# A Review of Anticoagulation Reversal & Updates on Peripheral Administration of Vasopressors

Hope Hoffman, PharmD

Jelena Lakic, PharmD

PGY-2 Critical Care Pharmacy Residents

PennState Health
Milton S. Hershey Medical Center

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## Disclosures

No financial disclosures or conflicts of interest to disclose.

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**Slide 1**

**BK3** + vasopressor peripheral? I would make this the title of the presentation put in the program
Bardzel, Kayla, 9/17/2024

BK1

## Objectives

**Anticoagulation Reversal:**

- Identify common anticoagulants and their reversal agents
- Discuss appropriate indications for anticoagulation reversal

**Peripheral Administration of Vasopressors:**

- Recognize risks and benefits of peripheral vasopressor administration
- Review new recommendations and literature regarding peripheral administration of vasopressors

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# Anticoagulation Reversal

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**Slide 3**

**BK1** I think we should put all of the learning objectives for both sections on this slide

Bardzel, Kayla, 9/17/2024

## Bleeding Severity

Initial patient evaluation should aim to determine onset, location, and severity of bleeding as well as determining if the bleed is ongoing.

Definition of a **Major Bleed** (≥ 1 of the following):

- Bleeding in a critical site
- Hemodynamic instability
- Overt bleeding with hemoglobin drop ≥ 2 g/dL or administration of ≥ 2 units of packed red blood cells

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Tomaselli et al. ACC. 2020;76(5):594-622.

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## Reversal of Specific Agents

- Warfarin
- Factor Xa Inhibitors (apixaban, rivaroxaban, edoxaban)
- Dabigatran
- Heparin & LMWH

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# Warfarin Reversal



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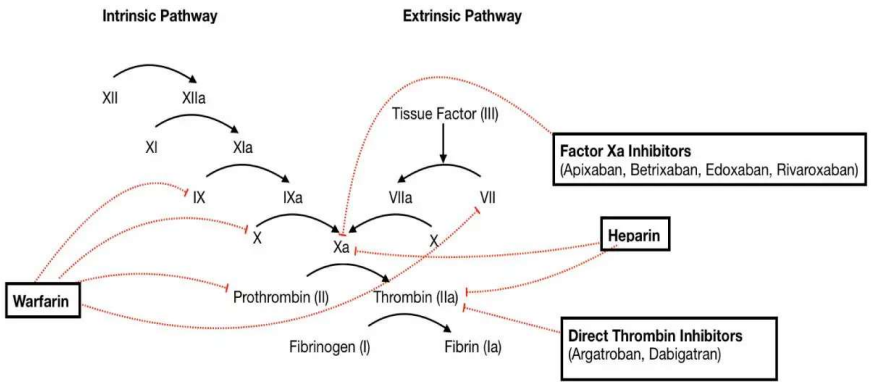
## Warfarin: Mechanism

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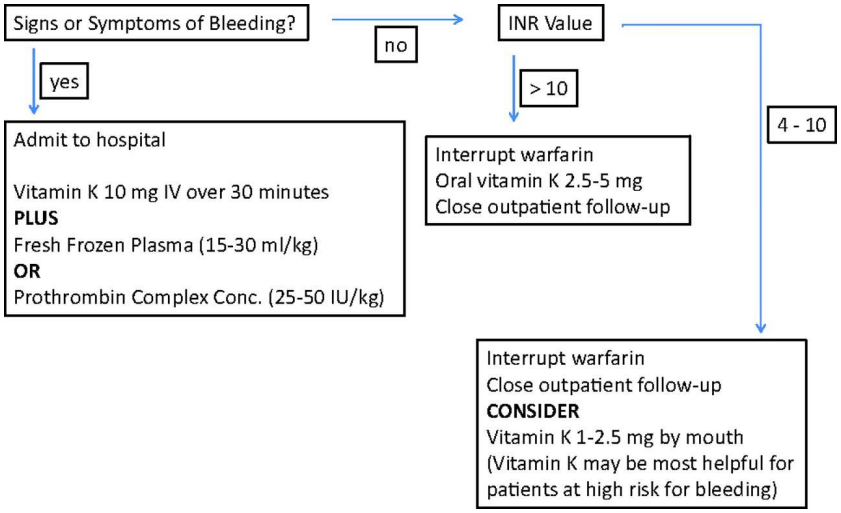
# Warfarin: Reversal

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Garcia et al. AHA. 2012;125(23):2944-2947.

