CHAPTER 23

ADULT CRITICAL CARE

23.1 INTRODUCTION AND PRINCIPLES OF CRITICAL CARE

INTRODUCTION

Critical care is the discipline that entails specialised medical and nursing care for patients who have, are at risk of, or are recovering from serious, life-threatening injuries and illnesses.

Critical care involves constant, intensive monitoring and comprehensive care including multiple modalities of vital physiologic organ support to sustain life during a period of life-threatening organ system insufficiency. Additionally, it involves intensive resuscitation and appropriate end-of-life care.

Critical care is usually delivered in the intensive care unit (ICU). However, it actually consists of a continuum of care provided throughout the health care chain including the pre-hospital environment, emergency department, hospital ward, high-care wards, and follow-up clinic.

LoE:IVb[i]

Effective critical care requires if possible, a multidisciplinary team to deal with these complex patients. In addition to medical and nursing personnel, such multidisciplinary teams must include inter alia physiotherapists, occupational therapists, dieticians, critical care technologists and social workers.

23.1.1 GENERAL PRINCIPLES OF PHARMACOLOGY IN CRITICAL ILLNESS

» Pharmacokinetic (PK, “what the body does to the drug”) and pharmacodynamic (PD, “what the drug does to the body”) variations in critical care patients occur secondary to underlying illness, rapidly changing multiorgan dysfunction, and the use of multiple supportive modalities.
» Therapeutic response and clinical outcomes are affected by altered drug absorption, plasma protein binding, volume of distribution, renal and hepatic clearance, and affinity of binding of drug molecules to target receptors. These PK and PD changes in critical illness can contribute to

suboptimal dosing, adverse outcomes, increased risk of medication errors, and adverse drug reactions.

» Loading doses may be required to achieve timeous therapeutic responses (e.g. phenytoin, beta-lactam, antimicrobials, vancomycin), especially for medicines with a long plasma half-life. Maintenance doses should be adjusted based on extent and trend of organ dysfunction, and clinical indication for the therapy.
» Careful dose titration based on clinical observation is required for medications with a rapid onset of action, or where vital parameters can be readily monitored.
» Therapeutic drug monitoring (TDM) is recommended, where possible, to assist in dose adjustment.
» Where renal replacement therapy is used, dosing should be tailored to account for changes in volume of distribution and clearance of medications.
» Polypharmacy may contribute to adverse outcomes secondary to drug interactions or toxicity.

LoE:IVb[ii]

23.2 RESPIRATORY SUPPORT

DESCRIPTION

The purpose of mechanical ventilation is to support the work of breathing, ensure adequate oxygenation, facilitate clearance of carbon dioxide, and minimise the trauma caused by ventilatory support.

Indications for mechanical ventilation include:

» Hypoxaemic respiratory failure
» Excessive work of breathing:
  – Inability to meet normal respiratory demands due to respiratory muscle weakness, e.g. Guillain-Barre Syndrome, opioid toxicity, or suxamethonium apnoea. Indicated by elevated PCO_2, or reduced minute ventilation via respiratory rate or tidal volume.
  – Inability to meet increased respiratory demand, e.g. asthma, chronic obstructive pulmonary disease (COPD), metabolic acidosis. Indicated by a PCO_2 that can be low, normal, or high but is often inappropriately high for clinical scenario; tachypnoea; respiratory distress; impending fatigue.
» Neuroprotection: patient with brain injury that requires mechanical ventilation for PCO_2 and PO_2 control.

GENERAL MEASURES

Concomitant respiratory support using strategies such as high flow nasal oxygenation, non-invasive mechanical ventilation, and invasive mechanical ventilation.

A detailed ventilation management strategy including initiation, titration and weaning of ventilation is presented in APPENDIX 23.I.

23.3 CARDIOVASCULAR SUPPORT

DESCRIPTION

Patients are often admitted to ICU for cardiovascular support, the commonest reason being for the treatment of shock. Although it is important to treat the underlying cause, patients may need cardiovascular monitoring and support in ICU while this is happening.

GENERAL MEASURES

In the critically ill patient, the following should be considered:

» Parenteral dosing of medications
» Balanced salt solutions for resuscitation

Monitoring should include (1) continuous ECG, oxygenation (SpO_2, arterial blood gases), (2) continuous blood pressure monitoring (preferably invasive blood pressure monitoring if available), (3) central venous pressure, and (4) urine output.

For cardiac arrest: see section 20.1 Cardiac arrest in adults.
For post-cardiac arrest care: see section 20.2: Post-cardiac arrest care.
For Acute Coronary Syndromes see section 3.2.1: ST elevation myocardial infarction (STEMI) and section 3.2.2: Non ST elevation myocardial infarction (NSTEMI) and Unstable angina (UA).
For dysrhythmias: see section 3.3: Cardiac dysrhythmias..
For hypertension: see section 3.6: Hypertension.
For hypertensive urgency: see section 3.6.2: Hypertensive urgency.
For hypertensive emergency: see section 3.6.3: Hypertensive crisis, Hypertensive emergency.
For Acute cardiac failure see acute pulmonary oedema: section 20.10: Pulmonary oedema, acute andCongestive Cardiac Failure: section 3.4: Congestive cardiac failure (CCF).

23.3.1 SHOCK

R57

DESCRIPTION

Shock is defined as a state where perfusion is inadequate to meet the metabolic needs at a cellular level. There are various forms of shock each requiring their own specific treatment.

LoE:IVb[iii]

GENERAL MEASURES

The therapeutic aim for all types of shock is to restore perfusion and maintain an adequate blood pressure, e.g. Mean Arterial Pressure (MAP) >65mmHg.

Management includes fluid therapy and administration of vasoactive medication that may vary depending on the type of shock (See section 20.11: Shock):
For hypovolaemic shock: see section 20.11.1: Hypovolaemic shock.
For distributive shock: see section 20.11.2: Distributive shock.
For anaphylactic shock: see section 20.7: Anaphylaxis/ anaphylactic shock.
For neurogenic shock: see section 20.11.2.1: Neurogenic shock.
For septic shock: see section 20.11.2.2: Septic shock and section 23.10: Sepsis in ICU.
For cardiogenic shock: see section 20.11.3: Cardiogenic shock.
For obstructive shock: see section 20.12.4: Obstructive shock.

MEDICINE TREATMENT

Fluid therapy

Balanced salt solutions are the preferred resuscitation fluids for shock.
Adequacy of fluid resuscitation should be guided by measures of fluid responsiveness.

LoE:IIIb[iv]

CAUTION
Avoid colloids for shock resuscitation in patients with sepsis and acute kidney injury.

LoE:IIIb[v]

Vasoactive therapy

Vasoactive therapy is indicated in a shocked patient that fails to respond to fluid therapy.

- Adrenaline, IV, 0.01-1.0 mcg/kg/min as a continuous infusion.
  - Aim to achieve a target MAP >65mmHg within 30 minutes.
  - *LoE:IVb*[vi]

If shock is suspected to be cardiogenic in origin:

- Dobutamine, IV, 5-20 mcg/kg/min as a continuous infusion.

LoE:IVb[vii]

FLUID THERAPY FOR SHOCK

DESCRIPTION

» Balanced salt solutions are the preferred resuscitation fluids for shock.
» Adequacy of fluid resuscitation should be guided by measures of fluid responsiveness.

LoE:IIIb[viii]

CAUTION
Avoid colloids for shock resuscitation in patients with sepsis and acute kidney injury.

LoE:IIIb[ix]

VASOACTIVE MEDICINES FOR SHOCK

DESCRIPTION

Vasoactive therapy is indicated in a shocked patient that fails to respond to fluid therapy.

MEDICINE TREATMENT

- Adrenaline, IV, 0.01-1.0 mcg/kg/min as a continuous infusion.
  - Aim to achieve a target MAP >65mmHg within 30 minutes.

LoE:IVb[x]

If shock is suspected to be cardiogenic in origin:

- Dobutamine, IV, 5-20 mcg/kg/min as a continuous infusion.

LoE:IVb[xi]

23.4 RENAL SUPPORT

DESCRIPTION

Acute kidney injury (AKI) in critical care is a complex, heterogenous clinical syndrome presenting with varying severities, trajectories, and outcomes.

LoE: IVb[xii]

See section 7.1.4: Acute Kidney Injury, for further details.

Table 23.1: Staging/Severity of Acute Kidney Injury

Stage	Serum creatinine	Urine output
1	1.5-1.9 times baseline **OR** ≥26.5 µmol/l (≥ 0.3 mg/dl) increase	<0.5ml/kg/h for 6-12 hours
2	2.0-2.9 times baseline	<0.5ml/kg/h for ≥ 12 hours
3	3 times baseline **OR** Increase in serum creatinine to ≥353.6 µmol/l (≥ 4.0 mg/dl) **OR** Initiation of kidney replacement therapy **OR** In patients <18 years, decrease in eGFR to <35 ml/min per 1.73 m^2	<0.3ml/kg/h for ≥ 24 hours **OR** Anuria for ≥ 12 hours

Taken from: Kidney Disease: Improving Global Outcomes (KDIGO). Acute Kidney Injury (AKI). 2012 Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Acute Kidney Injury (AKI). 2012. Available at: https://kdigo.org/guidelines/acute-kidney-injury/

LoE:IVb[xiii]

GENERAL MEASURES

In all patients at risk for, and with AKI:

» Avoid nephrotoxic agents (e.g. aminoglycosides; amphotericin B, NSAIDs).
  – Where medication cannot be avoided, dose appropriately with use of therapeutic drug monitoring where available.
» Dose-adjust medications for reduced GFR
» Ensure volume status is appropriate.
» Ensure optimal perfusion pressure.
» Consider functional haemodynamic monitoring.
» Monitor urine output (UO) and serum creatinine.
» Avoid hyperglycaemia.
» Consider alternatives to radiocontrast material.
» Search for reversible causes and treat.
» Consider invasive diagnostic workup.

Fluid therapy

» Use balanced salt solutions.
» For patients at high risk of AKI that also require imaging with iodine-based contrast media (e.g. eGFR <30ml/min/1.73m^2, renal transplant, large volume of contrast medium to be used, intra-arterial administration of

contrast medium), ensure adequate intravenous volume expansion with 0.9% sodium chloride solution if not already volume replete.

Nutrition in acute kidney injury

» Provide total energy intake of 20-30 kCal/kg/d in all AKI stages.
» Feeds may be given orally, enterally, or parenterally depending on gut functionality and integrity.
» Do not restrict protein intake with the goal of preventing or delaying Kidney Replacement Therapy (KRT).
» Consult a dietitian as necessary and refer to the National Department of Health Clinical Nutrition Guidelines

LoE:IVb[xiv]

CAUTION

The following drugs are NOT RECOMMENDED for the prevention of AKI:

» Diuretics
» Low dose dopamine
» N-acetyl cysteine in critically ill patients with hypotension or for prevention in post-surgical AKI.

The following class of drug is NOT RECOMMENDED for the treatment of AKI:

» Diuretics (except in the management of fluid overload).

23.4.1 KIDNEY REPLACEMENT THERAPY (KRT)

DESCRIPTION

Acute kidney injury (AKI) may affect 60% of ICU patients with up to two-thirds of these patients going on to require kidney replacement therapy (KRT).

LoE:IVb[xv]

KRT is commonly used in critically ill patients to achieve solute clearance, maintain acid-base status, and remove fluid excess.

Indications for acute Kidney Replacement Therapy (RRT):

» Stage 3 acute kidney injury deemed unlikely to resolve in the next few days
» Refractory fluid overload
» Clinical features of uraemia (e.g. gastritis, pericarditis, delirium, seizures)
» Life threatening acidosis
» Refractory hyperkalaemia
» Life threatening overdoses requiring KRT removal (e.g. lithium, theophylline, methanol, ethylene glycol, carbamazepine, and valproic acid)

Choice of mode of KRT:
» KRT may be continuous (CKRT) or intermittent (IKRT), and includes sustained low efficiency dialysis (SLED).
» There is no evidence that one method is superior compared to the others.
» CKRT is preferable in patients with hemodynamic instability, acute brain injury, increased intracranial pressure, generalized cerebral oedema, or liver failure.

MEDICINE TREATMENT

To reduce circuit hypercoagulability:
- Unfractionated Heparin, 5000 units diluted in 50ml 0.9% sodium chloride (100 units/ml), administered directly into the RRT circuit.
  - Initial bolus: 10-20 units/kg.
  - Continue running infusion at 5-10 units/kg/hour.
  - Monitor using daily Activated Partial Thromboplastin Time (aPTT).
  - Maintain aPTT between 45-55 seconds.

LoE:IVb[xvi]

OR
- Enoxaparin, SC, 40mg daily

LoE:IVb[xvii]

Note:
» Only use heparin if there is no bleeding risk. Use saline flushes if there is a significant risk of bleeding.

23.5 HAEMATOLOGICAL SUPPORT

23.5.1 THROMBOPROPHYLAXIS

DESCRIPTION
See section 2.8: Venous thrombo-embolism.

GENERAL MEASURES
» All critically ill patients should receive pharmacological (i.e. unfractionated heparin, low-molecular-weight heparin [LMWH]) OR mechanical (intermittent pneumatic compression devices) thromboprophylaxis.
» Pharmacological thromboprophylaxis is superior to mechanical prophylaxis and should be used, unless contraindicated.
» If mechanical thromboprophylaxis is used, it should be provided with intermittent pneumatic compression devices which fit the patient well and cover both legs up to mid-thigh.

MEDICINE TREATMENT

- Low-molecular weight heparin (LMWH), e.g.
- Enoxaparin, SC, 40mg daily.
  - Reduce dose to 20 mg daily if eGFR <30 ml/min.

LoE:IVb[xviii]

<u>If LMWH is unavailable or contraindicated:</u>

- Unfractionated heparin, SC, 5000 IU 12 hourly.

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Note:

» Dose of enoxaparin must be adjusted in kidney disease and for patients with increased body mass.

» Avoid pharmacological thromboprophylaxis in patients with active bleeding, significant coagulopathy, or elevated risk for spontaneous or procedural bleeding.

23.5.2 ANAEMIA IN CRITICAL CARE

D64.9

DESCRIPTION

» Anaemia is common in critical illness.

» Anaemia results in reduced tissue oxygen delivery which may cause or worsen organ dysfunction. The underlying cause should be investigated and treated.

» Avoid unnecessary phlebotomy to reduce the risk of iatrogenic anaemia.

» The benefits of treating anaemia must always be weighed against the risks of blood transfusion.

