Peripherally administered noradrenaline for septic shock, refractory to fluid resuscitation.

Background

The focus of this guideline is patients diagnosed with septic shock refractory to fluid resuscitation, as septic shock is associated with a high risk of death[1], and with every hour treatment is delayed, mortality increases by 5.3%[2].

Currently the gold standard treatment for the hypotension of septic shock is the insertion of a Central Venous Catheter (CVC) and administration of noradrenaline[3]. In many organisations, CVC use is restricted to specific ward areas, and there may be a delay in safely inserting a CVC in unwell patients on wards or in the Emergency Department (ED)

Currently when these delays occur, bridging measures such as continued and excessive fluid resuscitation are implemented leading to fluid accumulation, resulting in pulmonary oedema causing prolonged ventilation, progression of acute kidney injury[3], and peripheral oedema leading to critical illness myopathy and prolonged hospital and ICU admission[4]. In certain circumstances, in addition to the continued use of fluid resuscitation, clinicians may choose to start an infusion of the vasopressor metaraminol. However, with sustained use of metaraminol tachyphylaxis develops (due its mechanism of action causing the displacement of endogenous noradrenaline from sympathetic nerve endings)[5]. This results in an end point where all the endogenous noradrenaline is displaced, and thus no further benefits are achieved with subsequent doses or higher infusion rates[6] resulting in sub optimal Mean Arterial Pressure (MAP).

However, an option of administering peripheral noradrenaline is now being used within the Trust. This is supported by four systematic reviews[7,8,9,10], International consensus for its use in septic shock (Surviving Sepsis Campaign (2021))[3] and national guidelines from the Intensive Care Society (ICS) (2020)[11]. This practice has been adopted internationally and nationally in other UK hospitals as a bridging measure until a CVC can be inserted.

Indication and criteria

1. Diagnosis of septic shock refractory to fluid resuscitation, i.e. Mean Arterial Pressure (MAP) <65 mmHg, serum lactate > 2 mmol/L and minimum 30ml/kg crystalloid already infused (if clinically appropriate).
2. Adult >18 years.
3. Central venous access for noradrenaline infusion is not immediately available.
4. Decision to admit to the ICU has been confirmed.

Contra-indications

1. Patients <18 years
2. Not appropriate for ICU admission i.e. treatment escalation plan in place (if unclear to be discussed with ICU consultant on call).

Cautions

Not applicable.

Adverse effects

1. Minor adverse events: Extravasation/infiltration, cellulitis, thrombophlebitis (low risk)[10].
2. Major adverse events: Ischaemic limb, necrosis of tissue, venous thrombosis (rare)[10].

Interactions[12]

Inadvisable combinations:
Volatile halogen anaesthetics: severe ventricular arrhythmia (increase in cardiac excitability).

Imipramine (tricyclic) antidepressants: paroxysmal hypertension with the possibility of arrhythmia (inhibition of the entry of sympathomimetics into sympathetic fibres).

Serotoninergic-adrenergic antidepressants (duloxetine and venlafaxine): paroxysmal hypertension with the possibility of arrhythmia (inhibition of the entry of sympathomimetics into sympathetic fibres).

Combinations requiring precautions for use:
Non-selective MAO inhibitors: increase in the pressor action of the sympathomimetic which is usually moderate. Should only be used under close medical supervision.

Selective MAO-A inhibitors, Linezolid and Methylene Blue: by extrapolation from non-selective MAO inhibitors, risk of increase in the pressor action. These should only be used under close medical supervision.

Monitoring

1. All monitoring will be undertaken by: a Critical Care Outreach Team (CCOT) Nurse, Intensive Care Unit Specialist Registrar (ICU SpR), Advanced Critical Care Practitioner (ACCP) or Anaesthetist trained in the use of vasopressors.
2. Blood Pressure (BP) monitoring: Invasive Arterial Blood Pressure (IABP) monitoring is preferred. However, if there is a delay in accessing this, do not delay the administration of peripheral noradrenaline, the use of Non-Invasive Blood Pressure (NIBP) monitoring set at 5 minute intervals as a minimum is appropriate in this situation. A target Mean Arterial Blood Pressure (MAP) must be specified as part of the prescription (normally > 65 mmHg).
3. The cannula site must be monitored using the Visual Infusion Phlebitis score (VIP) every 15 minutes for the first hour and then hourly if score remains 0.

