Evidence-based use of peripheral vasopressors

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University of Michigan
Disclosures  None
Agenda

• Review guidelines about vasopressor administration route
• Highlight keys to safe peripheral vasopressor use
• Take a look at current practices
How do you start vasopressors?

A. Place a central line then start vasopressors centrally 0%

B. Start vasopressors peripherally but place central line ASAP 0%

C. Start vasopressors peripherally and only place a central line if a patient’s vasopressor requirements are high or they have another indication for central access 0%
How would you start vasopressors in this patient?

**Traditional** - A. Place a central line then start vasopressors centrally

**2021 SSC** - B. Start vasopressors peripherally but place a central line asap

**New alternative?** - C. Start vasopressors peripherally and only place a central line if patient’s vasopressor requirements are high or there is another indication for access

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44. For adults with septic shock, we *suggest* starting vasopressors peripherally to restore MAP rather than delaying initiation until a central venous access is secured.

*Weak recommendation, very low quality of evidence.*

**Remark:**
When using vasopressors peripherally, they should be administered only for a short period of time and in a vein in or proximal to the antecubital fossa.
How we give vasopressors is changing

1. Concerns about fluid overload → Early vasopressor initiation
2. Awareness of CLABSI and line complications
Why central administration?
Infuse LEVOPHED into a large vein. Avoid infusions into the veins of the leg in the elderly or in patients with occlusive vascular disease of the legs [see Warnings and Precautions (5.1)]. Avoid using a catheter-tie-in technique.
Case reports of catastrophic tissue injury

Loubani et al. *J Crit Care.* 2015
Case reports of catastrophic tissue injury

Central administration became standard
How should we give vasopressors?

**Central** vs **Peripheral**

Disadvantages
- Take time
- Complications (3.1-3.7%)

How should we give vasopressors?

Central vs Peripheral

New safety data
Newer safety data

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Study spotlight
1. Peri-operative study

Retrospective study of 14,385 patients across 2 hospitals in the Netherlands
Patients received peripheral norepinephrine peri-operatively
Durations were short (during surgery)

Results
0.035% (5) extravasations reported with no related complications

2. ICU-based study: Cardenas-Garcia (2015)

Prospective study of 734 ICU patients on vasopressors at a single center
Strict safety protocols
Mean duration: 49 ± 22 hours

Results
Extravasation rate: **2.3%**
No tissue injury
Only 13% required a central line

### TABLE 1. Summary of the Requirements for PIV Access Used for Infusion of VM

<table>
<thead>
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<tr>
<td>Vein diameter &gt; 4 mm measured with ultrasonography</td>
</tr>
<tr>
<td>Position of PIV access documented to be in the vein with ultrasonography</td>
</tr>
<tr>
<td>Upper extremity only, contralateral to the blood pressure cuff</td>
</tr>
<tr>
<td>Intravenous line size 20 gauge or 18 gauge</td>
</tr>
<tr>
<td>No hand, wrist, or antecubital fossa PIV access position</td>
</tr>
<tr>
<td>Blood return from the PIV access prior to VM administration</td>
</tr>
<tr>
<td>Assessment of PIV access function every 2 hours as per nursing protocol</td>
</tr>
<tr>
<td>Immediate alert by nursing staff to the medical team if line extravasation</td>
</tr>
<tr>
<td>72 hours maximum duration of PIV access use</td>
</tr>
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</table>

**NOTE:** Abbreviations: PIV, peripheral intravenous; VM, vasoactive medication.

Prospective study of 635 ICU patients on norepinephrine at a single center

Strict safety protocols

Median duration: 5.8 hours (but up to > 48 hours)

Results

Extravasation rate: **5.5%**

No tissue injury

51.6% avoided a central line

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**Initial Protocol Requirements (February 2019)**

- Two available PIV which are 20 or 22 gauge
- PIV must be placed above the wrist and below the antecubital fossa
- PIV placement must be confirmed via ultrasonography
- Assessment of PIV patency every 2 hours
- Maximum norepinephrine dose of 15 mcg/min
- Maximum infusion time of 48 hours
- Included patients must be able to report pain or discomfort

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Peripheral vasopressors appear to be safe

....in single-centered studies with strict protocols.
Peripheral vasopressors appear to be safe

....in single-centered studies with strict protocols.