GENERAL MEASURES

Transfusion triggers:

» The transfusion trigger is the haemoglobin (Hb) level at which one should consider a blood transfusion.

» The final decision to transfuse red blood cells should also consider the patient's clinical condition.

» Transfuse the patient to obtain an Hb above the transfusion trigger depending on the type of bleeding.

<u>Non-bleeding patient:</u>

In the non-bleeding patient, an Hb <7 g/dl is an appropriate transfusion trigger.

This includes patients with:
» Septic shock
» Trauma without bleeding
» Upper gastrointestinal bleeding

Note:
» Elderly patients, and those with stable coronary artery disease do not appear to require a higher transfusion threshold.
» Uncertainty is noted for the following clinical scenarios:
» critically ill patients with an acute coronary syndrome
» traumatic brain injury
» cerebrovascular accidents
» critically ill oncology patients
» Transfusion may be appropriate in these scenarios in a patient with a Hb of 7-9 g/dl after considering the patient's clinical condition.

Bleeding patient:
The decision to transfuse the bleeding patient should not be based on a single Hb level, but should be determined by the:
» Amount and rapidity of blood loss.
» Likelihood of bleeding control.
» Physiological state of the patient.

Non-transfusion alternatives:
» Cell-salvage(blood salvage) may reduce the need for red blood cell transfusions, if available.

MEDICINE TREATMENT

- Red blood cells, IV, one unit immediately.
  - Only one unit of red blood cells should be ordered and transfused at a time. After each unit, the need for another unit should be reviewed prior to ordering the next unit.
  - Exceptions to this include large volume blood loss where a massive transfusion protocol may be more appropriate (See section 23.5.7: Massive transfusion protocol).

LoE:IVb[xx]

CAUTION
» Intravenous iron should not be used as it does not appear to reduce transfusion requirements or improve outcomes in the critically ill patient
» Erythropoietin should not be used in the critically ill patient unless indicated, as it has minimal effect on transfusion requirements, does not improve patient outcomes, and may be associated with adverse effects including thrombosis.

23.5.3 THROMBOCYTOPAENIA AND PLATELET DYSFUNCTION IN CRITICAL CARE

D69.6

DESCRIPTION

Qualitative and quantitative platelet disorders are common in critically ill patients and may be due to decreased production of platelets or increased consumption/sequestration.

Common causes of thrombocytopaenia and/or platelet dysfunction include sepsis, blood loss, dilutional thrombocytopaenia, medical conditions (e.g. uraemia), and medications including antiplatelet drugs (e.g. aspirin and clopidogrel) and heparin.

- Heparin-induced thrombocytopaenia should be considered in a patient whose platelet count decreases by >50% within 5-10 days of initiating heparin, especially if thrombotic complications have also developed. If this occurs, STOP all heparin products and consult a specialist.

The decision to transfuse platelets depends on:

» Whether the patient is bleeding.
» Whether the patient is to undergo a procedure.
» Aetiology of the thrombocytopaenia.
» Patient's platelet count.
» Results of coagulation testing.

LoE:IIIb[xxi]

Platelet transfusions are indicated in the following settings:

» Prophylactic: if platelet count <20 x 10^9/L.
  – A platelet count of <10 x 10^9/L is an acceptable alternative if the patient is not septic, not bleeding, and has a slow decline in platelet count.
» Prophylactic prior to invasive procedures/surgery:
  – Indicated if platelet count <50 x 10^9/L. Alternative thresholds may be used for the following indications:
    - Epidural catheter placement/removal: <75 x 10^9/L.
    - Neurosurgery or posterior ophthalmic surgery: <100 x 10^9/L.
    - Patients with intracranial haemorrhage: <100 x 10^9/L.
» Empiric: in large volume blood transfusion (where more than 4 units of packed cells required).
» Therapeutic: if platelet count <50 x 10^9/L and the patient is bleeding.
  – Transfusion may be deferred in the presence of normal thromboelastography (where available).

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GENERAL MEASURES

An assessment of haemostasis should be conducted with viscoelastic testing where available, e.g. thromboelastography (TEG), as this provides a functional assessment of whole blood clotting. A normal viscoelastic test may eliminate the need for a platelet transfusion even in the presence of thrombocytopaenia.

General measures to reduce bleeding in patients with thrombocytopaenia or platelet dysfunction include:

» Careful review of all anticoagulant and antiplatelet medication.
» Thorough assessment of other components of the coagulation system.
» Attention to maintaining normothermia and eucalcaemia.

Aspirin and clopidogrel are the most commonly used antiplatelet medications, and their antiplatelet effects may last up to 7 days. The need for platelet transfusions in the setting of platelet dysfunction should be discussed with a specialist.

MEDICINE TREATMENT

- Platelet cells, IV, one unit immediately.
    - One unit of pooled platelets should be transfused at a time.

Note:

» The need for further platelet transfusions should be based on platelet count, viscoelastic testing (if available), and the presence or absence of ongoing bleeding.

REFERRAL

» Heparin induced thrombocytopaenia: Consult a specialist.
» Platelet transfusions in the setting of platelet dysfunction: Consult a specialist.

23.5.4 PLASMA TRANSFUSION

DESCRIPTION

Plasma transfusions may be needed in the following scenarios:

» Coagulopathy due to multiple factor deficiencies, e.g. disseminated intravascular coagulation (DIC), or large volume blood loss.
» Thrombotic thrombocytopaenic purpura
» Scoline apnoea

Where available, viscoelastic testing (e.g. thromboelastography/TEG) should complement or replace standard coagulation testing as this provides a more clinically relevant assessment of functional coagulation.

Consult a specialist for further advice as necessary.

Choice of plasma product
Fresh frozen plasma (FFP) and lyophilized or freeze-dried plasma (FDP) may be treated as clinically interchangeable products with respect to their coagulant effect.

Indications for plasma transfusion
» Prophylaxis: prior to invasive procedures/surgery if International Normalised Ratio (INR) >2.
» Empiric: Large volume blood transfusion (>4 units of packed cells required. See section 23.5.7: Massive transfusion protocol).
» Therapeutic: if patient is bleeding and has an INR >2.

MEDICINE TREATMENT
Plasma Transfusion
For prophylaxis or therapy:
- Freeze-dried plasma, IV, 15 mL/kg immediately.
  - Repeat dose if the patient's clinical response and/or the coagulation function testing results indicate continued need.

Empiric use in large volume blood transfusion:
- Freeze-dried plasma, IV, 1 unit immediately.
  - Should be given for every unit of red blood cells when it is anticipated that >4 units of red blood cells will be required.

LoE:IVb[xxiii]

23.5.5 COAGULATION FACTORS

DESCRIPTION
Cryoprecipitate
» Cryoprecipitate is a source of fibrinogen, factor VIII, factor XIII, and von Willebrand factor.
» Active bleeding with a low fibrinogen level (<2g/L) is the main indication for cryoprecipitate in critical care and is common in obstetric haemorrhage and trauma.
» Cryoprecipitate administration may also be guided by viscoelastic testing in major haemorrhage.

MEDICINE TREATMENT
- Cryoprecipitate, IV, 1 unit per 10 kg total body weight (South African National Blood Services), or 1 pooled unit (Western Cape Blood Services)

LoE:IVb[xxiv]

Vitamin K-dependent clotting factors:
For warfarin poisoning, see section: 19.19 Anticoagulant (Warfarin and Rodenticide Superwarfarin) Poisoning.

For other coagulation factor-related disorders, see Chapter 2: Blood And Blood Forming Organs.

23.5.6 ANTIFIBRINOLYTIC MEDICATION

DESCRIPTION
Tranexamic acid is an antifibrinolytic agent that acts by inhibiting the activation of plasminogen, an enzyme responsible for fibrinolysis. Tranexamic acid may be considered in the following settings:
» Adjunctive medication in the prevention and treatment of bleeding.
» Where viscoelastic testing shows evidence of hyperfibrinolysis.

MEDICINE TREATMENT
Severe trauma (if given within 3 hours):
- Tranexamic acid, IV:
  - Loading dose: 1 g over 10 minutes as a bolus infusion.
  - Maintenance dose: 1 g added to 100 ml 0.9% saline over 8 hours as an infusion.

LoE:Ia[xxv]

Bleeding postpartum obstetric patients:
- Tranexamic acid, IV, 1 g over 10 minutes as a bolus infusion.

<u>If bleeding persists (after 30 minutes):</u>
- Tranexamic acid, IV, 1 g added to 100mls 0.9% saline over 8 hours as an infusion.

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Note:
» Benefit is greatest if initiated in the 1st hour. Initiation of tranexamic acid more than 3 hours after the initial insult may increase the risk of bleeding and mortality.

23.5.7 MASSIVE TRANSFUSION PROTOCOL

DESCRIPTION

Major haemorrhage may be defined as blood loss >150 ml/min, loss of >50% of blood volume in 3 hours, or loss of entire blood volume in 24 hours.

A massive transfusion may also be defined by the transfusion of >4 units of red blood cells in 1 hour, replacement of >50% of blood volume in 3 hours (>5 units in 3 hours), or the replacement of entire blood volume in 24 hours (>10 units in 24 hours). *LoE:IVb*[xxvii]

In the setting of major haemorrhage, blood and blood products are most efficiently and effectively administered using a massive transfusion protocol (MTP).

Essentials of the protocol:

» The massive transfusion protocol is designed to facilitate the transfusion of large volumes of blood (at least 6 units of red blood cells) and blood products.
» MTP aims to avoid acute coagulopathy in major haemorrhage that is associated with trauma and other causes during the resuscitation phase.
» Blood components are given in fixed ratios initially. Further blood product administration is ideally guided by point of care coagulation testing.
» An MTP should be a collaboration between the treating unit/institution and the providing blood service. The exact details of the protocol will differ depending on the specifics of the treating unit/institution (See Figure 23.1 below for an example of a massive transfusion protocol).

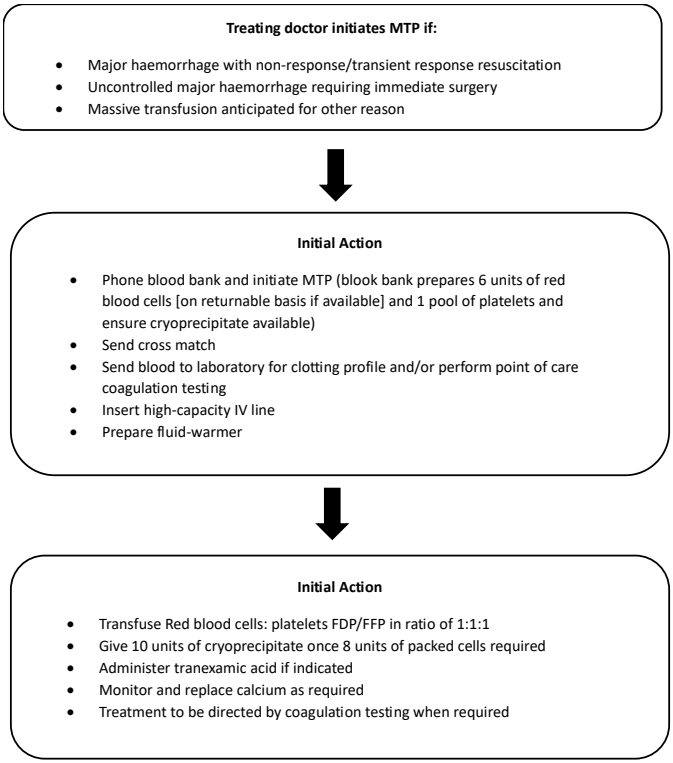

Figure 23.1 Massive Transfusion Protocol Approach

23.6 NEURO-PSYCHOLOGICAL SUPPORT

DESCRIPTION

ICU patients are treated with many interventions that may be distressing and uncomfortable. Pain, restlessness, agitation, and delirium may have untoward effects.

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23.6.1 PAIN MANAGEMENT

R52

DESCRIPTION

Prioritization of effective pain control is imperative for optimising the care of critically ill patients. Recognizing the impact of uncontrolled pain on anxiety and psychological distress also underscores the importance of a holistic approach to care. A comprehensive treatment approach for critically ill patients places a strong emphasis on timely and appropriate pain management, positively influences physiological stability and patient, reduces the incidence of complications, and improves overall quality of care. Current guidelines recommend that pain management should be guided by routine pain assessment. An example of a pain assessment tool is given in Table 23.1.

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Table 23.1 Behavioural Pain Scale

Item	Description	Score
Facial Expression	Relaxed	1
	Partially tightened e.g., brow lowering	2
	Fully tightened e.g. eyelid closing	3
	Grimacing	4
Upper limb movements	No movement	1
	Partially Bent	2
	Fully bent with finger flexion	3
	Permanently retracted	4
Compliance with mechanical ventilation	Tolerating movement	1
	Coughing but tolerating ventilation for most of the time	2
	Fighting ventilator	3
	Unable to control ventilation	4
BPS score ranges from 3 (no pain) to 12 (maximum pain)		

Taken From: Sessler CN, Gosnell MS, Grap MJ, Brophy GM, O'Neal PV, Keane KA, et al. The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients. Am J Respir Crit Care Med. 2002 Nov 15;166(10):1338–44.

LoE:IvbXXX

GENERAL MEASURES

» Pharmacological treatment includes opioid and non-opioid medicines.
» Pain should be treated before sedation is considered.
» Table 23.2 provides some important characteristics to be considered when prescribing commonly used analgesics in the ICU.

» Paracetamol and ketamine are recommended adjuncts to reduce opioid consumption.
» Non-pharmacological strategies such as positioning, music, massage and relaxation therapies may also be beneficial.
» See section 12.4: Perioperative analgesia for more details on pain management.

MEDICINE TREATMENT

Parenteral therapy

If paracetamol is required and patient is nil per mouth:

- Paracetamol, IV, 1 g 6 hourly for 24 hours (Specialist initiated).
  - If required beyond 24 hours prescription would need to be authorised by a specialist.

LoE:Ivb[xxxi]

Regional anaesthesia

» Local anaesthetic agents can be considered for regional analgesia e.g. epidural (see section 12.8: Epidural anaesthesia), para-vertebral, and peripheral nerve blocks where expertise is available and appropriate (see section 12.9: Peripheral nerve block or wound infiltration).