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# Vitamin K

**Mechanism**: increases hepatic production of vitamin-K dependent clotting factors (II, VII, IX, and X)

**Administration**: intravenous infusion or oral

**Dose**:

| Bleeding | INR | Vitamin K Dose & Route |
|---|---|---|
| **Minor bleeding** | 4 to 10 | *CONSIDER* 1 to 2.5 mg PO |
| | >10 | 2.5 to 5 mg PO |
| **Major bleeding** | N/A | 10 mg IV |

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# Inactivated Prothrombin Complex Concentrate (PCC)

**Mechanism**: provides repletion of vitamin K-dependent clotting factors as a pooled human plasma

**Types of PCC:**

**3 Factor-PCC (Profilnine)**

- Factor II
- Factor IX
- Factor X

**4 Factor-PCC (KCentra)**

- Factor II
- Factor VII
- Factor IX
- Factor X
- Proteins C & S

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Tomaselli et al. ACC. 2020;76(5):594-622.

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# 4F-PCC Dosing

Weight-Based Dosing:

| Pre-Treatment INR | 4F-PCC Dose | Maximum Dose |
|---|---|---|
| 2 to <4.0 | 25 units/kg | 2,500 units |
| 4 to 6 | 35 units/kg | 3,500 units |
| INR > 6 | 50 units/kg | 5,000 units |

Fixed Dosing:

| Indication | Dose Range |
|---|---|
| Intracranial Hemorrhage | 1,500 to 2,000 units |
| Other Bleeds | 1,000 to 2,000 units |

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Frontera et al. *Neurocrit Care*. 2016;24:6-46.

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**Slide 11**

**BK11** can add in FEIBA - some hospitals utilize this
Bardzel, Kayla, 9/18/2024

# Factor Eight Inhibitor Bypassing Agent (FEIBA)

**Indication**: reversal of anticoagulant factors that inhibit either factor VIII and/or factor IX in patients with hemophilia A or B

**Mechanism**: restores impaired thrombin generation in patients with hemophilia leading to hemostasis

**Contains**:

- Inactivated factors II, IX, and X
- Activated factor VII



FEIBA [Package Insert]. 2024.



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# Factor Eight Inhibitor Bypassing Agent (FEIBA)

**Dose**:

| Indication | Dose (units/kg) | Duration |
|---|---|---|
| **Control/Prevention of Bleeding** | | |
| Joint Hemorrhage | 50-100 q12h | Until pain/disabilities resolve |
| Mucous Membrane Bleeding | 50-100 q6h | |
| Soft Tissue Hemorrhage | 100 q12h | Until resolution of bleed |
| Severe Hemorrhage | 100 q6-12h | Until resolution of bleed |
| **Perioperative Management** | | |
| Preoperative | 50-100 x1 dose | Immediately prior to procedure |
| Postoperative | 50-100 q6-12h | Until resolution of bleed |
| **Other** | | |
| Routine Prophylaxis | 85 q48h | N/A |



FEIBA [Package Insert]. 2024.



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## Fresh Frozen Plasma (FFP)

**Mechanism**: nonspecific reversal agent that repletes coagulation factors obtained from whole blood

**Contains**:
- Factor V, VII, X, XI, XIII
- Fibrinogen
- Plasma protein
- Electrolytes

**Dose**: 10-15 mL/kg

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Tomaselli et al. *ACC*. 2020;76(5):594-622.

