
   - Alteplase lock 1 mg per lumen administered post-dialysis via a hemodialysis central venous catheter for patients with ongoing dialysis access issues as per Renal Unit Procedures for up to 3 treatments per week, then must be reassessed by a Nephrologist
   - Alteplase dwell 1 mg per lumen for blood flow (QB) less than or equal to 200 mL/min as per Renal Unit Procedures
   - Alteplase infusion 4 mg administered intravenously for QB greater than 200 mL/min but less than 300 mL/min as per Renal Unit procedures

100 mg Vials

1. For intravenous or intra-arterial treatment of acute cerebral infarction according to protocol
2. Treatment of pulmonary embolism in hemodynamically unstable patients requiring pressor support
3. Treatment of pulmonary embolism in hemodynamically stable patients, in consultation with Respirology
Appendix 7: Sample Order Set for Occluded CVC

<table>
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<th>STAT Label</th>
<th>Osler Standard Order Set</th>
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</thead>
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<tr>
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<td>kg</td>
</tr>
<tr>
<td>HEIGHT:</td>
<td>cm</td>
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<tr>
<td>ESTIMATED DATE OF DISCHARGE:</td>
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<td>☐ NO KNOWN ALLERGIES</td>
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</table>

**Osler Standard Order Set**

**Patient Identification**

**Alteplase Instillation for Thrombotic Occlusion of Central Venous Access Device Order Set (Not for Use in Dialysis)**

Fill in required blanks and check appropriate boxes. To delete order, draw line through and initial. Orders not checked will not be implemented.

**Use with caution in patients with known or suspected CVAD infection**

**Alteplase Administration**

- Instill Alteplase 2 mg into the occluded line x one dose (further order required for additional doses)
- Clamp line and allow Alteplase to dwell in the line
- After 30 minutes dwell time assess lumen patency by attempting to aspirate lumen contents into the syringe

**If CVAD is functional**

- Aspirate 5 mL of blood to remove Alteplase and the residual clot, discard aspirate
- Flush the CVAD lumen with 10 mL 0.9% NaCl

**If CVAD function has not been restored**

- Allow Alteplase to remain in lumen for an additional 120 minutes
- After additional 120 minutes dwell time assess lumen patency by attempting to aspirate lumen contents into the syringe

**If CVAD is functional after second dwell time**

- Aspirate 5 mL of blood to remove Alteplase and the residual clot, discard aspirate
- Flush the CVAD lumen with 10 mL 0.9% NaCl

**If CVAD function is not restored after one dose of Alteplase or any subsequent occlusion**

- Notify Physician of a persistent occlusion and obtain new order

---

**Prescriber Signature and Mnemonic**

**Date/Time**

**Transcribed By**

**Date/Time**

**Checked By**

**Date/Time**
ASSOCIATED DOCUMENT TO

Alteplase Instillation for Thrombotic Blockage of Central Venous Access Device Order Set 10 100 206

Inclusion Criteria
- Patient with Central Venous Access Device (CVAD) that has a partial or complete catheter blockage demonstrated by the inability to flush or aspirate fluid from a line using a 10 mL syringe after having implemented non-invasive interventions
- Patient with blockage due to Thrombus

Exclusion Criteria
Patient with known history of Hypersensitivity to Alteplase, L-arginine, Phosphoric Acid, and Polysorbate 80
OR
Patient who has undergone any of the following procedures within the past 48 hours:
- Coronary artery bypass graft
- Organ biopsy
- Hemostatic defects
- Obstetrical delivery
- Puncture of non-compressible vessels

Alteplase Reconstitution

Reconstitute recombinant alteplase to a final concentration of 1 mg/mL as follows:

1. Aseptically withdraw 2.2 mL of Sterile Water for Injection, USP (diluent is not provided)
2. Inject the 2.2 mL of Sterile Water for Injection, USP, into the recombinant alteplase vial, directing the diluent stream into the powder. Slight foaming is not unusual; let the vial stand undisturbed to allow large bubbles to dissipate
3. Mix by gently swirling until the contents are completely dissolved. Do not shake. The reconstituted preparation results in a colorless to pale yellow transparent solution containing 1 mg/mL recombinant alteplase at a pH of approximately 7.3
4. Recombinant alteplase contains no antibacterial preservatives and should be reconstituted immediately before use. The solution may be used within 8 hours following reconstitution when stored at 2 to 30°C
5. Withdraw 2 mL (2 mg) of solution from the reconstituted vial

No other medication should be added to solutions containing recombinant alteplase.

Any unused solution should be discarded.