Table 23.2: Commonly used analgesics in the ICU

Drug	Category of Analgesic	Loading dose	Maintenance dose	Onset	Duration	Adverse effects
Paracetamol (PO/IV)	Simple analgesic	-	PO: 1g/6h IV: 1g/6h	PO:30 mins IV: 5 mins	4-6 h	Hepatotoxic Interacts with warfarin (↑INR) and CYP 450 inducers
Tramadol (PO/IV) Less potent (20% of morphine).	Weak opioid	-	PO/IV: 50-100 mg/6h	PO:30 mins IV: 15 mins	3-6 h	Less constipation and respiratory depression
Fentanyl (IV)	Strong opioid	20-100 mcg	50-100 mcg/h	1 min	0.5-1 h	Nausea, constipation Respiratory depression Muscle rigidity
Morphine (IV)		2-10 mg	2-5 mg/h	5 min	4 h	Nausea, constipation
Ketamine (IV)	Adjunctive analgesic	0.25-0.5 mg/kg	0.05-0.4 mg/kg/h *Very low dose (1-2 mcg/kg/h- opioid sparing)* Higher doses may be required in polytrauma and Traumatic Brain Injury	30 sec	10 mins	Sympathetic stimulation Hallucinations, Delirium Increased secretion Dissociative state Liver/renal dysfunction → active metabolite accumulation.

Guidance for prescribing: Combinations of medicines from different classes may be considered where needed. *LoE:Ivb*[xxxii]

23.6.2 SEDATION

DESCRIPTION

Most patients may not require routine sedation, however, patients with the following conditions may require pharmacological sedation:

» severe acute respiratory failure
» status epilepticus
» raised intracranial pressure/ traumatic brain injury
» status asthmaticus

GENERAL MEASURES

For patients whom sedation is indicated, a combination with analgesia (analgo-sedation) is recommended. This means that the pain is treated first, with consideration made for sedation where required.

Its use is guided by a sedation assessment tool, e.g. Richmond agitation sedation scale (RASS; See Table 23.3). The target RASS score is -2 to 0, with lighter sedation preferred over deeper sedation. It is important to exclude and manage delirium before routine sedation is administered (see section 23.6.3 below).

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Table 23.3: Richmond agitation sedation scale (RASS)

Score	Term	Description	Type of stimulation
+4	Combative	Overly combative, violent, immediate danger to staff	Without Stimulation
+3	Very agitated	Pulls or removes tube(s) or catheter(s); aggressive	
+2	Agitated	Frequent non-purposeful movement, fights ventilator	
+1	Restless	Anxious but movements not aggressive or vigorous	
0	Alert and calm		
-1	Drowsy	Not fully alert, but has sustained awakening (eye opening/ eye contact) to *voice* (≥10 seconds)	Verbal Stimulation
-2	Light sedation	Briefly awakens with eye contact to *voice* (<10 seconds)	
-3	Moderate sedation	Movement or eye opening to *voice* (but no eye contact)	
-4	Deep sedation	No response to voice, but movement or eye opening to *physical stimulation*	Physical Stimulation
-5	Unarousable	No response to *voice or physical stimulation*	

Taken From: Khan BA, Perkins AJ, Gao S, Hui SL, Campbell NL, Farber MO, et al. The CAM-ICU-7 Delirium Severity Scale: A Novel Delirium Severity Instrument for Use in the Intensive Care Unit. Crit Care Med. 2017 May;45(5):851–7.

LoE:IVb[xxxiv]

The properties of the different sedative agents can be used to help select an appropriate choice. See Table 23.4 for commonly used sedative agents and their properties in critically ill patients. The choice of agent being dictated by patient clinical presentation and any contraindications.

Table 23.4: Commonly used sedatives in the ICU

Drug	Load	Maintenance	Onset	Duration	Adverse effects
Propofol IV	-	5-50 mcg/kg/min or 50-200 mg/h Titrate every 5min	1 min	3-10 mins	PRIS — Vasodilation, inotropy ↑Triglyceride
Midazolam IV	1-5 mg	1-5 mg/h	<5 mins	30 mins	↑delirium risk
Lorazepam IV	1-4 mg	1-5 mg/h	15 mins	6-8 h	↑delirium risk

PRIS = Propofol related infusion syndrome

LoE:IVb[xxxv]

23.6.3 DELIRIUM IN CRITICAL CARE

F05

DESCRIPTION

The risk of delirium is increased in patients with severe illness, with a prevalence of 40-60% in non-ventilated patients, and 50-80% in mechanically ventilated patients. Diagnosing delirium can be difficult due to its highly variable presentation. Symptoms may fluctuate over the course of a day with periods of reduced attention, awareness, and other features of cognitive dysfunction, along with periods of lucidity. Patients may present with agitated, disruptive and/or uncooperative behaviour (hyperactivity), sluggishness, lethargy, stupor (hypoactivity), or a mixture of these features. This variability is further complicated by the influence of analgo-sedatives and medical and surgical interventions. Delirium is associated with increased duration of mechanical ventilation, length of ICU and hospital stay, long-term cognitive impairment, and mortality.

Risk factors for delirium include: advanced age; pre-existing dementia; history of coma and/or other neurological disorders, hearing and visual impairment, pre-ICU emergency surgery or trauma, blood transfusions; and increased severity of underlying illness. Precipitating factors include sleep deprivation, pain, environmental insults (e.g., noise, physical restraint use, catheters), and psychoactive medicine use (e.g., benzodiazepines)..

LoE:IIb[xxxvi]

GENERAL MEASURES

Prevention, early recognition, and non-pharmacological management steps are recommended while the underlying critical illness is treated.

Strategies to prevent delirium include:

- regular patient reorientation
- noise reduction
- cognitive stimulation
- visual and hearing aids
- minimize use of sedative medicines
- early mobilization
- adequate hydration

» Recognise delirium early with daily clinical assessment and screening using a validated tool (See CAM-ICU 7 screening tool in Table 23.5).
» Be alert to hypoactive delirium, where the patient may be poorly responsive to questions.
» Screen for delirium in the absence of sedative effects.
» Use screening to explain what the symptoms mean and to reassure the patient and their relatives.

» Exclude:
  - Alcohol withdrawal delirium.
  - Psychosis, mania, or depression (either new onset or related to discontinuation of chronic medicines).

General management includes:
» Searching for, and correction of, precipitating factors.
» Intensified preventative strategies, particularly:
  - Pain control.
  - Minimising sedation.
  - Maintaining a calm, containing environment.
  - Re-orientating and explain all procedures to the patient.
  - Educating visitors (encourage visits).
  - Maintaining normal circadian rhythm.

Table 23.5: CAM-ICU 7 screening tool

Items	Grading
1. Acute Onset or Fluctuation of Mental Status Has the patient's mental status changed from his/her baseline? **OR** Has the patient had any fluctuation in mental status in the past 24 hours as evidenced by fluctuation on a sedation/ level of consciousness scale (i.e., RASS/SAS, GCS), or previous delirium assessment?	Absent = 0 Present = 1
2. Inattention Say to the patient "*I am going to read you a series of 10 letters. Whenever you hear the letter "A," indicate by squeezing my hand." Read letters from the following letter list in a normal tone 3 seconds apart. <u>SAVEAHAART</u> (Errors are counted when the patient fails to squeeze on the letter "A" and when the patient squeezes on any letter other than "A")*	≥ 8 correct (absent): Give score of 0 4-7 correct (Present): Give score of 1 0-3 correct (Severe): Give score of 2
3. Altered Level of Consciousness Present if the actual RASS score is anything other than alert and calm (zero)	RASS = 0 (Absent) Give score of 0 RASS = 1 or -1 (Present) Give score of 1 RASS >1 or RASS <-1 (Severely altered) Give score of 2
4. Disorganized Thinking <u>Yes/No Questions</u> i. Will a stone float on water? ii. Are there fish in the sea? iii. Does one pound weigh more than two pounds? iv. Can you use a hammer to pound a nail? Errors are counted when the patient incorrectly answers a question. <u>Command:</u> Say to patient "Hold up this many fingers (Hold two fingers in front of patient). Then say "Now do the same with the other hand" (Do not repeat number of fingers). An error is counted if patient is unable to complete the entire command.	Correct ≥ 4 (Absent) Give score of 0 Correct = 2-3 (Present) Give score of 1 Correct ≤ 1 (Severely disorganised) Give score of 2
Interpretation: 0-2: no delirium, 3-5: mild to moderate delirium, and 6-7: severe delirium.	

CAM-ICU: Confusion Assessment Method for the Intensive Care Unit; Richmond Agitation Sedation Scale; SAS: Sedation- Agitation Scale; GCS: Glasgow Coma Scale

Khan BA, Perkins AJ, Gao S, Hui SL, Campbell NL, Farber MO, Chlan LL, Boustani MA. The Confusion Assessment Method for the ICU-7 Delirium Severity Scale: A Novel Delirium Severity Instrument for Use in the ICU. Crit Care Med. 2017 May;45(5):851-857. doi: 10.1097/CCM.0000000000002368. PMID: 28263192; PMCID: PMC5392153.

LoE:IVb[xxxvii]

MEDICINE TREATMENT

For treatment recommendations, see section 20.8: Delirium with perceptual disturbances.

For delirium with severe agitation and/or aggression: See section: 15.1 Aggressive disruptive behaviour in adults.

Note:
» Antipsychotic medicines may reduce agitated behaviour and distress, but there is no evidence that they treat the delirium itself.
» For alcohol withdrawal see section 15.8.1: Alcohol Withdrawal Delirium (Delirium Tremens).

23.6.4 MOOD DISORDERS

See section 15.3: Mood disorders.

23.6.5 SEIZURES

See section 14.4: Epilepsy.

23.6.6 INTRACRANIAL PRESSURE MANAGEMENT

See section 14.12.2: Brain oedema due to traumatic injury.

23.7 GASTRO-INTESTINAL SUPPORT

23.7.1 NUTRITION

DESCRIPTION

Critically ill patients have increased nutritional requirements due to an increased metabolic rate. Therefore, they require careful management of their nutritional requirements.

GENERAL MEASURES

» Commence nutritional support as soon as possible.
» Oral, enteral or parenteral route should be initiated once it is safe to reduce the risk of adverse events associated with the overuse of enteral/parenteral feeding.
» Consider choice of feed to meet patient-specific fluid, caloric, and protein requirements.

REFERRAL

» Consult dietitian as appropriate and refer to the National Department of Health Clinical Nutrition Guidelines (https://criticalpoint.co.za/wp-content/uploads/2016/10/DOH-enteral-nutrition-guidelines.pdf and https://criticalpoint.co.za/wp-content/uploads/2017/09/DOHParenteral-nutrition-guidelines.pdf).

See section 12.13.1: Nutritional support

LoE:IVb[xxxviii]

23.7.2 STRESS ULCER PROPHYLAXIS

K25.0/K25.1/K25.2/K25.3/K25.9/K26.0/K26.1/K26.2/K26.3/K26.9/K27.0/K27.1/K27.2/K27.3/K27.9

DESCRIPTION

Stress-related mucosal disease is an acute, erosive gastritis comprising conditions that range from stress-related injury to stress ulcers. Stress-related injury is due to superficial mucosal damage that manifests as erosions, while stress ulcers are due to deep, focal mucosal damage penetrating the submucosa. Stress ulcers occur in up to 9% of all patients admitted to critical care units, and the risk is higher in those that do not receive stress ulcer prophylaxis. Stress ulcers can cause clinically important gastrointestinal bleeding and lead to hemodynamic instability, an increased need for red blood cell transfusions, increased length of stay in the ICU, as well as increased mortality.

LoE:IVb[xxxix]

GENERAL MEASURES

» Initiate oral or enteral feeding as soon as it is safe to do so.

MEDICINE TRATMENT

- Pantoprazole, IV, 40mg daily.
  - Stop stress ulcer prophylaxis once the patient is tolerating enteral feeds as prolonged PPI use increases the risk of hospital acquired pneumonia.

LoE:IIb[xl]

23.7.3 REGURGITATION AND ASPIRATION

K21.0/K21.9/J69.0

DESCRIPTION

Gastroesophageal reflux is common in patients treated in critical care units. Contributing factors include mechanical ventilation causing elevated intrathoracic pressure, reduced/absent lower oesophageal sphincter tone, and GI dysmotility. Gastroesophageal reflux is an important risk factor for aspiration, pneumonia, and acute lung injury.

GENERAL MEASURES

» Avoid regurgitation of gastric contents by decreasing intragastric pressure.
» Nurse patient at 30-45 degrees with the head up.
» Obtain Chest X-ray to confirm suspected aspiration.
» Use a nasogastric tube and confirm placement with x-ray imaging and/or pH analysis of aspirate.
» Maintain oropharyngeal hygiene.

LoE:IVb[xli]

» If aspiration suspected, suction oropharynx and endotracheal tube thoroughly.

23.7.4 DIARRHOEA

A09.0/K52.8/K52.9

DESCRIPTION

Up to 62% of critically ill patients experience at least one episode of diarrhoea during their admission. Risk factors include the use of enteral nutrition (particularly those with high osmolarity), duration of antimicrobial use, and the use of suppositories. Diarrhoea increases the risk of complications including renal dysfunction, dehydration, electrolyte disturbance, as well as impairment of dermal integrity. There is also evidence that the development of GI problems is associated with worse outcome in critically ill patients.

LoE:IVb[xlii]

GENERAL MEASURES

» Send stool specimens to evaluate potential causes.

Consider Clostridium (Clostridioides) difficile diarrhoea

» (See section 1.3.4: Clostridium difficile diarrhoea) and feed-related diarrhoea as potential causes.

MEDICINE TREATMENT

» Treatment will depend on the identified aetiology.
» See section 1.3: Diarrhoea for specific treatment.

23.7.5 LIVER SUPPORT

See section 1.2.2: Liver Failure, Acute.

REFERRAL

Consult specialist unit to evaluate suitability for liver transplantation.

23.7.6. ACUTE SEVERE PANCREATITIS

K85.0/K85.1/K85.2/K85.3/K85.8/K85.9

DESCRIPTION

Approximately 10–30% of patients with acute pancreatitis develop a severe form that requires management in a critical care unit. Acute severe pancreatitis is a life-threatening disease with an in-hospital mortality rate of up to 15%. The severity of acute pancreatitis is determined by the development of organ failure for >48 hours and local complications including infected (peri-)

pancreatic necrosis, haemorrhagic or systemic complications, and infective pancreatitis.

LoE:IVb[xliii]

GENERAL MEASURES

For general management of acute pancreatitis, see Section 1.16: Pancreatitis, Acute.

