Causes of catheter occlusions — May occur soon after insertion of a device or develop at any time during the course of IV therapy in the long-term use of CVADs.

Catheter occlusion is the most common noninfectious complication. About 42% of catheter occlusions are due to nonthrombotic causes, including precipitates, malpositioning, mechanical failure, constriction by a suture and lipid deposits or drug precipitates within the catheter lumen. Thrombotic occlusions result from the formation of a thrombus within, surrounding, or at the tip of the catheter.

References:
The role of central venous access devices

- Central venous access devices (CVADs), also known as central venous catheters or central lines, have become a mainstay for patients requiring intravenous (IV) administration of medications and other fluids
- More than 7 million CVADs are implanted every year in patients in the United States

Access to central venous circulation

- The tip of a CVAD is generally placed in the lower third of the superior vena cava (SVC) near its junction with the right atrium. Because the blood-flow rate here is approximately 2 liters per minute, infusates are rapidly hemodiluted and distributed in the central venous system

CVAD insertion and tip sites

Types of CVADs

Non-tunneled catheters
- Also called subclavian, percutaneous, or short-term catheters
- Typically used for days or weeks for all types of IV therapy, to draw blood, and to monitor central venous pressure
- May be placed bedside or, if necessary, in an emergency setting, without sedation

Peripherally inserted central catheters (PICCs)
- Can be used for a variety of IV therapies, as well as for obtaining blood samples in a variety of care settings from diverse patient populations
- May be placed bedside or in an outpatient setting

Tunneled catheters
- Designed for long-term use and frequent venous access
- Provide more reliable IV access for extended courses of antibiotics, chemotherapy, and parenteral nutrition
- Surgically inserted

Implanted ports
- Consist of 2 attached parts: the catheter and portal body with reservoir
- Long-term dwell capacity, requiring little maintenance when not in use
- Useful for cyclically infused therapies, such as chemotherapy. Blood draws may also be done through the port
- Surgically inserted
Causes of catheter occlusions in the long-term use of CVADs

- Occlusions may occur in up to 25% of CVADs
  - May occur soon after insertion of a device or develop at any time during the course of IV therapy

One in 4 catheters may become occluded

Catheter occlusion is the most common noninfectious complication in the long-term use of CVADs

- About 58% of catheter occlusions are thrombotic
- Thrombotic occlusions result from the formation of a thrombus within, surrounding, or at the tip of the catheter
- About 42% of catheter occlusions are due to nontrombotic causes, including precipitates, malpositioning, mechanical obstructions, and other factors

Nonthrombotic catheter occlusions

Mechanical occlusions

- Mechanical occlusions may result from malposition during insertion and use, or catheter migration
- Factors influencing the incidence of malposition include an increase in intrathoracic pressure from coughing, sneezing, or vomiting; arm movements; forceful flushing of the catheter; and thrombus formation

Precipitates

- Precipitates can form as a result of drug crystallization, drug-drug incompatibilities, or drug-solution incompatibilities
- Drug precipitates in the catheter may occur in conjunction with thrombus formation and should always be considered during assessment of an occlusion, since this may have implications for how the occlusion should be managed

Lipid residue

- Lipid residue can accumulate in central venous catheters, often following the administration of lipid-containing, three-in-one total parenteral nutrition admixtures or drugs with oleaginous vehicles

Salvaging catheters with nonthrombotic occlusions

- In many instances, mechanical problems, such as kinked tubing or clogged in-line filters, can be identified and corrected
  - Possible interventions to reposition catheters include patient positioning, rapid flushing of the catheter guidewire, catheter exchange, fluoroscopic catheter guidance, or partial catheter withdrawal
- Catheters occluded by calcium-phosphate precipitates can be treated with 0.1 N hydrochloric acid
  - Sodium bicarbonate (1 mEq/mL) is used to dissolve substances known to dissolve in an alkaline environment
  - Lipid occlusions have been treated with ethanol (70%) or sodium hydroxide (0.1 mmol/mL)
  - The use of incompatible drugs or solutions should be avoided
Thrombotic catheter occlusions

When introduced into the body, all catheters begin to accumulate fibrin. This is the body’s natural attempt to protect itself against a foreign body. The fibrin starts to form a layer around the outside of the catheter within minutes of insertion, beginning at either the line entry site or where the tip contacts the vein.9,10

**Intraluminal thrombus**11
- Occurs when blood refluxes inside the catheter lumen
- Common causes of reflux include patient coughing, inadequate flushing after blood draws or after checking for blood return, or improper use of flush syringes

**Fibrin tail, or flap**11
- Extends from the catheter tip but is drawn inward, blocking the opening of the catheter lumen on aspiration attempts
- Results in an ability to infuse fluids but an inability to withdraw blood

