EVIS: IMP Prescribing

EVIS Training Module 2
Version: 3.0 23.01.2025

Study: EVIS – Early Vasopressors in Sepsis
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Intervention Arm IMP: Peripheral Norepinephrine

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Peripheral norepinephrine: Dose table

(Intervention arm)

Norepinephrine dose: Target to MAP ≥ 65 mmHg

Table applies only for norepinephrine infusion containing 16 micrograms/ml

Patient weight*	Starting dose of 0.05 micrograms / kg / min		Maximum dose of 0.15 micrograms / kg / min	
	Total drug dose per hour (micrograms / hour)	Flow rate per hour ** (ml / hr)	Total drug dose per hour (micrograms / hour)	Flow rate per hour ** (ml / hr)
40kg	120	7.5	360	22.5
50kg	150	9.4	450	28.1
60kg	180	11.3	540	33.8
70kg	210	13.1	630	39.4
80kg	240	15.0	720	45.0
90kg	270	16.9	810	50.6
100kg	300	18.8	900	56.3
110kg	330	20.6	990	61.9
120kg***	360	22.5	1080	67.5

Key:

* Round to nearest 10 kg for dosing

* * Round to nearest whole ml if pumps cannot accommodate 1 decimal place

* * * Calculate to exact kg for weights above 120kg

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Peripheral norepinephrine: Dose calculation

(Intervention arm)

- Calculate exact dose for patients > 120kg

Calculation

Worked example for 123kg patient for norepinephrine starting dose of 0.05 micrograms/kg/min

Peripheral norepinephrine: Dosing info

(Intervention arm)

- **Study treatment duration:** Up to 48 hours from time of randomisation
- **Route of administration:** peripheral venous cannula
- **Preparation:** solution containing norepinephrine 16 micrograms/ml
- **Diluent:** 0.9% sodium chloride or 5% glucose

- **Other peripheral vasopressors:** Patients in this arm should not receive any other peripheral vasopressor infusion during the 48 hour treatment duration

- **Dose up and down up-titrations**
  - Guidance in protocol but check with research team as local policy can be used
  - If target MAP ≥ 65mmHg achieved immediately post-randomisation initial infusion rate must be zero. Rate can be increased at any point during 48 hour study period.

Peripheral norepinephrine: Titration guidance

(Intervention arm)

- **Dose up-titration guidance**
  - If MAP < 65 mmHg within 15 mins of infusion starting, ↑ infusion rate to maximum of 0.10 micrograms/kg/min
  - Reassess after 15 minutes. If MAP < 65mmHg then ↑ infusion rate incrementally to max 0.15 micrograms/kg/min
  - If MAP < 65 mmHg after 15 minutes at 0.15 micrograms/kg/min consider rescue IV fluids and discuss further treatment escalation with senior medical staff

- **Dose down-titration guidance**
  - If MAP > 80mmHg for > 60 mins at 0.15 micrograms/kg/min consider down-titration and ↓ infusion rate to 0.10 micrograms/kg/min
  - Reassess after 30 minutes. If MAP > 80mmHg then ↓ infusion rate to 0.05 micrograms/kg/min
  - Reassess after 30 minutes.
    - If MAP > 80mmHg titrate infusion rate down incrementally and **STOP**
    - If MAP remains > 65mmgHg and < 80mmHg adjust the infusion rate at treating clinician discretion

Peripheral norepinephrine: Weaning & need for central line

(Intervention arm)

- **Weaning:**
  - If MAP ≥ 65mmHg on stable dose reduce dose as per normal practice.
  - Infusion can be restarted at any point within the 48 hour post-randomisation treatment period if required to achieve target MAP ≥ 65mmHg

- **Need for central line:**
  - Clinically, boluses or short infusion of additional peripheral vasopressor at a higher dose may be required whilst a central line is being placed
  - Patients are considered ‘off-trial’ from the time the decision is made to place a central line

Peripheral norepinephrine: Infusion stopping rules

(Intervention arm)

- **Peripheral norepinephrine infusion must be <u>immediately</u> and <u>permanently</u> stopped infusion if:**
  - Systolic BP > 180 mmHg **OR**
  - Diastolic BP > 110 mmHg

  } that fails to resolve despite following local treatment protocols
  - Tachyarrhythmia (ventricular tachycardia or ventricular fibrillation) that is life-threatening
  - Suspected local extravasation of IMP if graded severe (Grades 3 or 4) using table

	Grade of Extravasation				
	0	1	2	3	4
Colour of skin	Normal	Pink	Red	White / Blanched	Blackened
Integrity of skin	Intact	Blistered	Superficial skin loss	Tissue loss exposing subcutaneous tissue	Tissue loss exposing muscle / bone with a deep crater or necrosis
Oedema	Absent	Non-pitting	Pitting		
Mobility of limb	Full	Slightly limited	Very limited	Immobile	
Action	Continue to monitor	Re-site PVC and recommence PVI. Continue to monitor.		Permanently **<u>STOP</u>** PVI. Follow protocol and local extravasation policy.	