Measures specific to critical care management

» Provide supportive therapy for organ failure, including fluid support (see section 23.3.7.6: Fluid therapy for shock).
» Address the underlying cause e.g. gall stones.
» Treat sepsis (see section 23.10: Sepsis in ICU).

REFERRAL

Refer for surgical consultation for complications including:

» Pancreatic abscess.
» Pancreatic necrosis.
» Pancreatic pseudocyst.
» Abdominal compartment syndrome.

23.7.7 ACUTE CHOLECYSTITIS

K81.0

DESCRIPTION

Acute acalculous cholecystitis is a specific complication of critical illness that warrants organ support, antimicrobial therapy, and consultation for surgical intervention.

LoE:IVb[xliv]

GENERAL MEASURES

See section 1.27: Cholecystitis, acute and cholangitis, acute.

REFERRAL

All patients for surgical consultation and intervention.

23.7.8 ABDOMINAL COMPARTMENT SYNDROME

R19.8

DESCRIPTION

Abdominal compartment syndrome is defined as the presence of intra-abdominal hypertension, with sustained intra-abdominal pressures exceeding 20 mmHg, along with evidence of new-onset organ dysfunction. Abdominal compartment syndrome can be classified as primary, i.e. due to direct injury

of the abdomen or pelvic region, or secondary, i.e. referred pressure from other compartments. Mechanisms of causes resulting in abdominal compartment syndrome can be broadly categorised into decreased abdominal wall compliance, increased intraluminal contents, collection of contents in the abdominal cavity, and capillary leak and fluid resuscitation. Abdominal compartment syndrome is associated with severe critical illness and multi-organ failure and has a high risk of mortality (40-100%) which necessitates urgent intervention.

LoE:IVb[xlv]

GENERAL MEASURES

Relieve intra-abdominal pressure via:

- nasogastric tube
- urinary catheter
- drainage of intra-abdominal collections
- appropriate positioning
- sedation
- analgesia
- muscle relaxation (if ventilated)
- surgical decompression

REFERRAL

» Consider surgical consultation for decompression.

23.8 METABOLIC AND ENDOCRINE SUPPORT

23.8.1 THYROID DISORDERS IN CRITICALLY ILL PATIENTS

DESCRIPTION

Non-specific alterations can occur in critically ill patients. The majority revert to normality upon full recovery from the underlying physical insult. The transient dysfunction is attributed to changes in thyroid stimulating hormone (TSH) regulation, altered peripheral metabolism of thyroid hormones, and altered binding of thyroid hormone to thyroid binding globulin.

CAUTION

Thyroid function assessment is not routinely recommended and should be guided by the clinical history and evaluation.

23.8.1.1 SICK EUTHYROID SYNDROME

E07.8

DESCRIPTION

Thyroid dysfunction occurs as a response to the oxidative stress of critical illness and is proportional to the severity of disease. Low T3 levels are often seen soon after ICU admission. High T4 may also be noted early but subsides over time with multiple organ dysfunction syndrome. Thyroid function frequently returns to normal within a few months of disease resolution.

23.8.1.2 HYPERTHYROIDISM

See section 8.18: Hyperthyroidism.

23.8.1.3 THYROID CRISIS

E05.5

DESCRIPTION

See section 8.18.5: Thyroid Crisis.

GENERAL MEASURES

» Treat precipitant factors.

Hemodynamic:

» For volume resuscitation: use balanced salt solutions.

Respiratory

» Supplemental oxygen
» Ventilatory support

Hyperthermia

» Incorporate cooling/ targeted temperature management.
» Use cool, balanced salt solutions initially.
» Apply ice packs and cooling blankets.
» Dextrose solutions may be suitable for continued cooling to cope with high metabolic demands.
» Treat cardiac arrhythmias, if necessary (See section 3.3. Cardiac dysrhythmias).

Metabolic:

» Monitor and correct electrolyte abnormalities.

MEDICINE TREATMENT

For details, see section 8.18.5: Thyroid crisis.

Beta-adrenergic receptor blockade:

- Atenolol, oral, 50 mg daily.
  - Increase to 100 mg if response is suboptimal and patient can tolerate increased beta-adrenergic receptor blockade.
  - An NG tube may be used for administration if an IV formulation is unavailable.

LoE:IVb[xlvi]

Hyperthermia:

- Paracetamol, oral, 1000 mg, 4–6 hourly as required (to a maximum of 4g in 24 hours).
  - Maximum single dose: 15 mg/kg/dose.

23.8.1.4 HYPOTHYROIDISM

See section 8.11: Hypothyroidism.

23.8.1.5 MYXOEDEMA COMA

E03.5/E03.9

DESCRIPTION

Myxoedema coma is an uncommon condition characterized by severe hypothyroidism which may present with an altered mental status, lethargy, hypothermia, decreased organ function, and other non-specific features associated with hypothyroidism. Myxoedema coma is a life-threatening condition with a high mortality rate of up to 30%; rapid recognition is critical to avoid end-organ damage. Despite the name, coma is an uncommon presentation and is not necessary to make the diagnosis, however, its presence is a poor prognostic indicator.

LoE:IVb[xlvii]

GENERAL MEASURES

» Treat precipitant factor.
» Provide organ support, as needed.
» Use passive rewarming measures.
» Manage hypoglycaemia and hyponatraemia.
» Be cautious of upper airway compromise due to macroglossia and/or supraglottic myxoedema.

LoE:IVb[xlviii]

MEDICINE TREATMENT

- Hydrocortisone, IV, 100 mg 8 hourly.

Thyroid hormone replacement

- Levothyroxine (T4), oral.
  - Loading dose: 200 mcg as a single dose.

- Maintenance dose: 100 mcg, daily.
- Medication can be administered via NG tube if an IV formulation is unavailable.

LoE:IVb[xlix]

23.8.2 ADRENAL INSUFFICIENCY

See section 8.2: Adrenal insufficiency (Addison Disease).

23.8.2.1 RELATIVE ADRENAL INSUFFICIENCY

E27.4/E27.9

DESCRIPTION

This is a transient, disproportionate reduction of glucocorticoids in relation to the severity of stress. Note that absolute cortisol levels may be normal. The prevalence of relative adrenal insufficiency is high in septic shock. See section 23.10: Sepsis in ICU for more details.

MEDICINE TREATMENT

See section 23.10: Sepsis in ICU.

23.8.2.2 ADDISONIAN CRISIS

E27.2

DESCRIPTION

Acute adrenal (Addisonian) crisis is a potentially fatal condition that occurs because of insufficient circulating corticosteroids. It is usually caused by impairment of the hypothalamic-pituitary axis, but may also be due to anatomic destruction of the adrenal gland (e.g. in disseminated tuberculosis or fungal infections, or other disease that infiltrate the adrenal gland), adrenal haemorrhage (e.g. septicaemia induced Waterhouse-Friderichsen syndrome), or more commonly, steroid withdrawal.

GENERAL MEASURES

Acute adrenal insufficiency is an emergency and requires immediate therapy.

Principles of management include:

» Treating precipitating cause.
» Providing organ support.

MEDICINE TREATMENT

- Hydrocortisone, IV, 100 mg 6 hourly.

LoE:IVb[l]

23.8.3 HYPOGLYCAEMIA

E10.0/E10.6/E11.0/E11.6/E12.0/E12.0/E12.6/E13.0/E13.6/E14.0/E14.6/E16.0/E16.1/E16.2

DESCRIPTION

Hypoglycaemia, defined as a glucose concentration <4 mmol/L, is common in critically ill patients, and is associated with increased mortality. Risk factors associated with hypoglycaemia in critically ill patients include severity of illness, intensive/strict glucose control, continuous veno-venous haemodialysis, decreased nutritional feeds without adjustment of insulin infusions, prior diagnosis of diabetes mellitus, sepsis, and the need for inotropic support. See section 8.6.1: Hypoglycaemia for further details.

GENERAL MEASURES

» Assess and treat precipitating factors.
» Maintain a target glucose concentration of 6-10 mmol/L.
» Monitor glucose every 15 minutes.
» Provide organ support (respiratory, cardiovascular, neurological).

LoE:IVb[ii]

MEDICINE TREATMENT

<u>If awake and alert:</u>

- Glucose, oral, 20 g, immediately.
  - Alternatively, a carbohydrate-rich supplement may be given if tolerated.

<u>If obtunded, or glucose level <2.5 mmol/L:</u>

- Dextrose 50%, IV, 20 ml immediately.

<u>If hypoglycaemia recurs or dextrose 50% IV solution is not available:</u>

- Glucagon, SC, 1 mg immediately.

LoE:IVb[ii]

23.8.4 HYPERGLYCAEMIA

E10.0-1/E11.0-1/E12.0-1/E13.0-1/E14.0-1/R73.9

DESCRIPTION

Hyperglycaemia (blood glucose concentration >11 mmol/L) occurs in up to 50% of critically ill patients (also called stress hyperglycaemia or critical illness hyperglycaemia). An elevated blood glucose in patients with previously undiagnosed diabetes and without significantly elevated glycated haemoglobin (Hb_{A1c}) levels (>6.5%) is suggestive of stress hyperglycaemia.

LoE:IVb[iii]

Hyperglycaemia is associated with increased mortality, length of hospitalisation, and potentially an increased risk of hospital acquired infections.

See section 8.6.2: Diabetic Ketoacidosis (DKA) And Hyperosmolar Hyperglycaemic State (HHS) for further details.

GENERAL MEASURES

» Maintain a glucose target in ICU: 6-10 mmol/L.
» Balanced salt solutions are preferred to normal saline for fluid resuscitation.
» Continuous insulin infusion therapy should be considered to achieve glycaemic targets.
» Risk of hypoglycaemia should be considered when choosing the method of insulin administration.

23.9 TOXICOLOGY IN ICU

DESCRIPTION

See Chapter 19: Poisonings.

GENERAL MEASURES

» Poisoning should always be considered in patients who present with an altered level of consciousness.
» A thorough collateral history and toxicology screen may assist with making the diagnosis.
» Toxicology screens; where available, may have varied diagnostic reliability in patients with suspected poisoning. These results should always be interpreted in conjunction with a comprehensive clinical assessment.
» Consider whether positive results are due to iatrogenic administration of sedatives/analgesics commonly used to manage patients.
» Exert due caution in making the diagnosis of brain death or deciding on neurological futility if poisoning have not been excluded (See section 23.12: End of life care, determination of death).
» Although patients may fit a specific toxidrome or have a history of ingesting a specific toxin, consider whether patients may have ingested more than one toxin.

For guidance on specific toxins, see Chapter 19: Poisonings.

23.10 SEPSIS IN ICU

A41.9

DEFINITION

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. Organ dysfunction is defined as an acute increase in SOFA (Sequential Organ Failure Assessment) score of at least 2 points. Patients with sepsis have a significantly higher mortality than those with an infection without sepsis.

LoE:IVb[liv]

Septic shock is characterised by hypotension requiring vasopressors to maintain MAP ≥ 65mmHg despite adequate fluid resuscitation, plus a serum lactate >2mmol/l. Patients with septic shock have a significantly higher mortality (>20%) than those with sepsis without septic shock.

Table 23.6: Sequential organ failure assessment (SOFA) score

System	Score				
	0	1	2	3	4
Respiration					
PaO_2/FIO_2 mmHg (kPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7)	<100 (13.3)
				with respiratory support	
Coagulation					
Platelets, $x10^3$ µ/L	≥ 150	<150	<100	<50	<20
Liver					
Bilirubin in µmol/L (mg/dL)	<1.2 (20)	1.2-1.9 (20-32)	2.0-5.9 (33-101)	6.0-11.9 (102-204)	>12.0 (204)
Cardiovascular	MAP ≥ 70mmHg	MAP < 70mmHg	Dopamine <5[a] or dobutamine (any dose)[a]	Dopamine 5.1.-15[a] or adrenaline ≤ 0.1[a]	Dopamine >15[a] or adrenaline >0.1[a]
Central Nervous System					
Glasgow Coma Scale[b]	15	13-14	10-11	6-9	<6
Serum creatinine in µmol/L (mg/dl)	110 (<1.2)	110-170 (1.2-1.9)	171-299 (2.0-3.4)	300-440 (3.5-4.9)	440 (>5.0)
Urine output, ml per day				<500	<200

FIO_2 = Fraction of inspired oxygen; MAP = mean arterial pressure; PaO2 = partial pressure of oxygen

[a] Catecholamine doses are given as per $\mu g.kg^{-1}.min^{-1}$ for at least 1 h.

[b] Glasgow Coma Scale scores range from 3 to 15; higher score indicates less severe neurological disorder

Adapted from: Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. Intensive Care Med. 1996;22:707–710

LoE:IVb[iv]

23.10.1 SEPSIS IN ICU: INITIAL RESUSCITATION

MEDICINE TREATMENT

- Balanced-salt solution crystalloid, IV, 30ml/kg over 3 hours.
  - Aim for an initial haemodynamic target of MAP >65mmHg.
  - Further fluid challenge should be guided by one or more of the following:
    - Dynamic markers of fluid responsiveness, e.g. passive leg raising, pulse pressure variation, stroke volume variation.
    - Lactate clearance: aim for a lactate clearance of >20% over 2 hours.
    - Capillary refill time: aim for a capillary refill time of <3 seconds.

LoE:IVb[iv]

CAUTION
Avoid colloids for shock resuscitation in patients with sepsis and acute kidney injury.

23.10.2 SEPSIS IN ICU: HAEMODYNAMIC SUPPORT

MEDICINE TREATMENT

<u>If fluid therapy alone does not rapidly correct MAP to ≥65mmHg:</u>

- Adrenaline, IV, 0.01-1.0mcg/kg/min given as an infusion.

LoE:IVb[vii]

  - Aim to achieve a target MAP >65 mmHg within 30 minutes.
  - Increasing the adrenaline infusion rate above 1 mcg/kg/min is not recommended in the absence of clear, reversible causes such as hypovolaemia, bleeding, tension pneumothorax etc.

<u>In patients with significant left ventricular dysfunction and no improvement with adrenaline,</u> **ADD:**

- Dobutamine, IV, 500 mg in 200 ml 0.9% saline as a continuous infusion.

- Start infusion at 5ml/hr
- Check MAP regularly (every 10-30 minutes until target is reached) and titrate infusion rate by 2.5 ml/hr to reach target MAP (≥65mmHg).
- Infusion rates exceeding 20 ml/hr are usually not required.