**Mural thrombus**10-12
- Forms where the catheter touches or “rubs” the vein wall
- Common sites are the entry site, anywhere along the catheter path, and the catheter tip

**Fibrin sheath**10,11
- Forms when fibrin adheres to the external catheter surface, often beginning at the entry site, and may encase all or part of the catheter like a sock
- May completely cover the opening of the catheter tip

Catheter occlusions can be partial or complete7
- Partial occlusion: ability to infuse but not withdraw fluids, or the presence of sluggish flow*
- Complete occlusion: inability to infuse or aspirate

**Aspirating for a positive blood return may reveal a partial occlusion**

*One quantitative measure for sluggish flow is a blood return of less than 3 mL in 3 seconds, as recommended by the Oncology Nursing Advisory Board.13
Catheters deliver life-sustaining therapies

Catheters can be used either short or long term for the infusion of:

- Parenteral nutrition
- Chemotherapy or other vesicant or irritating solutions
- Blood and blood products
- Antibiotics
- Medication/solutions in patients with limited peripheral access
- Therapy that is ongoing or continued at home

CVADs are also useful when frequent blood tests are required, reducing the need for repeated venipuncture.

Why is it important to ensure central line patency?

- An occluded line may compromise patient care by:
  - Disrupting therapies or delaying procedures
  - Interrupting administration of medications and solutions
- Replacement of an occluded line may:
  - Increase patient discomfort and trauma
  - Increase cost of care

Documentation of CVAD functionality assessment is recommended by key societies, and should include:

- Device patency
- Absence of signs and symptoms of complications
- Lack of resistance when flushing
- Presence of a blood return upon aspiration

"Documentation reflects the continuity, quality, and safety of care."

—INS Infusion Therapy Standards of Practice, 2016, page S28, standard 10.4

INS=Infusion Nurses Society.
Recognizing signs of CVAD occlusion

- Central vascular access devices (CVADs) [should be] regularly assessed for patency and proper function as defined by the ability to flush the catheter without resistance and the ability to yield a blood return.4

With a blood flow through the SVC of approximately 2 liters per minute, a free-flowing blood return should be readily achievable.1 Lack of blood return or a sluggish flow may indicate a catheter occlusion or a malpositioned tip, and further assessment of the line will be necessary.3

Signs of a CVAD occlusion include:
- Inability to withdraw blood or sluggish blood return
- Sluggish flow
- Inability to flush or infuse through the CVAD
- Frequent occlusion alarms on electronic infusion device
- Infiltration/extravasation or swelling/leaking at the infusion site

CVAD occlusions should not be left untreated because another lumen is patent3

Recommended routine assessment of catheter patency

- Vascular access devices (VADs) [should be] flushed and aspirated for a blood return prior to each infusion to assess catheter function and prevent complications.3

Prior to the administration of any medications or solutions, the nurse should always:
- Aspirate for a positive blood return
- Check for other indications of an occlusion
- Attempt to flush to determine resistance, flushing with an adequate volume of saline or appropriate solution
- Palpate the insertion site to determine tenderness
- Assess the patient for any pain or discomfort

Institutions should adopt standardized procedures to manage thrombotic occlusions. This includes educational and skill-development needs of team members, followed by the design of appropriate educational materials and training.13
Recommended algorithm for assessing and treating occluded catheters

- Cathflo is recommended for the treatment of partial or complete thrombotic occlusions, after ruling out nonthrombotic obstruction, by clinical practice guidelines of the INS, the Association for Vascular Access, the Oncology Nursing Society, and other treatment algorithms.

Indication
Cathflo® Activase® (alteplase) is indicated for the restoration of function to central venous access devices as assessed by the ability to withdraw blood.

Important Safety Information

Contraindications
Cathflo Activase should not be administered to patients with known hypersensitivity to Alteplase or any component of the formulation.

Precautions
General
Certain causes of catheter dysfunction should be considered before treatment with Cathflo Activase (e.g. catheter malposition, mechanical failure, constriction by a suture and lipid deposits or drug precipitates within the catheter lumen).

Bleeding
The most frequent adverse reaction associated with all thrombolytics in all approved indications is bleeding. Should serious bleeding in a critical location (e.g., intracranial, gastrointestinal, retroperitoneal, pericardial) occur, treatment with Cathflo Activase should be stopped and the drug should be withdrawn from the catheter.

Infections
Cathflo Activase should be used with caution in the presence of known or suspected infection in the catheter.

Adverse Reactions
In clinical trials, the most serious adverse events reported after treatment were sepsis, gastrointestinal bleeding, and venous thrombosis.