Do hospitals have similar safety protocols?
A survey of hospital vasopressor policies

Hospital vasopressor policies

Hospitals surveyed: n=62

Policy on vasopressor administration: n=52 (83.9%)

- No vasopressor policy, n=9
- Unsure, n=1
- No policy details provided, n=1

Central-only: n=13 (25.0%)
Central-preferred: n=19 (36.5%)
Peripheral-friendly: n=19 (36.5%)
Policy limits on peripheral vasopressors

Vasopressor-based limits
- Duration
- Dose
- Agent
  - Type
  - Single agent

IV-based limits
- IV size
- IV location
- Monitoring
- Ultrasound-guided IV placement
Take-Away: Policies varied widely
Vasopressor Limits

n=38
IV Limits

n=38
Policies vary widely.
What is most important?
What is most important?

Definitely needed
- Monitoring
- Extravasation management plans

May be needed
- Dose caps
- Duration limits
- PIV requirements

Not needed/harmful
- Agent restrictions
What is most important?

**Definitely needed**
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Monitoring

Rationale: Extravasation happens. Catching it early prevents tissue injury.

• Studies have required monitoring every 2 hours “for patency”

**Monitoring**

**Rationale:** Extravasation happens. Catching it early prevents tissue injury.

- Studies have required monitoring every 2 hours “for patency”

![IV monitoring requirement chart]

By visual inspection, aspiration, or both

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Extravasation management plans

**Rationale:** Extravasation happens. We need to know what to do.

- Studies have included explicit **extravasation management plans**
  - Easily accessible phentolamine & nitrofurazone
  - Clear, nursing-driven response protocols
  - Nursing and team education

What is most important?

**Definitely needed**
- Monitoring
- Extravasation management plans

**May be needed**
- Dose caps
- Duration limits
- PIV requirements

**Not needed/harmful**
- Agent restrictions
Dose caps

**Rationale**: Higher doses may be more likely to cause injury

- $\leq 0.1 \text{ mcg/kg/min}: 15.8\%$
- $0.1-0.2 \text{ mcg/kg/min}: 21.1\%$
- $0.2-0.3 \text{ mcg/kg/min}: 15.8\%$
- $0.3-0.5 \text{ mcg/kg/min}: \text{None}$
- Other: 42.1\% (escalation, concentration)
Dose caps

**Rationale:** Higher doses may be more likely to cause injury

**Evidence**
- Most studies cap doses around 0.15-0.3 mcg/kg/min
- Cardenas-Garcia had mean peak 0.7 mcg/kg/min with no tissue injury

**My practice:** Place central line when adding a second vasopressor
Duration limits

Rationale: Longer duration increases risk of extravasation
Duration limits

Rationale: Longer duration increases risk of extravasation

Evidence:
• Cardenas-Garcia: mean 49 hours
• Yerke: time of infusion ≠ extravasation

My practice: With good monitoring and assessment of IV patency, durations longer than 24 hours are reasonable

Why it matters: Theoretical central line saved with dose and duration limits

IV requirements

Rationale: Larger, proximal IVs are less likely to extravasate
IV requirements

**Rationale**: Larger, proximal IVs are less likely to extravasate

**Evidence**
- Studied protocols include:
  - PIV 18-20G +
  - Avoid legs, hands
  - Ultrasound confirmation

*Yerke et al. Chest. 2023.*
IV requirements

Rationale: Larger, proximal IVs are less likely to extravasate

Evidence

• Studied protocols include:
  • PIV 18-20G +
  • Avoid legs, hands
  • Ultrasound confirmation

But there are violations & still safe

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**IV requirements**

**Rationale:** Larger, proximal IVs are less likely to extravasate

**Evidence**

- Studied protocols include:
  - PIV 18-20G +
  - Avoid legs, hands
  - Ultrasound confirmation

My practice: Use large IVs in forearm or upper arm and confirm with ultrasound when possible

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But there are violations & still safe

What is most important?