Note:

LoE:IVb[lviii]

» While noradrenaline is recommended in international guidelines as a first-line vasopressor for septic shock, there is no evidence that it offers additional benefits over adrenaline.
» Given the lack of availability and increased cost of noradrenaline, its routine use is not recommended.
» Dopamine should not be used due to an increased risk of mortality and arrhythmias.

LoE:IVb[lix]

23.10.3 SEPSIS IN ICU: ANTIMICROBIAL THERAPY

DESCRIPTION

Early administration of antimicrobial therapy is one of the most effective interventions to reduce mortality in patients with sepsis and should be treated as an emergency. Various aspects including timing of antimicrobials, choice of antimicrobial agent, and dosing require careful consideration.

Timing

» Start empirical antimicrobials therapy within 1 hour of the presumptive diagnosis of sepsis or septic shock.
» Take appropriate samples for microbiology, ideally prior to commencing or changing antimicrobials. However, do not delay antimicrobial administration to collect samples as the risk of mortality increases hourly in untreated sepsis.

Dosing

» See Appendix 1: Antimicrobial Medicines for antimicrobial-specific guidance on dosing.
» Prescribe the higher dose of an antimicrobial dosing range, provided there that it is safe to do so.
» Consider extending the duration of infusion for certain antimicrobials (notably beta-lactams, see note on continuous infusions below).
» The initial or loading dose does not need to be adjusted in the presence of renal dysfunction. However, subsequent dosing may require dose adjustment depending on renal function and the use of renal replacement therapy.

» Extending the infusion duration of beta-lactam antimicrobials may improve effectiveness by increasing the time above the MIC (See Table 23.7).

Table 23.7. Examples of possible continuous infusion dosing regimens

Antimicrobial	Loading dose	Maintenance dose
Amoxicillin/Clavulanic acid	1.2 g over 30 mins.	1.2 g infusion given over 4 hours, 6 hourly dosing interval. *LoE:IIIb*[lx]
Piperacillin/Tazobactam	4.5 g over 30 mins.	4.5 g infusion given over 4 hours, 6 hourly dosing interval.
Meropenem	1 g over 30 mins.	1 g infusion given over 4 hours, 6 hourly dosing interval. *LoE:IIIb*[lxi]

Choice of antimicrobial

The causative organism is usually not known at the time of clinical deterioration. In view of this critically il patients should receive a broader spectrum agent while awaiting culture results followed by subsequent de-escalation to an agent with the narrowest spectrum that will treat the causative organism.

Choose appropriate broad-spectrum empiric antimicrobial therapy based on the following factors:

» Site of sepsis
» Likely causative organisms
» Risk factors for healthcare-associated infections: Hospitalisation for >48 hours, previous antimicrobial therapy or hospitalisation within 3 months, residence in long-term care facility, or chronic wound care.
» Local antibiograms
» Patient factors: organ dysfunction, allergies

When culture and sensitivity results are available and the clinical picture allows, change empiric antimicrobial therapy to the agent that has the narrowest spectrum and that is the most cost-effective. De-escalation is crucial in reducing selective pressure and combatting antimicrobial resistance.

Additional antimicrobials that are prescribed empirically to treat suspected atypical and anaerobic organisms, MRSA, or invasive fungal infections should be carefully considered based on current local epidemiology, and deferred until microbiology results are available if possible. Discuss with a clinical microbiologist. Source control is essential in managing infections in all patients, including those in ICU. Effective source control should be achieved as soon as possible.

Table 23.8: Example of an ICU Empiric Antimicrobial Guideline

Infection	Community Acquired Infection	Healthcare Associated Infection	Suspected Multidrug-resistance
Upper Gastro-intestinal tract (GIT)	Amoxicillin/clavulanic acid ± Gentamycin[#] + Fluconazole	Piperacillin-tazobactam ± Amikacin[#] + Fluconazole	Meropenem[*] + Fluconazole
Lower GIT Urological Gynaecological	Amoxicillin/clavulanic acid ± Gentamycin[#]	Piperacillin-tazobactam ± Amikacin[#]	Meropenem[*]
	For pelvic inflammatory disease, add: Metronidazole		
Infected pancreatic necrosis (suspected)		Piperacillin-tazobactam ± amikacin	Meropenem
Pneumonia in HIV negative patient	Amoxicillin/clavulanic acid + Azithromycin	Piperacillin-tazobactam ± Amikacin[#] ± Vancomycin[^]	Meropenem[*] ± Vancomycin[^]
Pneumonia in HIV positive patient (with bilateral infiltrates)	+Cotrimoxazole + Anti-TB Rx[*]		
Meningitis	Ceftriaxone	Meropenem	
Skin and soft tissue	Amoxicillin/clavulanic acid	Piperacillin-tazobactam ± Vancomycin[^]	Meropenem[*] ± Vancomycin[^]
	For necrotizing fasciitis, add: Clindamycin ± Gentamycin[#]	+ Clindamycin + Amikacin[#]	+ Clindamycin
Catheter-related bloodstream infection		Piperacillin-tazobactam ± Amikacin[#] ± Vancomycin[^]	Meropenem ± Vancomycin[^]
Infective endocarditis	Ampicillin + Cloxacillin + Gentamicin	Meropenem ± Vancomycin[^]	
Tetanus	Metronidazole		
Suspected Clostridium Difficile Enterocolitis	Enteral Vancomycin (IV prep via NGT)		

Infection	Community Acquired Infection	Healthcare Associated Infection	Suspected Multidrug-resistance

^ If from unit with high rate of MRSA (methicillin resistant staphylococcus aureus) or recent MRSA within ICU.
# Decision to embark on dual therapy with an aminoglycoside should be based on assessment of potential benefits of expanded antibiotic coverage based on local susceptibility patterns.

Note:
» Recommendations included in the table may require modifications subject to local resistance patterns
» The choice of carbapenem depends on unit policy/most cost-effective option. If the patient has seizures/ CNS disorder, consider meropenem over imipenem.
» For patients with AKI (acute kidney injury): If serious gram-negative sepsis suspected, consider continuing aminoglycoside with therapeutic drug monitoring, or prescribe beta-lactam antimicrobial as monotherapy, depending on clinical scenario.

Carbapenem-resistant Enterobacterales bacteraemia
U83.7
Carbapenem-resistant Enterobacterales (CRE) are Gram-negative bacteria with reduced susceptibility to at least one of the carbapenem antimicrobials. The clinical outcomes of patients infected with CREs are worse than for other infections and it is imperative that these organisms do not spread to other patients in the unit. Strict adherence to infection control is essential.

These patients should be discussed with clinical microbiologists and infectious disease physicians. Choose an antimicrobial agent that tests susceptible and is active at the site of the infection. Often, limited therapeutic options are available.

In these cases, ceftazidime-avibactam can be considered for CRE bacteraemia, in consultation with a specialist and antimicrobials stewardship team, where the infecting organism is proven to be sensitive to ceftazidime-avibactam on bacterial culture. Use should be avoided in patients with a poor prognosis. Duration of treatment is dependent on indication and clinical response. Duration of treatment should not exceed 14 days.

MEDICINE TREATMENT

- Ceftazidime-avibactam, 2.5 g, IV, 8 hourly (Microbiologist or Infectious Disease specialist initiated).

Use should be avoided in patients with a poor prognosis.

- Duration of treatment is dependent on indication for treatment and clinical response.
- Duration of treatment should not exceed 14 days.

LoE:IVb[lxii]

<u>If the patient is suspected to have a fungal infection, start empirical therapy:</u>

- Amphotericin B, IV, 1 mg/kg/day for 2 weeks or until diagnostic results confirm/exclude fungal infection.
  OR
  - Fluconazole, IV:
    - Loading dose: 800 mg daily.
    - Maintenance dose: 400 mg daily.

LoE:IIa[lxiii]

Note:
The choice between these antifungals should be determined by:
» presence of kidney disease and other organ dysfunction.
» previous anti-fungal therapy.
» local fungal sensitivity patterns.
» site of infection

Duration of antimicrobial therapy
» Shorter durations of antimicrobial therapy may be effective. Please monitor clinical response closely
» Duration of antimicrobial therapy may be individualised by the use of clinical response and biomarkers.
» Antimicrobials may be stopped 48 hours after clinical response or if procalcitonin levels drop below 0.5 ng/l or 80% of peak.
» The failure to respond to a short course of antimicrobials should prompt consideration of antimicrobial resistance or inadequate source control.
» Certain infections (infective endocarditis, empyema, septic arthritis, invasive fungal infections) may, however, still require prolonged antimicrobial therapy.

Source control
The specific anatomical site of infection should be identified as soon as possible and if source control is required (e.g. by surgical intervention) this should be done as soon as medically and logistically possible. Patients with sepsis and septic shock should undergo a period of stabilisation and optimisation prior to source control. This should have clearly defined targets, interventions, and timelines.

23.10.4 SEPSIS IN ICU: ADJUNCTIVE THERAPY

MEDICINE TREATMENT

Steroid Therapy

If the patient with shock requires ≥0.25 mcg/kg/min of adrenaline for >4 hours:

- Hydrocortisone 50mg, IV, 6 hourly until resolution of shock.

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Glycaemic control

» Blood glucose should be maintained between 6-10 mmol/l, using insulin therapy if required. See section 23.8.3: Hypoglycaemia and 23.8.4: Hyperglycaemia for further details.

23.11 SAFETY IN ICU

23.11.1 PATIENT SAFETY

Important patient safety issues in critical care include:

» Proper patient identification
» Timely response to critical tests
» Appropriate and safe use of clinical alarms
» Improvement of staff communication
» Appropriate and safe use of medicines
» Infection prevention and control

All patient safety incidents (PSI) are to be reported on the South African National Patient Safety Incident Reporting and Learning (NPSIRL) System and acted upon appropriately as per the processes of the system. (https://www.knowledgehub.org.za/elibrary/national-guideline-patient-safety-incident-reporting-and-learning-health-sector-south)

23.11.2 PATIENT TRANSFER AND HANDOVER

The following aspects need to be ensured before transferring critically ill patients:

» Decision to transfer is made by the responsible senior
» Adequate and appropriate communication between referring and receiving teams
» Experienced and well-trained transfer team capable of managing any deterioration
» Patient to be stabilized as far as possible with on-going organ support provided for duration of transfer.
» Appropriately secured airway for transfer
» Appropriate monitoring with sufficient battery back-up

» Appropriate level of sedation and pain control
» Adequate oxygen for transfer duration
» Adequate volumes of medications and fluids for duration of transfer
» Prevention of pressure damage and adequate wounds and fractures management
» Emergency medications and equipment
» Appropriate and detailed documentation to accompany patient

Consider the following strategies to improve ICU handovers:
» Standardize the process into specific phases, for example:
  – Pre-handover preparation
  – Equipment and technology handover
  – Information handover
  – Discussion and plan
» Complete urgent clinical tasks before the information transfer.
» Allow only patient-specific discussions during verbal handovers.
» Require that all relevant team members be present.
» Provide training in team skills and communication.

23.12 END OF LIFE CARE

DESCRIPTION

When it has been assessed that continued therapy is unlikely to be beneficial, an active end-of-life (EOL) care process needs to be initiated. The following should be considered:
» In South Africa (SA), EOL care issues are regulated by *inter alia* The SA Constitution Act 108 of 1996, the Health Professional Act of 1974, the National Health Act 61 of 2003, HPCSA Ethical Guidelines (Booklets), Children's Act 38 of 2005 and Common Law.
» Health Care Workers (HCWs) are not obligated to provide treatments that they deem to be unnecessary, unethical, unreasonable, or non-beneficial, and as such may be withheld or withdrawn.
» The patient's wishes in the form of an advance directive (e.g. Living Will) must be taken into consideration with EOL decision-making
» Build consensus among the multidisciplinary HCW team, patients, and/or their surrogate decisions makers, in a structured manner, by using clear communication skills.
» Timely and regular family conferences are essential to provide information (diagnosis, prognosis, therapy), address the family's concerns, gain insight into the patient's wishes, and understand family dynamics and coping mechanisms. (see Appendix 23.II for Family Meeting Form).
» In South Africa, the legal surrogate decision maker is determined in the following order: (i) spouse/partner; (ii) parent; (iii) grandparent; (iv) major child; and (v) sibling.

- » To resolve a disagreement, a second opinion from an independent practitioner, or a peer review team, or an ethics committee may be consulted. Legal recourse should be a last resort.
- » The agreed management plan for EOL care, and decisions about the use of life-sustaining treatment within that plan, should be clearly documented in the patient's medical records.
- » The method employed varies widely and is influenced by ICU protocols, physician beliefs, the clinical scenario as well as patient and family preferences. Additionally cultural factors, religious background (of the physician and the family) as well as the regional legal framework also influence the approach that is utilized.
- » The patient may experience pain, anxiety, delirium, respiratory distress, dyspnoea, vomiting, excessive broncho-pulmonary secretions and stridor. It is the physician's medical and ethical responsibility to ensure these issues are prevented and appropriately managed.
- » The HCW team may experience distress, anxiety and grief. A formal debriefing meeting should be held to alleviate HCW burnout by providing adequate emotional support in an atmosphere that is conducive of trust and mutual understanding.

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See Chapter 24: Medicines for palliative care for further details.

Definitions

- » *Advanced Directive:* A legally-binding, pre-existing, pre-written document wherein the patient reflects their EOL care wishes during times of incapacitation that clinicians are expected to respect.
- » *Withholding therapy*: Decision not to initiate or escalate a life-sustaining therapy or other therapies.
- » *Withdrawing therapy*: Decision to actively stop current life-sustaining therapy.
- » *Do Not Resuscitate (DNR) or No Cardiopulmonary Resuscitation (No CPR) orders*: Pre-emptive order to withhold cardiopulmonary resuscitation.

Determination of death

Brain death

Death is defined as the clinical endpoint characterized by the irreversible loss of consciousness and the inability to breathe. An accurate clinical examination is important to ensure the correct determination of death and should be performed in the absence of potential confounders (factors leading to an incorrect determination of death, e.g. poisoning, severe electrolyte derangements). If confounders are present, the clinical assessment should be

deferred until these have resolved, or confirmatory testing is available to make a diagnosis of death.

A diagnosis of death requires the presence of 3 conditions: persistent coma, absence of brainstem reflexes, and the lack of ability to breathe independently/apnoea.

Table 23.9 presents a summary of the clinical assessment process. Full details can be accessed here: South African guidelines on the determination of death, http://www.samj.org.za/index.php/samj/article/view/13264/9746.