Dose
See Appendix 2.

Administration
See Appendix 2.

Pharmacokinetics[12]
Two stereoisomers of noradrenaline exist, the biologically active L-isomer is the one present in Noradrenaline (norepinephrine) 1mg/ml Concentrate for solution for infusion.

Absorption

After intravenous administration noradrenaline has a plasma half-life of about 1 to 2 minutes.

Distribution

Noradrenaline is rapidly cleared from plasma by a combination of cellular reuptake and metabolism. It does not readily cross the blood-brain barrier.

Biotransformation

Methylation by catechol-o-methyltransferase (COMT)

Deamination by monoamine oxidase (MAO)

Ultimate metabolites from both is 4- hydroxy-3-methoxymandelic acid

Intermediate metabolites include normetanephrine and 3,4- dihydroxymandelic acid.

Elimination

Noradrenaline is mainly eliminated as glucuronide or sulphate conjugates of the metabolites in the urine.

Therapeutic Drug Monitoring
Not applicable.

Appendix 1: Peripheral noradrenaline flow chart.

Indication:

1. Diagnosis of septic shock refractory to fluid resuscitation i.e. Mean Arterial Pressure (MAP) <65 mmHg, serum lactate > 2 mmol/L and minimum 30ml/kg crystalloids infused (if clinically appropriate).
2. Adult >18 years.
3. Central venous access and noradrenaline infusion are not immediately available.
4. Decision to admit to the ICU has been confirmed.

↓

Peripheral noradrenaline can only be administered when:

1. Decision to admit to Intensive Care Unit (ICU) has been confirmed.
2. The ICU SpR or above has authorised and prescribed the use of peripheral noradrenaline on the specified proforma (appendix 2). 'Noradrenaline peripheral – see separate proforma' must also be prescribed on PRN section of the paper chart or EPMA.
3. There is an appropriately trained member of staff able to prepare, administer and monitor the infusion i.e. ICU SpR, CCOT Nurse, ICU ACCP or Anaesthetist experienced in the use of vasopressors.

↓

Peripheral IV access:

1. Site cannula proximal to the wrist, avoid sites of flexion in awake patients, must **NOT** be distal to previous puncture site, and ensure cannula flushes easily with 10ml sodium chloride 0.9%.
2. Insert second cannula (as back up) at least 20g or larger and to the same location criteria as 1st cannula (2nd cannula to be attached to 1L crystalloid via double lumen Y connector).
3. Ensure double lumen Y connector is primed and attached to the first cannula to enable double pumping if required.
4. Label line clearly for Noradrenaline use only.
5. Ensure the giving set administration line is anchored to the patient to reduce risk of cannula displacement.

↓

Noradrenaline preparation and administration

1. Dilution solution: 0.9% sodium chloride.
2. Dilution instructions: dilute 4mg Noradrenaline (4mL of Noradrenaline 1mg/mL) with 246mL 0.9% sodium chloride to achieve recommended concentration of 16 microgram/mL for peripheral administration. Only this concentration is to be used peripherally. **DO NOT** alter the strength of the concentration.
3. Administration: Via an infusion pump at a starting dose of 0.05 microgram/kg/min[12]. Titrate to desired effect.

↓

Monitoring:

1. Patient must have 1:1 monitoring care with appropriately trained CCOT Nurse, ICU SpR, ICU ACCP or Anaesthetist trained in the use of vasopressors.
2. IABP monitoring is preferred, but if unavailable use NIBP monitoring at maximum of 5 minute intervals, ensure that the BP cuff is on the opposite arm to the infusion.
3. Record Heart Rate (HR), BP and infusion rate on chart provided below.
4. Record the Visual Infusion Phlebitis score (VIP) every 15 minutes for the first hour and then hourly if score remains 0 on the chart provided below.
5. Record NEWS 2 as per NEWS score/trust policy.

Affix patient label

Appendix 2: Patient observation chart (print copies as required and file in patient notes).

Document: BP, MAP, HR, and infusion rate every 5 minutes whilst MAP <65, then every 15 minutes when MAP >65.
Document: VIP score every 15 mins for first hour, then at least hourly if score remains 0.
Document: at which infusion rate ml/hr when patient should be escalated to ICU.