**Definitely needed**
- Monitoring
- Extravasation management plans

**May be needed**
- Dose caps
- Duration limits
- PIV requirements

**Not needed/harmful**
- Agent restrictions
Limits on peripheral norepinephrine

Almost half of hospitals are prohibiting peripheral norepinephrine.
Less norepinephrine is used peripherally

![Bar chart showing the percentage of various medications used for peripheral and central route of initiation.](chart.png)

- **Peripheral**: 84.3% (Dopamine: 30.2%, Epinephrine: 27.6%, Phenylephrine: 19.0%, Norepinephrine: 7.5%)
- **Central**: 96.8% (Dopamine: 34.7%, Epinephrine: 29.0%, Phenylephrine: 19.8%, Norepinephrine: 13.3%)

*p=0.001*

Peripheral norepinephrine is the best studied.

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>N</th>
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<tr>
<td>Norepinephrine</td>
<td>ICU/ED</td>
<td>702</td>
</tr>
<tr>
<td></td>
<td>OR</td>
<td>14,385</td>
</tr>
<tr>
<td>Phenylephrine</td>
<td>ICU/ED</td>
<td>546</td>
</tr>
<tr>
<td>Dopamine</td>
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<td>106</td>
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+ 635 in Yerke = >1,300 ICU patients

Using peripheral access is not a reason to avoid norepinephrine!
Using peripheral access is not a reason to avoid norepinephrine!

Rare strong recommendation!
Vasopressin is a different story
Peripheral vasopressin should be used with caution

- Unlike norepinephrine: no antidote for extravasation, not well studied
Peripheral vasopressin should be used with caution

- Unlike norepinephrine: no antidote for extravasation, not well studied
- Policies often prohibit peripheral use

A majority prohibit peripheral vasopressin
Yet, vasopressin is best in less severe shock

**Table 4. Rates and Risks of Death from Any Cause According to the Severity of Shock.**

<table>
<thead>
<tr>
<th>Stratum</th>
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<th>Vasopressin Group</th>
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<tr>
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<td>28-day mortality</td>
<td>85/200 (42.5)</td>
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<td>0.05</td>
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<td>90-day mortality</td>
<td>83/180 (46.1)</td>
<td>69/193 (35.8)</td>
<td>0.04</td>
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* Patients with more severe septic shock were defined as those who required at least 15 µg of norepinephrine per minute or the equivalent at the time of randomization. Those with less severe septic shock were defined as those who required 5 to 14 µg of norepinephrine per minute or the equivalent at the time of randomization.
Yet, vasopressin is best in less severe shock

Table 4. Rates and Risks of Death from Any Cause According to the Severity of Shock.*

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These are the patients who may avoid central lines with peripheral norepinephrine!

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0.07-0.2 mcg/kg/min
What should we do about vasopressin?

We need more data on peripheral vasopressin safety

In the meantime, place a central line to add vasopressin
There are key elements of peripheral vasopressor safety protocols.

... but actual hospital policies vary widely.
There are key elements of peripheral vasopressor safety protocols.

... but actual hospital policies vary widely.