LoE IVb: [lxvi]

Table 23.9: Determination of brain death

Clinical domain	Test	Remarks
Coma	Apply pressure to the following areas: – condyles at the temporomandibular joint – supra-orbital notches – All four extremities	– Non-spinal reflex responses are incompatible with a brain death diagnosis. – Consultation with an experienced practitioner is recommended if the origin of a response is unclear. – Ancillary testing may be needed if responses are ambiguous.
Brain-stem reflexes	– Pupillary light reflex – Corneal reflex – Pain response in trigeminal distribution – Vestibulo-ocular reflex (Cold caloric test)	– All brain-stem reflexes must be absent to determine brain death. – Beware of drugs causing pupillary constriction or dilation, e.g. opioids or anticholinergic drugs. – Be mindful of spinal cord injuries – Assess brainstem mediated response rather than peripheral sensation/motor function.
Apnoea test	– Pre-oxygenate the patient with 100% oxygen for 10 minutes. – Perform a baseline arterial blood gas. measurement. – Disconnect the patient from the mechanical ventilator. – Supply continuous oxygen via a T-piece (preferred) or through a catheter inserted through the endotracheal tube and placed above the carina. – Observe continuously for any spontaneous breathing.	– Only proceed with the apnoea test if all above reflexes are absent. – Apnoea must persist in the presence of an adequate stimulus to spontaneous ventilation, i.e. an arterial PaCO2 >60 mmHg (8 kPa) and an arterial pH <7.30. – Take an arterial blood gas to document the rise in PaCO2 and change in pH. At the end of the test, reconnect the patient to the mechanical ventilator. – Monitor the patient's SpO_2 throughout the procedure. – Testing should be aborted if spontaneous respirations, hypotension, hypoxaemia (SpO_2 <85%), or arrhythmia is noted.

Adapted from Thomson D, Joubert I, De Vasconcellos K, Paruk F, Mokogong S, Mathivha R, McCulloch M, Morrow B, Baker D, Rossouw B, Mdladla N, Richards GA, Welkovics N, Levy B, Coetzee I, Spruyt M, Ahmed N, Gopalan D. South African guidelines on the determination of death. South Afr J Crit Care. 2021 Mar 1;37(1):10.7196/SAJCC.2021v37i1b.466. doi: 10.7196/SAJCC.2021v37i1b.466. PMID: 37214191; PMCID: PMC10193841.

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General remarks:

» The following features are incompatible with brain death: decerebrate or decorticate posturing, true extensor or flexor motor responses to painful stimuli or witnessed seizures.

Ancillary testing:
» When performed correctly, the clinical exam is the most accurate way of testing neurological function. Ancillary tests require the assumption of an intact neurological stimulus-integration-response arc.
» It is recommended that the clinical exam be completed to the fullest extent possible prior to conducting ancillary tests such as cerebral angiography, transcranial dopplers, radionuclide/scintigraphy studies, etc (see full details in the South African guidelines on the determination of death, http://www.samj.org.za/index.php/samj/article/view/13264/9746).

Circulatory death
Circulatory death is the preferred term when death is determined on circulatory grounds. This terminology is preferred to terms such as cardiac or cardiorespiratory death and is in alignment with the latest guidelines.

To make an assessment of death on circulatory grounds, one of the following criteria must be met:
» It is inappropriate to attempt cardiopulmonary resuscitation.
» Attempts at cardiopulmonary resuscitation have failed.
» Treatment aimed at sustaining life has been withdrawn. This may occur if further treatment is deemed unlikely to offer additional benefit to the patient, or to respect the patient's wishes via advanced directive, or as expressed by their legal surrogate decision maker.

The absence of mechanical cardiac function should be confirmed using a combination of the following:
» absence of a central pulse on palpation
» absence of heart sounds on auscultation.

In the hospital setting, circulatory cardiac function can also be assessed by looking for pulsatile flow with direct intra-arterial pressure monitoring, or by looking for contractile activity using echocardiography.

Once this has been determined, the patient should be observed by the person responsible for confirming circulatory death for at least five minutes for confirmation.

Note:
» Any spontaneous return of circulatory or respiratory activity during the five-minute observation period should prompt a reset and repeat of the observation period.
» Return of circulatory or respiratory activity is not an indication to begin resuscitation efforts where this has been determined to be inappropriate.

APPENDICES

APPENDIX 23.I: MANAGEMENT OF VENTILATION

1. Initiation of ventilation

Once a patient has been intubated and is appropriately sedated, the ventilator is set as follows:

a. Select the level of support:
   i. Assist-Control: Pressure Control or Volume Control
      The ventilator delivers the same breath during every inspiration, whether initiated by the ventilator or by the patient.
   ii. Synchronised Intermittent Ventilation: Pressure Control or Volume Control.
      Minimum rate is set and patient may initiate additional supported breaths.
   iii. Spontaneous: Invasive Continuous Positive Airway Pressure (CPAP) with Pressure Support.
      All breaths are initiated by the patient (no set rate) and a pressure support above Positive End Expiratory Pressure (PEEP) is provided.
b. Select the level of supplemental oxygen concentration:
   i. F_iO_2 at 1 (or 100%).
c. Set the trigger:
   i. Machine Triggered: Respiratory Rate at 12 to 15 breaths per minute.
   ii. Patient Triggered: Sensitivity - Pressure 2cmH2O or Flow 1-2 L/min.
d. Set the Control:
   i. For Volume Control: set tidal volume at 5 to 8 ml/kg predicted body weight.
   ii. For Pressure Control: set the pressure above PEEP to 15 cmH2O (driving pressure).
e. Set the Cycle:
   i. Inspiratory:Expiratory Ratio at 1:2.
   ii. Flow Cycling: 30% of Maximum Inspiratory Flow.
f. Set the Baseline Pressure:
   i. Positive End Expiratory Pressure: 5cmH_2O.

The following should be monitored for the patient receiving invasive mechanical ventilation:

» Arterial blood gas
» Pulse oximetry
» All ventilator parameters

2. Titration of Ventilation

a. Ventilation must constantly be titrated to the patient's changing needs.
b. Incrementally reduce FiO2 by 0.1 (10%) every 10 minutes to 0.4 (40%) keeping oxygen saturation (SpO_2) ≥95%.
   Patients with, or at risk of Acute respiratory distress syndrome (ARDS) are able to tolerate SpO_2 ≥88%.
c. Adjust settings to target PCO_2 of 4.5-6.0 kPa:
   i. A lower PCO_2 will be targeted to temporarily compensate for a metabolic acidosis while the cause is being corrected.
   ii. A PCO_2 of 4.2-4.8kPa may be targeted in brain injured patients.
   iii. A higher PCO_2 may be tolerated in patients with, or at risk of, ARDS to minimise the need for harmful ventilator settings (permissive hypercapnia).
   iv. Do not let respiratory acidosis develop such that pH <7.20.

Note:

» The above are targets are guidelines and sometimes cannot be met. In these instances, more injurious/aggressive settings may be required for short periods.
» Mechanical ventilation may also be provided non-invasively (NIV) via face mask (specific instructions to be obtained from consultant regarding patient selection and initial settings).

3. Weaning of Ventilation:

» Weaning of ventilation is a continuous process and cannot be separated from titration of ventilation described above: it is simply the reducing limb of ventilation titration.
» Once a patient is stable on mechanical ventilation and requirements are no longer increasing, ongoing attempts must be made at the progressive stepwise reduction of ventilatory support.
» Reduce ventilatory support, beginning in this order:
   a. FiO_2: aim for FiO_2 of 0.4 (40%).
   b. Respiratory Rate (RR):
      i. Make multiple attempts to reduce the RR for short periods till the patient starts taking spontaneous breaths.
      ii. If the spontaneous rate is >10/min, place the patient on Pressure support/ Continuous positive airway pressure (PS/CPAP).
      iii. Adjust pressure support to maintain tidal volume as needed.
      iv. Observe to see if stable:
         – Pressure Support: progressively reduce PS while maintaining tidal volume >6ml/kg and pH >7.3 until PS = 6 cmH2O.

- PEEP: Reduce PEEP by 2cmH2O till PEEP = 6 cmH2O.

- Note: the minimum levels of PS and PEEP able to be set may vary as per the make of the ventilator

» The patient is ready for liberation from the ventilator once the patient requires minimal ventilatory support as described above and is stable with:
  - SpO_2 >92%, RR between 10 and 30 breaths/min, tidal volume >6ml/kg, and pH >7.3.
  - HR and BP within 20% of patient's normal; Minimal inotropic support; No new arrhythmias.
  - No respiratory distress: Alar flaring, Use of accessory muscles, Paradoxical abdominal movement.
  - No sweating.

» To assess patient readiness for extubation:
  - Assess for adequate level of consciousness, bulbar function, and muscle strength.
  - If patient can cough and maintain own airway, then consider extubation.
  - T-piece tests are no longer routinely recommended.

APPENDIX 23.II: FAMILY MEETING FORM

Date……Time…….Chairperson……..……

Patient……...

Hospital Number……

Meeting Number ….	Name/s and details
Family members	
Nursing Staff	
Other persons	
Purpose	
Surrogate decision maker	
Other	

Points Discussed	Tick if yes	Comment
Current status		
Prognosis		
Patient's wishes		
Clinical advice		
Family opinion		
Nursing input		
Decision(s)agreed		
Special requests		
Do Not Resuscitate DNR status		
Other		

Name	Position (please tick)	Signature
	ICU Specialist	
	Nursing Sister	
	Surgeon/Clinician	
	Fellow	
	Registrar	
	Medical officer	
	Other-specify	

Signatures:

…….. ……

Doctor **Patient/Family Member**

……..

Witness

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[lxv] End of Life Care: Paruk F, Kissoon N, Hartog CS, Hodgson RE, Lipman J, Guidet B, Du B, Argent A. The Durban World Congress Ethics Round Table: III. Withdrawing Mechanical ventilation- The approach should be individualized. J Crit Care. 2014 Jun 4. pii: S0883-9441(14)00223-8. doi: 10.1016/j.jcrc.2014.05.022.

End of Life Care: Joynt GM, Lipman J, Hartog C, Guidet B, Paruk F, Feldman C, Kissoon N, Sprung CL. The Durban World Congress Ethics Round Table IV: Health care professional end-of-life decision making. J Crit Care. 2015 Apr;30(2):224-30. doi: 10.1016/j.jcrc.2014.10.011

[lxv] End of Life Care: Sprung CL, Paruk F, Kissoon N, Hartog CS, Lipman J, Du B, Argent A, Hodgson E, Guidet B, Groeneveld ABJ and Feldman C. The Durban World Congress Ethics Round Table Conference

Report: I. Differences between withholding and withdrawing life-sustaining treatments. Journal of Critical Care 2014 Dec;29(6):890-5. doi: 10.1016/j.jcrc.2014.06.022
[lxvi] End of Life Care: Thomson D, Joubert I, K De Vasconcellos, F Paruk, S Mokogong, R Mathivha, et al. South African Guidelines on the Determination of Death. South African Medical Journal [Internet]. 2014 [cited 2023 Nov 21];111(4b):367–80. Available from: http://www.samj.org.za/index.php/samj/article/view/13264/9746
[lxvii] End of Life Care: Thomson D, Joubert I, K De Vasconcellos, F Paruk, S Mokogong, R Mathivha, et al. South African Guidelines on the Determination of Death. South African Medical Journal [Internet]. 2014 [cited 2023 Nov 21];111(4b):367–80. Available from: http://www.samj.org.za/index.php/samj/article/view/13264/9746

SOUTH AFRICAN ADULT HOSPITAL HEALTHCARE LEVEL ESSENTIAL MEDICINES LIST
CHAPTER 23: ADULT CRITICAL CARE
NEMLC RECOMMENDATIONS FOR MEDICINE AMENDMENTS (2020-3)

Medicine recommendations, with supporting evidence and rationale are listed below.
Kindly review the medicine amendments in the context of the respective standard treatment guideline (STG).

Following external comment and clinical editing several amendments were made to the adult critical care chapter.

All reviews and costing reports may be accessed at: https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

The adult critical care chapter is a new chapter developed in the 2020-23 review cycle to replace the previous adult hospital level Chapter 23 Sedation. Critical care is a series of organ supports offered to patients. Therefore, in developing the chapter an organ systems support approach, in no particular order, was adopted.

Refer to the adult critical care chapter for the corresponding STG.

Medicines have been proposed for the newly developed adult critical care chapter and essential medicine list (EML) as follows.

- New medicines were added to the chapter following a medicine review
- Medicines on the EML, being used for a different or similar indication, were selected for addition to this chapter with a justification for extending the indication to critical care through a medicine review or evidence-base substantiation
- Medicines on the EML, being used for the same indication ('aligned' and cross referenced to other chapters).

This is the first iteration of the adult critical care chapter. The chapter remains a work in progress as medicine reviews for non EML items continue to be recommended for prioritization for future review cycles.