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## Onset/Duration of Warfarin Reversal Agents

| Agent | Onset of Action | Duration of Action |
|---|---|---|
| **Vitamin K (oral)** | 24 hours | Days |
| **Vitamin K (IV)** | 8-12 hours | Days |
| **Fresh Frozen Plasma** | Immediate | 12-24 hours |
| **PCC** | Immediate | 12-24 hours |
| **Recombinant factor VIIa** | Immediate | 2-6 hours |
| **FEIBA** | 15-30 minutes | 8-12 hours |

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# Factor Xa Inhibitors Reversal



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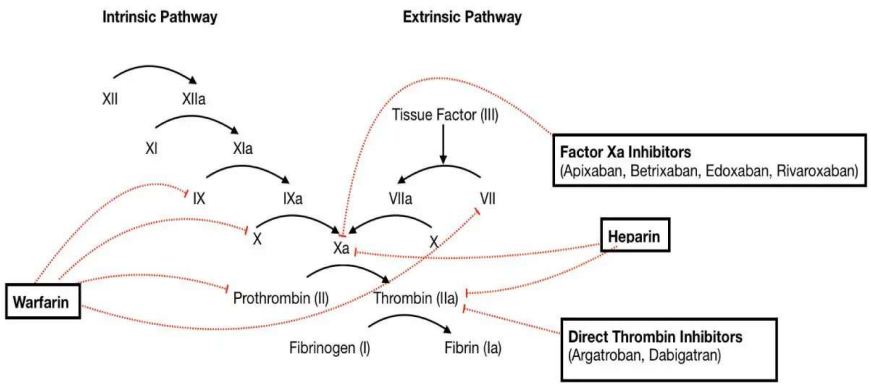
## Factor Xa Inhibitors: Mechanism



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## DOAC Reversal

Andexanet Alfa

4-Factor Prothrombin Complex Concentrate (4F-PCC)



## Andexanet Alfa

**Mechanism:** recombinant modified human factor Xa inhibitor

**Indication:** reversal of life-threatening or uncontrolled bleeds associated with rivaroxaban or apixaban use

**Warnings**: thromboembolic risk


Andexxa [Package Insert]. 2018.


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# Andexanet Alfa Dosing

| Anti-Xa Inhibitor | Last Dose | Time Since Last Dose | |
|---|---|---|---|
| | | < 8 hours or unknown | ≥ 8 hours |
| Apixaban | ≤ 5 mg | Low Dose | Low Dose |
| | > 5 mg or unknown | High Dose | |
| Rivaroxaban | ≤ 10 mg | Low Dose | |
| | > 10 mg or unknown | High Dose | |

| Dose | Initial IV Bolus | Continuous IV Infusion |
|---|---|---|
| Low Dose | 400 mg bolus infused at a rate of 30 mg/minute | 4 mg/minute continued for 120 minutes |
| High Dose | 800 mg bolus infused at a rate of 30 mg/minute | 8 mg/minute continue for 120 minutes |

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Andexxa [Package Insert]. 2018.

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BK7

# 4-Factor Prothrombin Complex Concentrate Dosing

**Weight-Based Dosing:**

25 to 50 units/kg (max 5,000 units)

**Fixed Dosing:**

2,000 units

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Tomaselli et al. *ACC*. 2020;76(5):594-622.
Frontera et al. *Neurocrit Care*. 2016;24:6-46.

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**Slide 22**

**BK7** Maybe include literature why fixed dosing for DOACs in ICH is not great
Bardzel, Kayla, 9/18/2024

## Dosing Strategies for 4F-PCC

| Study | Snyder et al, 2024 | Davis et al, 2021 |
|---|---|---|
| **Design** | Single center retrospective cohort study for reversal of apixaban or rivaroxaban | Multicenter retrospective cohort study for reversal of apixaban, rivaroxaban, or edoxaban-associated intracranial hemorrhage |
| **Intervention** | Fixed dose PCC (5,000 units or 2,000 units) compared to weight-based PCC (50 units/kg) | High dose 4F-PCC (≥ 35 units/kg) or low dose 4F-PCC (< 35 units/kg) |
| **Hemostatic Efficacy** | Fixed dose: 79.2 %<br>Weight based: 71.3 %<br>P = 0.24 | High dose: 89.2 %<br>Low dose: 46.7 %<br>95% CI 2.4-52.6, P = 0.002 |
| **Safety** | 30-Day Mortality<br>Fixed dose: 35.6 %<br>Weight based: 26.4 %<br>P = 0.18 | Thrombotic events<br>High dose: 8.2 %<br>Low dose: 6.7 %<br>95% CI 0.08-8.2, P = 0.87 |
| **Discussion** | Higher doses given in fixed dose cohort compared to weight-based dose group. No discussion of efficacy in ICH subgroup. | Higher dose PCC demonstrated increased efficacy for achieving hemostasis in patients with ICH with similar safety outcomes. |