Please see accompanying full Prescribing Information for additional Important Safety Information.

Cathflo Activase (alteplase) plays a key role in helping to restore function to catheters with thrombotic occlusions

- Cathflo, a recombinant form of t-PA, is the only lytic that is FDA approved for the restoration of function to CVADs.

Cathflo—a fibrin-specific MOA
- The fibrin-specific mechanism of action (MOA) of Cathflo addresses the root cause of thrombotic occlusions
- Cathflo binds to fibrin in the thrombus, converting entrapped plasminogen to plasmin, initiating local fibrinolysis

Cathflo pharmacokinetics
- Cathflo 2 mg does not reach pharmacologic levels in systemic circulation.

*The clinical significance of fibrin specificity is unknown.

Adapted from Midnight S.
Cathflo® Activase® (alteplase) may restore catheter function

- In the pivotal trials COOL-1 and COOL-2, the efficacy of Cathflo was evaluated in 1122 primarily adult patients.17

**Cumulative efficacy**

In COOL-1, Cathflo restored function to 88% (112/127) of central lines after up to 2 doses using a 120-minute dwell time for each in catheters with occlusions present for up to 24 hours.

In COOL-1 and COOL-2, Cathflo restored function to 68% (796/1043) of central lines after 1 dose and 88% (902/1043) of central lines after 2 doses in catheters with occlusions present for less than 14 days.

**First-dose efficacy**

In COOL-2, Cathflo restored function after 1 dose in 75% (747/995) of central lines after up to 120 minutes of dwell time in catheters with occlusions present for any duration.

**Occlusions >14 days efficacy**

In COOL-2, Cathflo restored function to 57% (30/53) of central lines after 1 dose and 72% (38/53) of central lines after 2 doses in catheters with occlusions present for longer than 14 days.

**Maintained patency**

In a subset of patients (n=346) who had a successful treatment outcome, 74% (256/346) of central lines maintained patency up to 30 days after treatment with Cathflo.

**88%**

**72%**

**74%**

Cathflo safety profile in adult and pediatric patients

Cathflo has a safety profile studied in both adult and pediatric patients as young as 2 weeks of age.16,17

- In the pivotal trials COOL-1 and COOL-2, the safety profile of Cathflo was evaluated in 1122 primarily adult patients.17
- CAPS evaluated the safety profile of Cathflo in 310 pediatric patients. The youngest patient in the study was 2 weeks old.16,17

**COOL-1 and COOL-2 (N=1122): Serious adverse events**

<table>
<thead>
<tr>
<th>Event</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sepsis</td>
<td>0.4%</td>
</tr>
<tr>
<td>Major hemorrhage</td>
<td>0.4%</td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td>0.3%</td>
</tr>
<tr>
<td>Venous thrombosis</td>
<td>0.3%</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>0.0%</td>
</tr>
<tr>
<td>Embolic event</td>
<td>0.0%</td>
</tr>
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</table>

**CAPS (N=310): Serious adverse events**

<table>
<thead>
<tr>
<th>Event</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Catheter-related complications</td>
<td>1.5%</td>
</tr>
<tr>
<td>Sepsis</td>
<td>1.0%</td>
</tr>
<tr>
<td>Fever</td>
<td>&lt;1.0%</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>0.0%</td>
</tr>
<tr>
<td>Major hemorrhage</td>
<td>0.0%</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>0.0%</td>
</tr>
<tr>
<td>Embolic event</td>
<td>0.0%</td>
</tr>
</tbody>
</table>

Adapted from Blaney M, et al.

- At least one due to catheter rupture.

The instillation of alteplase 2 mg (Cathflo Activase) is safe and effective in restoring catheter patency in patients.3

—INS Infusion Therapy Standards of Practice, 2016, page S105, standard 48, practice criterion G

Please see Indication and Important Safety Information on back cover. Please also see accompanying full Prescribing Information.
Reconstitution, dosing, and administration of Cathflo® Activase® (alteplase)

Cathflo is available in a single-use, 2-mg vial.17

Preparation of solution17

After WASHING hands using aseptic technique, reconstitute Cathflo to a final concentration of 2 mg/2 mL:

1. Aseptically WITHDRAW 2.2 mL of Sterile Water for Injection, USP (diluent is not provided). Do not use Bacteriostatic Water for Injection, USP.

2. INJECT the 2.2 mL of Sterile Water for Injection, USP, into the Cathflo 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. Complete dissolution should occur within 3 minutes. DO NOT SHAKE. The reconstituted preparation results in a colorless to pale yellow transparent solution at a pH of approximately 7.3.