A: NEW STANDARD TREATMENT GUIDELINE

SECTION	MEDICINE/MANAGEMENT	ADDED/DELETED/AMENDED/ NOT ADDED/ RETAINED
23.1 Introduction and Principles of Critical Care	No	n/a
23.2 Respiratory Support	No	n/a
23.3 Cardiovascular Support	Balanced Salt Solution	Added (as per therapeutic interchange database)
23.3.1 Shock	No	n/a
Vasoactive Medicines for Shock	**Treatment:** Adrenaline, IV	Added
	Noradrenaline, IV	Not added
	If shock is suspected to be cardiogenic in origin use: Dobutamine, IV	Added (aligned to the Adult Hospital Level Chapter 3 Cardiovascular System)
23.4 Renal Support	Balanced Salt Solution	Added (as per therapeutic interchange database)
23.4.1 Kidney Replacement Therapy	**To reduce circuit hypercoagulability:** Unfractionated Heparin administered directly into the KRT circuit	Added
	To reduce circuit hypercoagulability: Enoxaparin, SC	Added

SECTION	MEDICINE/MANAGEMENT	ADDED/DELETED/AMENDED/ NOT ADDED/ RETAINED
23.5.1 Thromboprophylaxis	Enoxaparin, SC	Added
	If LMWH is unavailable or contraindicated: Unfractionated heparin, SC:	Added
23.5.2 Anaemia in Critical Care	Red cell transfusions	Added
23.5.3 Thrombocytopaenia and Platelet Dysfunction in Critical Care	Platelet transfusions	Added
23.5.4 Plasma Transfusion	**For prophylaxis or therapy:** FDP, IV	Added
	For prophylaxis or therapy: FFP, IV	Added to therapeutic interchange database
	Empiric use in large volume blood transfusion: FDP, IV	Added
	Empiric use in large volume blood transfusion: FFP, IV	Added to therapeutic interchange database
23.5.5 Coagulation Factors	Cryoprecipitate, IV	Added
	For all other coagulation factors; a cross reference provided to the Adult Hospital Level Chapter 2: Blood and Blood Forming Organs. For Warfarin Poisoning a cross reference provided to Section 19.9 Anticoagulant (Warfarin and Rodenticide Superwarfarin) Poisoning in the Adult Hospital Level Chapter 19: Poisonings.	
23.5.6 Antifibrinolytic Medication	**Severe trauma: (Give within 3 hours of the injury):** Tranexamic acid, IVI	Added
	Bleeding postpartum obstetric patients: Tranexamic acid, IVI	Added
	If bleeding persists (after 30 minutes): Tranexamic acid, IVI	Added
23.5.7 Massive Transfusion Protocol (MTP)	No	n/a
23.6 Neuro-Psychological Support	No	n/a
23.6.1 Pain Management	Paracetamol, IV (Specialist Initiation & Continuation)	Added
	Commonly used analgesics in the ICU: Morphine, IV	Added
	Commonly used analgesics in the ICU: Fentanyl, IV	Added
	Commonly used analgesics in the ICU: Tramadol, PO or IV	Added
	Commonly used analgesics in the ICU: Ketamine, IV	Added
23.6.2 Sedation **Commonly used sedation medicines in the ICU**	Haloperidol, IM	Not added
	Propofol, IV	Added
	Midazolam, IV	Added
	Lorazepam, IV	Added
23.6.3 Delirium in Critical Care	Cross references are provided to the Adult Hospital Level Emergencies and Injuries section 20.8: Delirium and Adult Hospital Level Mental Health Care Section: 15.1 Aggressive Disruptive Behaviour in Adults	
23.6.4 Mood Disorders	Cross reference provided to Adult Hospital Level Chapter 15 Mental Health Care; section 15.3: Mood Disorders	
23.6.5 Seizures	Cross reference provided to the Adult Hospital Level Chapter 14 Neurological Disorders; section 14.4: Epilepsy	

SECTION	MEDICINE/MANAGEMENT	ADDED/DELETED/AMENDED/ NOT ADDED/ RETAINED
23.6.6 Intracranial Pressure Management	Cross reference to the Adult Hospital Level Standard Treatment Guidelines -Chapter 14 Neurological Disorders; section 14.12.2: Brain Oedema Due to Traumatic Injury	
23.7 Gastro-Intestinal Support	No	n/a
23.7.1 Nutrition	No	n/a
23.7.2 Stress Ulcer Prophylaxis	Pantoprazole, IV	Added and aligned with paediatric hospital level STGS
23.7.3 Regurgitation and Aspiration	No	n/a
23.7.4 Diarrhoea	Cross reference provided to the Adult Hospital Level Chapter 1: Alimentary tract: Section 1.3: Diarrhoea	
23.7.5 Liver Support	Cross reference provided to the Adult Hospital Level Chapter 1: Alimentary tract: 1.2.2: Section Liver Failure, Acute	
23.7.6 Acute Severe Pancreatitis	Cross reference provided to the Adult Hospital Level Chapter 1: Alimentary tract: Section 1.16: Pancreatitis, Acute	
23.7.7 Acute Cholecystitis	Cross reference provided to the Adult Hospital Level Chapter 1: Alimentary tract: Section 1.27 Cholecystitis, acute, and cholangitis, acute	
23.7.8 Abdominal Compartment Syndrome	No	n/a
23.8 Metabolic and Endocrine Support	No	n/a
23.8.1 Thyroid Disorders in Critically Ill Patients	No	n/a
23.8.1.1 Sick Euthyroid Syndrome	No	n/a
23.8.1.2 Hyperthyroidism	Cross reference provided to the Adult Hospital Level Chapter 8: Endocrine System: Section 8.18: Hyperthyroidism	
23.8.1.3 Thyroid Crisis	Cross reference provided to the Adult Hospital Level Chapter 8: Endocrine System: Section 8.18.5: Thyroid Crisis	
	Supportive measures: Hemodynamic Atenolol, oral (via nasogastric tube)	Added
	Hyperthermia: Balanced Salt Solution, IV	Added as per therapeutic interchange database
	Hyperthermia: Paracetamol, oral	Added
23.8.1.4 Hypothyroidism	Cross reference provided to the Adult Hospital Level Chapter 8: Endocrine System: Section 8.11: Hypothyroidism	
23.8.1.5 Myxoedema Coma	Hydrocortisone, IV	Added
	Levo-thyroxine IV	Not Added
	Levothyroxine (T4), oral (via nasogastric tube)	Added
23.8.2 Adrenal	Cross reference provided to the Adult Hospital Level Chapter 8: Endocrine System: Section 8.2: Adrenal Insufficiency (Addison Disease)	
23.8.2.1 Relative Adrenal Insufficiency (RAI)	No	n/a
	Steroid replacement Hydrocortisone, IV	Added
23.8.3 Hypoglycemia	**If awake and alert:** Glucose, oral	Added
	If obtunded: Glucagon, SC	Added
23.8.4 Hyperglycemia	Cross reference provided to the Adult Hospital Level Chapter 8: Endocrine System: Section 8.6.2: Diabetic Ketoacidosis (DKA) And Hyperosmolar Hyperglycaemic State (HHS)	
23.9 Toxicology in ICU	For Specific toxins: Cross reference provided to the Adult Hospital Level Chapter 19: Poisonings	
23.10 Sepsis in ICU	No	n/a
23.10.1 Sepsis in ICU: Initial Resuscitation	Balanced Salt Solution, IV	Added as per therapeutic interchange database
23.10.2 Sepsis in ICU: Haemodynamic Support	Adrenaline, IV	Added
	Dobutamine, IV	Added
23.10.3 Sepsis in ICU: Antimicrobial Therapy	Aligned to Adult Hospital Level Systemic and Healthcare Associated Infections Guidance	
	Carbapenem-resistant Enterobacterales (CRE) bacteraemia: Ceftazidime-avibactam, IV	Added

SECTION	MEDICINE/MANAGEMENT	ADDED/DELETED/AMENDED/ NOT ADDED/ RETAINED
	Adjunctive therapy: **Corticosteroids** Hydrocortisone, IV	Added
	If the patient is suspected to have a fungal infection, start empirical therapy Amphotericin B, IV	Added
	If the patient is suspected to have a fungal infection, start empirical therapy Fluconazole, IV	Added
23.10.4 Sepsis in ICU: Adjunctive therapy	Hydrocortisone, IV	Added
	Fludrocortisone	Not Added
23.11.1 Patient Safety	No	n/a
23.11.2 Patient Transfer and Handover	No	n/a
23.12 End of Life Care	Cross reference provided to the Adult Hospital Level Chapter 24: Medicines used in Palliative Care	

23.1 INTRODUCTION AND PRINCIPLES OF CRITICAL CARE

A brief definition of critical care and what critical care entails is provided in the introduction to the chapter i.e., specialised medical and nursing care for patients, monitoring requirements, resuscitation, modalities of support and end of life care.[1] The introduction also stressors that critical care is a continuum of care and although critical care is usually delivered in an intensive care unit; care should be carried through from the pre-hospital environment and emergency department throughout the whole spectrum of the health system. High care is explicitly included as part of critical care as high care impacts on nursing requirements.

The introduction also covers general principles of pharmacology[2] in critical illness mentioning pharmacokinetic (PK) and pharmacodynamic (PD) variations in critical care patients, factors affecting therapeutic response and clinical outcomes, dosing (loading doses, maintenance doses and dose titrations), therapeutic drug monitoring and the impact of polypharmacy. These generic concepts are included in general to highlight concerns in critical care patients.

An external comment to include the role of physiotherapists, occupational therapists and dieticians was included through a multidisciplinary team approach. The role of critical care technologists and social workers are also included. All of these professionals are crucial in the early identification and management of patients in ICU to reduce hospital stay, decrease complications and enhance quality of life.

Level of Evidence: Guidelines

23.1.1 GENERAL PRINCIPLES OF PHARMACOLOGY IN CRITICAL ILLNESS

Pharmacokinetic (PK, "what the body does to the drug") and pharmacodynamic (PD, "what the drug does to the body") variations are included under general principles of pharmacology in critical illness. Increased volume of distribution in critically ill patients and renal and hepatic clearance principles are also highlighted in this section as reiterated as important concepts through external comment.

[1] Marshall JC, Bosco L, Adhikari NK, Connolly B, Diaz JV, Dorman T, et al. What is an intensive care unit? A report of the task force of the World Federation of Societies of Intensive and Critical Care Medicine. J Crit Care. 2017 Feb;37:270-276. doi: 10.1016/j.jcrc.2016.07.015.

[2] Chen J. Pharmacology in Critical Illness. In: Oropello JM, Pastores SM, Kvetan V. eds. Critical Care. McGraw Hill; Accessed April 04,2022.

23.2 RESPIRATORY SUPPORT

The focus of this STG is the purpose of and indications for respiratory support.

A detailed ventilation management strategy is provided in an appendix to the STG. A generic step by step guide is provided of initiation of ventilation, how to select the level of support and an explanation on setting the oxygen concentrations. With the understanding that ventilators will differ between different settings guidance is provided for setting the machine, monitoring the patient while on the machine, titration of the ventilator and liberating the patient from the ventilator. In summary, the appendix offers a practical guide on how to offer ventilatory support.

An external commentator raised the issue of dependence on make of the ventilator. Therefore, a note was added, to Appendix 23.I: Management of Ventilation, explicitly stating that the minimum levels of Pressure Support (PS) and a Pressure support above Positive End Expiratory Pressure (PEEP) able to be set may vary as per the make of the ventilator. Additionally, regarding patient's readiness for extubation, a note that T piece tests are no longer routinely recommended was also added to the Appendix 23.I: Management of Ventilation.

23.3 CARDIOVASCULAR SUPPORT

Balanced Salt Solution, IV: *Added as per therapeutic interchange database*

Based on an evidence review updated in 2019[3], the NEMLC recommends that sodium chloride 0.9% be the primary resuscitation fluid (including for septic shock). Ringer's lactate is included on the therapeutic interchange database for patients in whom balanced solutions may be more appropriate e.g., critically ill patients presenting with hyperchloraemia, patients previously receiving renal replacement therapy.

General cardiovascular principles such as parenteral dosing, fluid therapy, respiratory support and monitoring targeted at minimum hospital level of care are provided. The monitoring list compiled is only a minimum list in cognizance of the variability of the district level to regional level package of care. Continuous positive airway pressure (CPAP) for respiratory support is included under non-invasive ventilation. Continuous blood pressure monitoring e.g., invasive blood pressure monitoring is included, if available.

Thereafter, sub categories of cardiovascular support are outlined with cross references provided to the Adult Hospital Level Chapter 3 Cardiovascular System namely:

- **Cardiac Arrest:** Cross Referenced to Adult Hospital Level Chapter 3: Cardiovascular System: Section 20.1: Cardiac Arrest In Adults
- **Post-Cardiac Arrest Care:** Cross Referenced to Adult Hospital Level Chapter 3: Cardiovascular System: Section 20.2: Post Cardiac Arrest Care
- **Acute Coronary Syndromes**
  - **St Elevation Myocardial Infarction (STEMI)** Cross Referenced to Adult Hospital Level Chapter 3: Cardiovascular System: Section 3.2.1: St Elevation Myocardial Infarction (STEMI)
  - **NON-STEMI:** Cross Referenced to Adult Hospital Level Chapter 3: Cardiovascular System: Section 3.2.2: Non-St Elevation Myocardial Infarction (NSTEMI) And Unstable Angina (UA)

[3] NDoH Medicine Review. Ringer lactate for resuscitation in patients with hypovolaemia. Aug 2019. Microsoft Word - Ringer Lactate for resuscitation in Adults Medicine review update August2019 (health.gov.za)

- **Dysrhythmias** Cross Referenced to Adult Hospital Level Chapter 3: Cardiovascular System: Section 3.3: Cardiac Dysrhythmias
- **Hypertension** Cross Referenced to Adult Hospital Level Chapter 3: Cardiovascular System: Section 3.6: Hypertension
- **Hypertensive Urgency** Cross Referenced to Adult Hospital Level Chapter 3: Cardiovascular System: Section 3.6.2: Hypertensive Urgency
- **Hypertensive Emergency** Cross Referenced to Adult Hospital Level Chapter 3: Cardiovascular System: Section: Hypertensive Crisis, Hypertensive Emergency
- **Cardiac failure**
    - **Acute Pulmonary Oedema** Cross Referenced to Adult Hospital Level Chapter 3: Cardiovascular System: Section 20.10: Pulmonary Oedema, Acute
    - **Acute Coronary Syndromes** Cross Referenced to Adult Hospital Level Chapter 3: Cardiovascular System: Section 3.4: Congestive Cardiac Failure (CCF)

23.3.1. SHOCK

A definition[4] and broad aim are provided for shock.

For the management of different types of shock, cross references were provided to applicable sections in other chapters, namely Adult Hospital Level - Chapter 2: Emergencies and Injuries including:

- **Hypovolaemic Shock:** Cross Referenced to Adult Hospital Level Chapter 20: Emergencies and injuries: Section 20.12.1: Hypovolaemic Shock
- **Distributive Shock** including neurogenic shock, septic shock, sepsis in ICU and anaphylaxis/anaphylactic shock: Cross Referenced to Adult Hospital Level Chapter 20: Emergencies and injuries: Section 20.12.2: Distributive Shock including:
    - Section 20.12.2.1: Neurogenic Shock
    - Section 20.12.2.2: Septic Shock and section 23.10: Sepsis in ICU
    - Section 20.7: Anaphylaxis/Anaphylactic Shock
- **Cardiogenic Shock**: Cross Referenced to Adult Hospital Level Chapter 20: Emergencies and injuries: Section 20.12.3: Cardiogenic Shock
- **Obstructive Shock**: Cross Referenced to Adult Hospital Level Chapter 20: Emergencies and injuries: Section 20.12.4: Obstructive Shock

Fluid therapy for shock and vasoactive medicines for shock, previously represented as standalone STGs are now incorporated into section 23.3.1 Shock STG.

Fluid Therapy for Shock

Following external comment, the section for fluid therapy for shock was moved to precede vasoactive medicines for shock as fluid therapy for shock is the first step in the management of shock.