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## Andexanet Alfa vs. 4F-PCC: Annexa I Study

| Result | Andexanet Alfa | Usual Care | P Value |
|---|---|---|---|
| **Primary Hemostatic Efficacy** | 150/224 (67.0%) | 121/228 (53.1%) | 0.003<br>**NNT = 8** |
| **At Least 1 Thrombotic Event(s) within 30 Days** | 27/263 (10.3%) | 15/267 (5.6%) | 0.048<br>**NNH = 21** |
| **Death within 30 Days** | 73/263 (27.8%) | 68/267 (25.5%) | 0.51 |

**Hemostatic Efficacy:**

- Hematoma volume change ≤ 35 %
- NIHSS score change < 7 points
- No receipt of rescue therapy between 3 hours and 12 hours

NNT = Number Needed to Treat
NNH = Number Needed to Harm

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Connolly et al. N Engl J Med. 2024; 390(19):1745-1755.

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# Dabigatran Reversal



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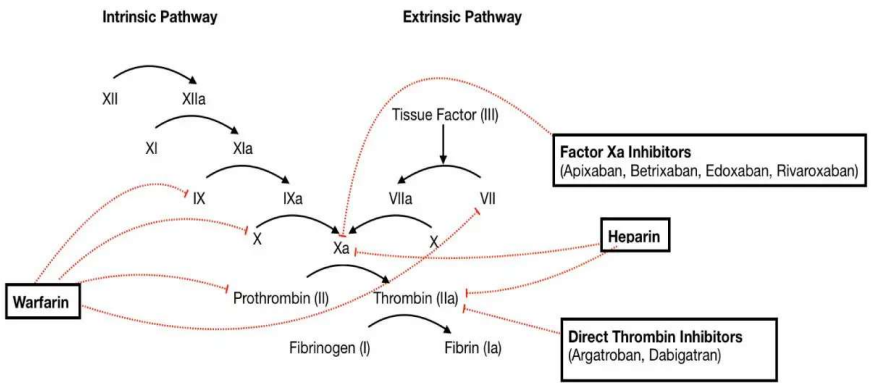
## Dabigatran: Mechanism





MyHematology. 2024.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## Dabigatran Reversal: Idarucizumab

**Mechanism**: humanized monoclonal antibody fragment that binds with high affinity to dabigatran and its metabolites to neutralize anticoagulant effect

**Indication**: immediate reversal of dabigatran for life-threatening or uncontrolled bleeding

**Dosing**: 5 g IV push x1 dose

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Idarucizumab [Package Insert]. 2015
Tomaselli et al. *ACC.* 2020;76(5):594-622.

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## Heparin & Enoxaparin Reversal

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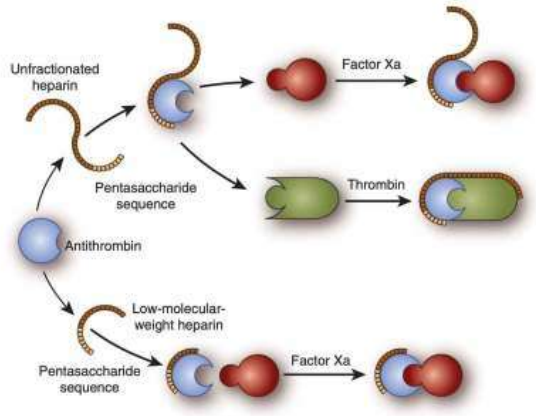
## Heparin and LMWH: Mechanism




Heparin functions by activating antithrombin-III to bind to serine proteases involved in coagulation, blocking their function (predominantly Factor Xa and Factor IIa a.k.a. thrombin). Low molecular heparin predominantly facilitates inhibition of Xa, whereas unfractionated heparin inhibits Xa and thrombin. This reaction consumes antithrombin-III (which remains permanently stuck to factor Xa and/or thrombin).