Target MAP: _____	**Start time:**				**Starting rate ml/hr:**				**Escalating at ml/hr:**				**Time of escalation:**										
Time	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:
BP																							
MAP																							
HR																							
Infusion rate (ml/hr)																							
VIP score																							

Infusion dose and infusion rate (concentration 16 microgram/ml):
Dose using IDEAL body weight instead of actual body weight

$$\frac{\text{Dose (micrograms/kg/minute) x } \textbf{Ideal body weight} \text{ (kg) x 60 (minutes)}}{\text{Concentration (micrograms/mL)}}$$

	Rate of infusion ml/hr											
mcg/kg/min (Ideal body weight)	45kg	50kg	55kg	60kg	65kg	70kg	75kg	80kg	85kg	90kg	95kg	100kg
0.01	1.6	1.8	2	2.2	2.4	2.6	2.8	3	3.2	3.4	3.6	3.8
0.02	3.4	3.7	4.1	4.5	4.9	5.3	5.6	6	6.4	6.8	7.1	7.5
0.03	5	5.6	6.2	6.8	7.3	7.9	8.4	9	9.6	10.1	10.7	11.3
0.04	6.8	7.5	8.2	9	9.8	10.5	11.3	12	12.8	13.5	14.3	15
0.05	8.4	9.4	10.3	11.3	12.2	13.1	14	15	15.9	16.9	17.8	18.8
0.06	10	11.2	12.4	13.5	14.6	15.8	16.9	18	19.1	20.3	21.4	22.5
0.07	11.8	13.1	14.4	15.8	17	18.4	19.9	21	22.3	23.6	24.9	26.3
0.08	13.5	15	16.5	18	19.5	21	22.5	24	25.2	27	28.5	30
0.09	15.2	16.8	18.6	20.3	21.9	23.6	25.3	27	28.7	30.4	32	33.8
0.10	16.8	18.7	20.6	22.5	24.4	26.3	28.1	30	31.9	33.8	35.6	37.5
>0.10	**Expedite CVC**											

Authorising Doctors name and signature:

Time/date:

Prescribers name and signature:

Time/date:

CCOT name and signature:

Time/date:

MGG Date: November 2023. Review: November 2026.
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Appendix 3: VIP and Infiltration scores:

VIP score:

I.V. site looks healthy	0	No signs of phlebitis – observe cannula
One of the following is evident: slight pain or redness near I.V. site	1	Possible first signs of phlebitis. **Plan** – re-site cannula
Two of the following are evident: Pain near I.V. site, erythema or swelling	2	Early stages of phlebitis. **Plan** – re-site cannula
All of the following are evident: Pain along path of the cannula, erythema & induration	3	Medium stage phlebitis. **Plan** – re-site cannula and consider treatment
All the following are evident & extensive: Pain along path of cannula, erythema, induration and palpable venous cord	4	Advanced stage of phlebitis or start of thrombophlebitis. **Plan** – re-site cannula and consider treatment
All the following are evident & extensive: Pain along path of cannula, erythema, induration and palpable venous cord, pyrexia	5	Advanced stage of thrombophlebitis. **Plan** – initiate treatment and re-site cannula

Infiltration Score:

Grade	Signs and Symptoms
0	No symptoms
1	Skin blanched Oedema Skin blanched Oedema <2.5cm in any direction Cool to touch With or without pain
2	Skin blanched Oedema 2.5-15cm in any direction Cool to touch With or without pain
3	Skin blanched Gross oedema >15cm Cool to touch Mild to moderate pain Possible numbness
4	Skin blanched Skin tight and leaking Skin discoloured, bruised, swollen Gross oedema >15cm in any direction Deep pitting tissue oedema Circulatory impairment Moderate or severe pain Infiltration of any blood product, irritant, or vesicant

Appendix 4: Infusion disruption, double pumping and stopping protocol.

Infusion disruption:

1. **Maintain BP as priority**.
2. Ensure IV crystalloids connected to second cannula are administered to maintain target MAP.
3. Consider bolus IV metaraminol via second cannula if MAP is below target.
4. Escalate and expedite CVC.

Extravasation:

1. Assess site and monitor with VIP and infiltration score, if >1 stop infusion (follow infusion disruption protocol above).
2. Attempt to aspirate cannula before removal.
3. Elevate affected limb if able and mark the borders of any developing erythema.
4. Administer analgesia if required.
5. Contact Plastics via switchboard for advice.
6. Document incident in patients notes and Datix.