Participant to remain in EVIS study (provided consent is still valid and in place) but protocol directed treatment must stop and the participant managed in line with standard practice

Intervention arm: Rescue and maintenance treatments

- **Rescue IV fluids:** If target MAP not reached at maximum norepinephrine dose of 0.15 micrograms/kg/min or clinician concerns of organ hypoperfusion, administer 250-1000ml balanced crystalloid* via peripheral IV route

- **Maintenance IV fluids:** At clinician discretion, maintenance rather than resuscitation IV fluid can be at a rate of no more than 125 ml/hour

- **Rescue vasopressors:** If target MAP not reached using maximum permitted dose and use of rescue IV fluids/concerns of organ hypoperfusion, then rescue vasopressor can be administered via a CENTRAL route. **PERMANENTLY STOP** peripheral norepinephrine infusion

- **For operative intervention:** Maintain treatment allocation where possible. Anaesthetist discretion permitted for other fluids, blood product and vasopressor use

* Compound sodium lactate or Plasma-lyte 148 solutions

Usual care (Control) arm IMPs

Usual care (Control Arm)

- The following balanced crystalloids are permitted:
  - Compound sodium lactate solution for infusion.
    (Also known as Ringers lactate solution or Hartmann's)
  - Plasma-lyte® 148 (pH 7.4) solution for infusion

- **Route of administration:** peripheral venous cannula
- **Initial treatment:** Fluid resuscitation titrated to target MAP ≥ 65 mmHg.

  Anticipate most patients will receive approximately 30ml/kg balanced crystalloid in the first 3 hours using 250-1000ml administered by rapid infusion
- **Ongoing treatment** (up to 45 hours post-randomisation): Further balanced crystalloid boluses for resuscitation titrated to target MAP ≥ 65 mmHg

Usual care: Rescue and maintenance treatments

- **The following are permitted:**
  - **Rescue vasopressors:** Rescue vasopressor of clinician choice administered via **a central** line
  - Participants should not receive any peripheral vasopressor infusion during the 48 hour study period even where peripheral administration is accepted practice at site
  - **Maintenance IV fluids:** Defined as any fluid at a rate of ≤125ml/hour
  - **Requirement for operative intervention:** Maintain treatment allocation where possible. Anaesthetist discretion permitted for other fluids, blood product and vasopressor use

Prescribing points & next steps

IMP Prescribing (1)

Only those trained and delegated prescribing responsibilities by the Principal Investigator on the site delegation log may **initiate** and prescribe EVIS Investigational Medicinal Products (IMPs)

WHY? To minimise potential risks that can occur if untrained staff prescribe study medicines

Intervention Arm: **Must be prescribed by trained investigator.**
Write prescription to allow dosing in line with protocol requirements that allows infusion to be temporarily stopped or reinstated as per protocol until the end of the 48 hour treatment period.
Prescribing for peripheral IV norepinephrine infusion must be clear and unambiguous

Subsequent prescriptions for control arm:
Balanced crystalloids are used in accordance with routine care so if necessary, subsequent prescriptions can be prescribed by treating clinicians as per usual practice

IMP Prescribing (2)

- Other prescribing reminders
  - IMPs must be prescribed as per routine practice at site OR in accordance with local EVIS processes
  - Must be clear that patient is participating in the EVIS Clinical Trial
  - Norepinephrine and noradrenaline are both British Approved Names – be consistent and prescribe in terms least likely to cause confusion
  - In the event an EVIS patient moves from one clinical area to another with different prescribing systems then acceptable for IMP prescription to be **transcribed** by someone other than trained investigator. However this should be clearly documented and performed in accordance with local procedures
  - Norepinephrine doses in EVIS are expressed solely in terms of norepinephrine base

Next steps

- Record your training on the **EVIS Training Log**

- **Want to know more:**
  - Ask your local EVIS research team
  - Study website www.evis.scot.nhs.uk (or scan the QRS code)
    - Study protocol
    - Associated documents
    - Training modules can be found on the EVIS website

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