Lai S et al. Kidney International 2013



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## Heparin and LMWH Reversal: Protamine

**Mechanism**: binds with heparin to form a stable salt

**Dose**:

| Anticoagulant | Protamine Dose | Monitoring |
|---|---|---|
| Heparin (therapeutic) | 1 mg protamine per 100 units UFH administered within the past 2-3 hours (max dose = 50 mg) | Repeat doses based on aPTT monitoring |
| Enoxaparin (therapeutic) | Last dose given < 8 hours ago<br>1 mg protamine per 1 mg LMWH (max dose = 50 mg) | Repeat doses considered if bleeding persists or if patient has renal insufficiency |
| | Last dose given 8-12 hours ago<br>0.5 mg protamine per 1 mg LMWH | |



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## Summary of Anticoagulation Reversal Agents

| Anticoagulant | Reversal Agent(s) |
|---|---|
| **Warfarin** | Vitamin K<br>Prothrombin Complex Concentrate<br>Fresh Frozen Plasma |
| **Factor Xa Inhibitors** | Prothrombin Complex Concentrate<br>Andexanet Alfa |
| **Dabigatran** | Idarucizumab |
| **Heparin/LMWH** | Protamine |

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# Peripheral Administration of Vasopressors

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# Vasopressor Overview

| Common Vasopressors | Vasopressor Indications |
|---|---|
| • Norepinephrine<br>• Epinephrine<br>• Vasopressin<br>• Phenylephrine | • Sepsis<br>• Shock states<br>• Spinal cord injury |

Preferred route of administration?
Central venous access

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*Araiza A, et al. CMAJ. 2022*
*Kalinoski M, et al. Br J Hosp Med (Lond). 2024* 33

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# Why Central Access?

Loubani OM, Green RS. A systematic review of extravasation and local tissue injury from administration of vasopressors through peripheral intravenous catheter and central venous catheters. *J Crit Care. 2015*

| | |
|---|---|
| **Design & Objectives** | **Systematic Review**<br>**Objective:** collect and describe all published reports of local tissue injury or extravasation from vasopressor administration via either central or peripheral access. |
| **Methods** | **Databases searched:** Medline, Embase, Cochrane<br>**Inclusion criteria:**<br>- Adults who received vasopressor via peripheral or central IV for therapeutic purpose |
| **Results** | N = 85 total articles included, 202 total patients<br>n = 325 local tissue injuries & extravasation events identified<br>n = 318 events from peripheral use<br>n = 7 events from central use |

**Conclusion:** Further studies are warranted to clarify the safety of vasopressor administration via peripheral IVs

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*Loubani OM, et al. J Crit Care. 2015* 34

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## Peripheral Vasopressor Administration – Risks, Benefits, & Challenges

| Risks | Benefits |
|---|---|
| • Extravasation injury<br>• Tissue ischemia & necrosis | • Faster access<br>• Less invasive<br>• Easier monitoring of IV site<br>• Useful in interim settings |

The challenges? Variety of approaches taken for peripheral administration, differing PIV sizes, & locations, differing pressor agents

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*Araiza A, et al. CMAJ. 2022*
*Kalinoski M, et al. Br J Hosp Med (Lond). 2024*

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## Yerke JR, et al. Peripheral administration of norepinephrine: a prospective observational study

| | |
|---|---|
| **Design** | Prospective observational cohort study taken place in a medical intensive care unit at the Cleveland Clinic from February 2019 – June 2021 |
| **Objectives** | **Primary outcome**: Can a protocol for peripheral norepinephrine administration safely reduce the following:<br>• Number of days a central venous catheter is in use<br>• Frequency of central venous catheter placement<br><br>**Secondary outcomes:** incidence of extravasation events |
| **Methods** | Inclusion criteria:<br>• 2 available PIVC which are 18, 20, or 22 gauge<br>• PIVC must be assessed every 2 hours for patency + aspiration for blood return assessment every 2 hours<br>• PIVC must be placed above wrist, below antecubital fossa and be confirmed via ultrasonography |