Administration17,18

After WASHING hands and applying gloves:

1. INSPECT the product prior to administration for foreign matter and discoloration. Solution should be inspected immediately before use.

2. WITHDRAW 2 mL (2 mg) of reconstituted solution from the vial.

3. SCRUB the hub. Apply vigorous friction to the hubs for 15 to 30 seconds.

Please see Indication and Important Safety Information on back cover. Please also see accompanying full Prescribing Information.

Administration, cont’d

1. INSTIL the appropriate dose of Cathflo into the occluded catheter using an appropriately sized syringe (see dosing chart below).

2. After 30 minutes of DWELL time, assess the catheter function by attempting to aspirate blood. If the catheter is functional, go to step 10; if not functional, go to step 9.

3. ASSESS catheter function after a total of 120 minutes of dwell time by attempting to aspirate blood. If the catheter is functional, go to step 10; if catheter is still occluded, a second dose of equal amount may be instilled. Repeat steps 1 through 8.

If catheter function has been restored, ASPIRATE 4 mL to 5 mL of blood in patients ≥10 kg or 3 mL in patients <10 kg to remove Cathflo and residual clot. Then gently irrigate the catheter with 0.9% Sodium Chloride, USP. Any unused solution should be discarded.

Dosing with Cathflo 2 mg17

<table>
<thead>
<tr>
<th>Patient weight</th>
<th>Cathflo dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥30 kg (66 lb)</td>
<td>2 mg in 2 mL</td>
</tr>
<tr>
<td>&lt;30 kg (66 lb)</td>
<td>110% of the internal lumen volume of CVAD, not to exceed 2 mg in 2 mL</td>
</tr>
</tbody>
</table>

Note: Store lyophilized Cathflo at refrigerated temperature (2°C-8°C/36°F-46°F). Cathflo should be reconstituted immediately before use. The solution may be used within 8 hours if stored at 2°C to 30°C (36°F-86°F).

If catheter function is not restored at 120 minutes after 1 dose of Cathflo, a second dose may be instilled

- Studies have not been performed with administration of total doses greater than 4 mg (two 2-mg doses)

Please see Dosage and administration section of the full prescribing information for the complete dosing information.

References:
- Kalka JM. The role of biofilm in vascular catheter-related infections. Wingerter L. Vascular access device thrombosis. Cummings-Winfield C, Mushani-Spaulding, S. Cathflo Activase in patients with infected catheters may release a localized infection into the systemic circulation. Cathflo Activase should be used with caution in the presence of known or suspected infection in the catheter. Using Cathflo Activase (alteplase) is indicated for the restoration of function to central venous access devices as assessed by the ability to withdraw blood. Please see full Prescribing Information for additional Important Safety Information.
- For more information visit www.cathflo.com
Don’t let sluggish flow disrupt therapy

Take charge with Cathflo Activase (alteplase) and help restore central line function

- Is there routine assessment of CVAD patency at your hospital?
- Ask your Genentech representative about resources to help you implement CVAD education and skill development

**Indication**
Cathflo Activase (alteplase) is indicated for the restoration of function to central venous access devices as assessed by the ability to withdraw blood.

**Important Safety Information**

**Contraindications**
Cathflo Activase should not be administered to patients with known hypersensitivity to alteplase or any component of the formulation.

**Precautions**

**General**
Certain causes of catheter dysfunction should be considered before treatment with Cathflo Activase (e.g. catheter malposition, mechanical failure, constriction by a suture and lipid deposits or drug precipitates within the catheter lumen).

Excessive pressure should be avoided when Cathflo Activase is instilled into the catheter.

**Bleeding**
The most frequent adverse reaction associated with all thrombolytics in all approved indications is bleeding. Cathflo Activase has not been studied in patients known to be at risk for bleeding events that may be associated with the use of thrombolytics. Caution should be exercised with patients who have any condition for which bleeding constitutes a significant hazard.

Should serious bleeding in a critical location (e.g., intracranial, gastrointestinal, retroperitoneal, pericardial) occur, treatment with Cathflo Activase should be stopped and the drug should be withdrawn from the catheter.

**Infections**
Cathflo Activase should be used with caution in the presence of known or suspected infection in the catheter. Using Cathflo Activase in patients with infected catheters may release a localized infection into the systemic circulation.

**Adverse Reactions**
In clinical trials, the most serious adverse events reported after treatment were sepsis, gastrointestinal bleeding, and venous thrombosis.

**Please see full Prescribing Information for additional Important Safety Information.**

To learn more about the management of thrombotically occluded catheters, please visit www.cathflo.com or call Genentech Customer Service at 1-800-551-2231 to locate your local Genentech clinical specialist.

www.cathflo.com