What are providers doing in practice?
CLOVERS gives us a window into practice

• Multi-center US trial of early vasopressors vs liberal fluids in sepsis-induced hypotension
• Vasopressors could be given using “Large Peripheral IV” or central line, per treating team
  • Presumably with a range of policies
Peripheral vasopressor use in CLOVERS

Overall, 500/750 (66.6%) received peripheral vasopressors

**Figure 1. Peripheral vasopressor use over time**
Percent of patients on vasopressors who received a peripheral vasopressor over the study period

Study Year

<table>
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<th>Year</th>
<th>Percent</th>
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<tr>
<td>2018</td>
<td>70%</td>
</tr>
<tr>
<td>2019</td>
<td>75%</td>
</tr>
<tr>
<td>2020</td>
<td>65%</td>
</tr>
<tr>
<td>2021</td>
<td>60%</td>
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<tr>
<td>2022*</td>
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*p for trend=0.079

*incomplete year, study ended January 2022

Peripheral vasopressors were very safe

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<th>28-day complications in CLOVERS</th>
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<td>Peripheral Vasopressors</td>
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<td><strong>0.6%</strong></td>
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<td>3/490 patients</td>
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**Key: Complication Grading**
- **Grade 1**: Asymptomatic
- **Grade 2**: Symptomatic
- **Grade 3**: Urgent intervention

*No Grade 4 (Life-threatening) or Grade 5 (Death)*
Peripheral norepinephrine is safe

28-day complications in CLOVERS

Peripheral Vasopressors

0.6%
3/490 patients

96% norepinephrine

CVC Placement

3.9%
14/363 patients

Peripheral initiation had practical advantages*

- Faster
- Less fluid
- Avoid central line

*adjusted for pre-specified patient characteristics, illness severity, study arm
Peripheral: fast, practical, & safe
Are these findings generalizable?

• CLOVERS encouraged peripheral vasopressors
Are these findings generalizable?

• Retrospective cohort study of Michigan hospitals: similar patterns
Peripheral initiation was common

Vasopressors within 6 hours
N=594

Route of administration of first vasopressor:

Peripheral IV
N=400
67.3%

Central Catheter
N=154
25.9%
131 Central line
19 PORT
4 PICC

Other Route
N=40
6.7%
3 Intraosseous
2 Midline catheter
35 Unknown
Peripheral initiation varied by hospital

Overall peripheral: 67%

ICC=0.17
MOR=2.19

Munroe et al. Under review. Please do not share.
Peripheral initiation was faster

![Box plot showing time to vasopressor delivery](image)

- **Peripheral**: 0 to 200 minutes
- **Central**: 200 to 400 minutes

**p = 0.002**

Munroe et al. Under review. Please do not share.
1 in 3 patients avoided a central line

Time to Central Line Placement by day 4 (N=400)

- None, 32.8%
- Day 1, 63.5%
- Day 4, 1.0%
- Day 3, 1.3%
- Day 2, 1.5%
- ≤6 hours, 41.3%
- 6-12 hours, 17.0%
- 12-24 hours, 5.3%

Munroe et al. Under review. Please do not share.
What is happening to these patients?

Munroe et al. Under review.
Please do not share.
Peripheral: fast, practical, & safe
But, we found a concerning disconnect between policy and practice

Practice patterns did not match reported policies
Peripheral initiation across Michigan hospitals

Overall peripheral: 67%

ICC=0.17
MOR=2.19

Munroe et al. Under review.
Please do not share.
Peripheral initiation by hospital policy

Hospital, by policy type:
- **Central**
- **Central-Preferred**
- **Peripheral-Friendly**
- **None**

![Bar chart showing peripheral initiation by hospital policy](image)

Munroe et al. Under review. Please do not share.
Hospitals have varying policies.

No relationship to how providers practice.
Conclusions

• Peripheral vasopressors have **advantages** and are **safe**
• Use varies widely but is very **common**
• Practices don’t match policies
• We need to update policies and guidelines to ensure when peripheral vasopressors are used, they are used safely
  • **Monitoring and extravasation management plans** are key
Alternative Options: Midline Catheters?

- 297 midlines vs 1660 PICCs used for vasopressors
- No difference in catheter-related complications
- Increased rate of any blood clots in midlines that needs further evaluation

Acknowledgements

Mentor: Hallie Prescott, MD, MSc
HMS team and member hospitals
CLOVERS team and the PETAL Network
Thank you

Questions?