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*Yerke JR, et al. Chest. 2024*

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## Yerke JR, et al. Peripheral administration of norepinephrine: a prospective observational study

| | |
|---|---|
| **Results** | **N = 635 patients**<br>***Median number of CVC days avoided per patient:*** 1 day, IQR (0-2)<br>***Number of patients never requiring a CVC line:*** 311 (51.6%)<br>***Extravasation of norepinephrine:***<br>• *n* = 35 patients<br>• No patient demonstrated tissue injury that warranted surgical intervention |
| **Discussion** | **Strengths**<br>• Development of protocol was a multidisciplinary approach<br>• Protocol education was performed among practitioners<br>**Limitations**<br>• Single center site study<br>• High rate of protocol deviations<br>• Lack of comparator group<br>• Selection bias |

**Conclusion:** administration of peripheral norepinephrine can be operationalized safely for patients and can prevent the need for central line placement

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*Yerke JR, et al. Chest. 2024*

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## Lewis T, et al. Safety of the peripheral administration of vasopressor agents

| | |
|---|---|
| **Design** | Single center, retrospective chart review done at New York University Langone Medical Center from January 2015 to April 2016 |
| **Objectives** | **Primary Outcome:** incidence of extravasation events related to peripheral IV use<br><br>*Extravasation events were defined as confirmed or possible due to the inability to attribute an extravasation event to a pressor agent based on the nursing flow sheet documentation alone |
| **Methods** | **Inclusion Criteria:**<br>• >18 years of age<br>• Received a vasopressor agent through a peripheral line in the ICU<br>**Exclusion Criteria:**<br>• Patients who had central line placement prior to vasopressor initiation<br>• Patients who received a vasopressor via peripherally for <1 hour |

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*Lewis T, et al. J Intensive Care Med. 2019.*

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## Lewis T, et al. Safety of the peripheral administration of vasopressor agents

| | |
|---|---|
| **Results** | **N = 202**<br>**Pressors evaluated**: norepinephrine, phenylephrine, vasopressin, epinephrine, dopamine<br>**Extravasation events**: n = 8 (3.9%), conservative management required in all events<br>• Injury grade 1: n = 2 (25%)<br>• Injury grade 2: n = 6 (75%)<br>**Pressors responsible for extravasation events:**<br>• Norepinephrine: n = 4 (50%)<br>• Phenylephrine: n = 4 (50%) |
| **Discussion** | **Strengths**<br>• Evaluated all common types of vasopressors when looking at extravasation events<br>**Limitations**<br>• Retrospective nature of study<br>• Limited details regarding extravasation events<br>• Documentation bias |

**Conclusion: Use of peripheral lines for vasopressor administration can be considered in patients with a contraindication for central access**

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*Lewis T, et al. J Intensive Care Med. 2019.*

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## Extravasation Management

- Aspirate remaining drug from IV line if possible, elevate site of extravasation
- May use warm compress, apply to site of extravasation
- Antidotes: phentolamine *or* topical nitroglycerin
- Phentolamine dosing
- 5-10 mg (diluted in 10mL NS). Divide dose in multiple subQ injections along the area of extravasation.

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*Mulieri, Extravasation Recommendation Guidelines. 2024.*

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BK10

## Key Takeaways

- Peripheral administration of vasopressors are a valuable option in certain clinical scenarios
- Considerations when initiating vasopressors throughout peripheral administration:
    - Site selection
    - Size of peripheral IV
    - Duration of therapy
- Monitoring of extravasation events is a multidisciplinary approach

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**Slide 41**

**BK10** Do you have recommendations on potential criteria that would allow for peripheral vasopressors in patients? Do you not want to use at all? Can you consider in some vs. others? What patient populations would you not consider for this?
Bardzel, Kayla, 9/18/2024