Double pumping protocol (peripheral to central noradrenaline):

1. CVC inserted and safe to use.
2. IABP monitoring must be in situ prior to double pumping when switching from peripheral to central noradrenaline.
3. Set syringe pump attached to CVC at 1/5 of peripheral noradrenaline rate (this equates to same dose) **Note:** this applies to **SINGLE** strength (80 microgram/ml) noradrenaline. If double strength noradrenaline attached to CVC then set syringe pump to 1/10 of peripheral noradrenaline rate.
4. When transitioned to CVC successfully, aspirate peripheral noradrenaline cannula and remove (**DO NOT** flush or administer medications via this cannula it must be removed).

Double pumping protocol (peripheral to peripheral noradrenaline):

1. Prepare the 2nd bag of peripheral noradrenaline when the 1st 250ml bag has 50ml of contents left.
2. Ensure BP monitor is set to shortest interval (normal 3 minutes).
3. Connect 250ml bag of peripheral noradrenaline concentration to the Y connector with the 1st bag of peripheral noradrenaline.
4. Set 2nd infusion pump at same rate as 1st infusion pump and start pumping (concentrations are the same).
5. When transitioned to 2nd 250ml bag of noradrenaline disconnect the first bag and dispose.

Stopping the infusion:

1. Only stop the infusion if the MAP is maintained, unsupported and infusion weaned off prior to ICU admission.
2. **DO NOT** remove infusion, the infusion should remain attached and cannula in situ until patient is admitted to the ICU as infusion may be required again before insertion of CVC.

References

1. National Institute for health and Care Excellence (2017) 'Sepsis (QS161)'
2. Bai, X., Yu, W., Ji, W., Lin, Z., Tan, S., Duan, K., Dong, Y., Xu, L. and Li, N. (2014) 'Early versus delayed administration of norepinephrine in patients with septic shock' *Critical Care,* 18, article number 532.
3. Surving Sepsis Campaign (2021) 'International guidelines for management of sepsis and septic shock 2021', *Critical Care Medicine (online special article)*, pp. e1063-e1143.
4. Wallace, H.A. and Regunath, H. (2022) Fluid Resuscitation (Stat Pearls). Available at: https://www.ncbi.nlm.nih.gov/books/NBK534791/
5. Nag, D.S., Samaddar, D.P., Chatterjee, A., Kumar, H., and Dembla, A. (2015) 'Vasopressors in obstetric anesthesia: A current perspective', World Journal of Clinical Cases, 3(1), pp. 58-64. Available at: https://doi.org/10.12998/wjcc.v3.i1.58
6. Yartsev, A. (2021) Metaraminol (deranged physiology). Available at: https://derangedphysiology.com/main/cicm-primary-exam/required-reading/cardiovascular-system/Chapter%20979/metaraminol (Accessed: 12 January 2023).
7. Loubani, O.M., and Green, R.S., (2015) 'A systematic review of extravasation and local tissue injury from administration of vasopressors through peripheral intravenous catheters and central venous catheters' Journal of Critical Care, 30(3), pp. 653.e9-653.e17.
8. Owen, V.S., Rosgen, B. K., Cherak, S.J., Ferland, A., Stelfox, H.T., Fiest, K.M., and Niven, D.J. (2021) 'Adverse events associated with administration of vasopressor medications through a peripheral intravenous catheter: a systematic review and meta-analysis' Critical Care, 25(1) article number 146.
9. Tian, D.H., Smyth, C., Keijzers, G., Macdonald, S.P., Peake, S., Udy, A., and Delaney, A. (2020) 'Safety of peripheral administration of vasopressor medications: A systematic review', Emergency Medicine Australasia, 32(2), pp. 220-227.
10. Tran, Q.K., Mester, G., Bzhilyanskaya, V., Afridi, L.Z., Andhavarapu, S., Alam, Z., Widjaja, A., Andersen, B., Matta, A., and Pourmand, A. (2020) 'Complication of vasopressor infusion through peripheral venous catheter: A systematic review and meta-analysis', The American Journal of Emergency Medicine, 38(11), pp. 2434-2443
11. Intensive Care Society (2020) 'Guidance For: The use of Vasopressor Agents by Peripheral Intravenous Infusion in Adult Critical Care Patients'.
12. Electronic Medicines Compendium (2023) 'Noradrenaline'.