Balanced Salt Solution, IV: *Added as per therapeutic interchange database*

[4] Cecconi M, De Backer D, Antonelli M, Beale R, Bakker J, Hofer C, Jaeschke R, Mebazaa A, Pinsky MR, Teboul JL, Vincent JL, Rhodes A. Consensus on circulatory shock and hemodynamic monitoring. Task force of the European Society of Intensive Care Medicine. Intensive Care Med. 2014 Dec;40(12):1795-815. doi: 10.1007/s00134-014-3525-z. Epub 2014 Nov 13. PMID: 25392034; PMCID: PMC4239778.

Based on an evidence review updated in 2019[5], the NEMLC recommends that sodium chloride 0.9% be the primary resuscitation fluid (including for septic shock). Ringer's lactate is included on the therapeutic interchange database for patients in whom balanced solutions may be more appropriate e.g., critically ill patients presenting with hyperchloraemia, patients previously receiving renal replacement therapy.

Due to the different fluid responsive monitors that might be available at different hospital e.g., district hospitals can do passive leg raising; a general statement on monitoring fluid responsiveness is provided in the STG.

Although this section of the chapter is related to shock, it is acknowledged that maintenance fluid support for patients not in shock is not addressed in the chapter and that a section on general/maintenance fluid support would be helpful in future iterations of the chapter e.g. calculation of daily fluid requirements, recommended types of fluid to use, and monitoring.

Vasoactive Medicines for Shock

Adrenaline, IV: *Added*
Noradrenaline, IV: *Not added*
Vasopressin, IV: *Not added*

The South African standard treatment guidelines (STGs) for Adult Hospital Level, 2019 edition (Section 20.11.2.2 Septic Shock), have previously recommended adrenaline for the treatment of septic shock that is unresponsive to a fluid challenge[6]. Additionally, adrenaline (epinephrine) has been historically included in the Adult Hospital Level STGs for other indications e.g., Chapter 20: Emergencies and injuries as an immediate emergency medicine treatment for cardiac arrest in adults and in Chapter 3: Cardiovascular System for persistent hypotension (section 20.1: Cardiac arrest).

Refer to the medicine review - Vasopressors, inotropes as monotherapy or in combination, 24 April 2023 (Updated: 6 October 2023)[7], below:

AHL_Ch23_Adult CriticalCare_Vasopres

Recommendation: The PHC/Adult Hospital Level Committee suggests not to use the option of noradrenaline for management of septic shock.

Rationale: There is limited evidence that noradrenaline (norepinephrine), with/without other catecholamines results in improved clinical outcomes (mortality, haemodynamic stability) or improved safety (dysrhythmias and lactate concentrations) compared to adrenaline (epinephrine). Furthermore, noradrenaline (norepinephrine) is cost-prohibitive compared to adrenaline at present, and is unlikely to have generic agents available for the foreseeable future.

Level of Evidence: Low to very low certainty evidence
Review indicator: Price reduction, availability of cost-effective noradrenaline products, or any new evidence of efficacy or harm.

5 NDoH Medicine Review. Ringer lactate for resuscitation in patients with hypovolaemia. Aug 2019. Microsoft Word - Ringer Lactate for resuscitation in Adults Medicine review update_August2019 (health.gov.za)

6 National Department of Health: National Department of Health: Essential Drugs Programme. Adult Hospital level STGs and EML. Chapter 20: Emergencies and Injuries.

7 National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Vasopressors, inotropes as monotherapy or in combination, April 2023. http://www.health.gov.za/. https://accessmedicine.mhmedical.com/content.aspx?bookid=1944&sectionid=143516493

NEMLC RECOMMENDATION (MEETING OF 12 OCTOBER 2023):
Although the available evidence was of low to very low certainty, NEMLC did not recommend noradrenaline over adrenaline for the initial management of septic shock that is unresponsive to a fluid challenge, due to the absence of clinically significant advantages in mortality or safety.

Following external comment, the upper range on the adrenaline dosing was revised to 1.0mcg/kg/min. The units for adrenaline dosing were standardized to mcg/kg/min from ug/kg/min throughout the chapter. [8]

A higher dosage of adrenaline is provided for the emergency setting in Chapter 20: Emergencies and injuries (e.g., Dilute 10 mg (10 ampoules) of adrenaline 1:1000 in 1 L sodium chloride 0.9%) versus a wider range which falls within the emergency dosing range for adrenaline in the adult critical care chapter for the intensive care setting (Adrenaline, IV infusion, 0.01-1.0 mcg/kg/min, aiming to achieve a target MAP > 65mmHg within 30 minutes). The context for adrenaline IV use in the critical care and the emergency setting are different, for example, prior to admission to the ICU there might have been a degree of adrenaline therapy which would have occurred. While unambiguity in the interpretation of the STGs is important, the infusion dose range and target as included in the adult critical care chapter for adrenaline IV of 0.01-0.1 mcg/kg/min is unlikely to cause any confusion considering the ICU context in which it is required. A cross-reference to the Adult Hospital Level - Chapter 20: Emergencies and injuries was not included as the doses do not need to be aligned.

External comments on the non-inclusion of noradrenalin as a vasoactive medicine for shock were noted. Commentators acknowledged, with evidence, that there is a lack of strong evidence demonstrating superiority of noradrenaline over adrenaline on mortality. Commentators further motivated that adrenaline has been considered in settings where noradrenaline is not available, in developing countries where noradrenaline is considerably more expensive (example in South Africa) or in patients with refractory septic shock and myocardial dysfunction. Thirdly, it was raised, through external comment, that the International Surviving Sepsis Campaign Guidelines 2021 edition issued a strong recommendation for noradrenaline as a first line vasopressor in septic shock. Concerns about adrenaline safety were also raised and mentioned as follows: serious cardiac arrhythmias, myocardial ischemia exacerbation, splanchnic hypoperfusion and hyperlactatemia (which might be a confounding factor when interpreting lactate as a marker of tissue hypoxia). Reports of cardiac events in patients with ischemic heart disease, as well as bowel ischemia in patients presenting for emergency gastrointestinal surgery, with the use of adrenaline to treat shock, were reported through external comment. It was raised through external comment that these deleterious effects had been frequently reported in patients with cardiogenic shock and therefore commentators felt that selected patients will still benefit from noradrenaline over adrenaline particularly in cardiogenic shock; and that it should be made available in reasonable quantities depending on budget.

The committee has recommended a medicine review of noradrenaline and/or other vasopressors as a second line alternative treatment for various types of shock in consideration of historical use in the EML in the case of adrenaline contra-indication, unavailability or ineffectiveness. Noradrenaline (norepinephrine) is now SAHPRA registered. The section on vasoactive medicines for shock) in the chapter which refers to additional treatment if target with adrenaline is not achieved will remain unfinalized until the recommended review is concluded in the next review cycle.

If shock is suspected to be cardiogenic in origin:
Dobutamine, IV: *Added (aligned to the Adult Hospital Level Chapter 3 Cardiovascular System)*

8 Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, Machado FR, Mcintyre L, Ostermann M, Prescott HC, Schorr C, Simpson S, Wiersinga WJ, Alshamsi F, Angus DC, Arabi Y, Azevedo L, Beale R, Beilman G, Belley-Cote E, Burry L, Cecconi M, Centofanti J, Coz Yataco A, De Waele J, Dellinger RP, Doi K, Du B, Estenssoro E, Ferrer R, Gomersall C, Hodgson C, Hylander Møller M, Iwashyna T, Jacob S, Kleinpell R, Klompas M, Koh Y, Kumar A, Kwizera A, Lobo S, Masur H, McGloughlin S, Mehta S, Mehta Y, Mer M, Nunnally M, Oczkowski S, Osborn T, Papathanassoglou E, Perner A, Puskarich M, Roberts J, Schweickert W, Seckel M, Sevransky J, Sprung CL, Welte T, Zimmerman J, Levy M. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock 2021. Crit Care Med. 2021 Nov 1;49(11):e1063-e1143. doi: 10.1097/CCM.0000000000005337. PMID: 34605781.

The STGs for Adult Hospital Level, 2019 edition (Section 20.11.2.3 Cardiogenic Shock), have previously recommended Dobutamine for the treatment of cardiogenic shock[9],[10].

23.4 RENAL SUPPORT

Balanced Salt Solution, IV: *Added as per therapeutic interchange database*

Based on an evidence review updated in 2019[11], the NEMLC recommends that sodium chloride 0.9% be the primary resuscitation fluid (including for septic shock). Ringer's lactate is included on the therapeutic interchange database for patients in whom balanced solutions may be more appropriate e.g., critically ill patients presenting with hyperchloraemia, patients previously receiving renal replacement therapy.

This STG includes a staging/severity of acute kidney injury[12] table (units shown in both µmol/l and mg/dl). Management principles provided are tailored for both district and regional hospitals. Following external comment a note to "dose-adjust medications for reduced GFR" is included under general measures as this is a critical part of avoiding further acute kidney injury.

Following external comment, a note of caution indicating "if not already volume replete" was added to the narrative following the instruction of intravenous volume expansion with 0.9% sodium chloride solution in order to avoid fluid overload.

The term renal replacement therapy has been revised to kidney replacement therapy throughout the chapter.

Nutrition in Acute Kidney Injury (AKI)

The nutritional requirements and text were included with the support and guidance from the NDOH nutrition programme. It was confirmed that a standalone protein product is not available on the EML however can be sourced through a non-pharmaceutical contract through the NDOH nutrition programme and related NDOH National Clinical Nutrition Guidelines[13].

A caution box on avoiding diuretics and dopamine in AKI is included in the STG.

23.4.1 KIDNEY REPLACEMENT THERAPY

To reduce circuit hypercoagulability:[14]

- Unfractionated Heparin administered directly into the KRT circuit: *Added*
- Enoxaparin, SC: *Added*

Unfractionated Heparin and Enoxaparin are EML items included for various coagulability issues in the STGs.

[9] Dobutamine: MCC registered South African package insert: Pharmaplan Cardiject® powder for IV infusion, 250 mg/vial.

[10] National Department of Health: National Department of Health: Essential Drugs Programme. Adult Hospital level STGs and EML. Chapter 20: Emergencies and Injuries.

11 NDoH Medicine Review. Ringer lactate for resuscitation in patients with hypovolaemia. Aug 2019. Microsoft Word - Ringer Lactate for resuscitation in Adults Medicine review update_August2019 (health.gov.za)

12 Kidney Disease: Improving Global Outcomes (KDIGO). Acute Kidney Injury (AKI). 2012 Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Acute Kidney Injury (AKI). 2012. Available at: https://kdigo.org/guidelines/acute-kidney-injury/

13 Fiaccadori E, Sabatino A, Barazzoni R, Carrero JJ, Cupisti A, De Waele E, Jonckheer J, Singer P, Cuerda C. ESPEN guideline on clinical nutrition in hospitalized patients with acute or chronic kidney disease. Clin Nutr. 2021 Apr;40(4):1644-1668. doi: 10.1016/j.clnu.2021.01.028. Epub 2021 Feb 9. PMID: 33640205.

National Department of Health. Directorate: Nutrition. National Renal Nutrition Practice Guidelines for Adults. June 2018. http://www.health.gov.za/.

14 Joannidis M, Oudemans-van Straaten HM. Clinical review: Patency of the circuit in continuous renal replacement therapy. Crit Care. 2007;11(4):218. doi: 10.1186/cc5937. PMID: 17634148; PMCID: PMC2206533.

Bellomo R, Ronco C. Anticoagulation during CRRT. In: Bellomo R, Baldwin I, Ronco C, Golper T., editors. Atlas of haemofiltration. Sydney: W.B. Saunders; 2002. pp. 63–68.

Following external comment, a description of kidney replacement therapy was added as acute kidney injury (AKI) may affect 60% of ICU patients with up to two-thirds of these patients going on to require kidney replacement therapy (KRT).[15,16]

The Committee suggested for the indications for KRT to be included in line with national agreed requirements (e.g., NDOH Renal programme) as an EML requisite. Input in line with the Renal Society was sought through nephrology experts from Groote Schuur Hospital who provided guidance on the EML package of care to be included in the STG.

An external comment to add Stage 3 acute kidney injury deemed unlikely to resolve in the next few days as an indication for KRT was accepted as large studies,[17,18,19] have shown that KRT can be safely delayed after stage 3 AKI development for a period of time and that KRT will be safely avoided in 40-50% of patients using this strategy. Indication of fluid overload was revised to refractory fluid overload and examples of clinical ureamia were provided (i.e.. gastritis, pericarditis, delirium, seizures) as part of indication for KRT. Carbamazepine and valproic acid were added as additional examples of life-threatening overdoses requiring KRT removal.

Additionally, based on expert renal input the medical terminology for Renal Replacement Therapy (RRT) has been updated to Kidney Replacement Therapy (KRT). Life threatening overdoses are included in the list of indications for KRT. Sustained low-efficiency dialysis (SLED) is included as a modality for KRT and liver failure added as an indication for Continuous Renal Replacement Therapy (CRRT). A warning to avoid using unfractionated heparin, and to use saline flushes instead, if there is risk of bleeding is provided.

Level of Evidence: IVb: Guidelines & Expert Opinion

23.5.1 THROMBOPROPHYLAXIS

The thromboprophylaxis STG was aligned to the Adult Hospital Level Standard Treatment Guidelines - Chapter 2: Blood and Blood Forming Organs Section 2.8: Venous Thrombo-Embolism.

Historically, a medicine evidence review was conducted to review comparative evidence of low molecular weight heparin (LMWH) vs unfractionated heparin (UFH) for the management of venous thromboembolism (VTE) and acute coronary syndromes (ACS)

Refer to the medicine review, LMWH for VTE and ACS (April 2018) below:

LMWH for VTE and ACS - Adult review_A

http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/286-hospital-level-adults

Please note that The Adult Hospital Level Standard Treatment Guidelines - Chapter 2: Blood and Blood Forming Organs is currently under review by NEMLC for the 2022-23 review cycle, and any updates to the STG will result in the thromboprophylaxis critical care STG being reconsidered.

Recommendations: Based on this evidence review, the NEMLC recommended that:

- LMWH preparations be recommended as the preferred therapeutic agent of choice versus UFH for the following indications:

15 Hoste, E.A., Bagshaw, S.M., Bellomo, R., Cely, C.M., Colman, R., Cruz, D.N., Edipidis, K., Forni, L.G., Gomersall, C.D., Govil, D. and Honoré, P.M., 2015. Epidemiology of acute kidney injury in critically ill patients: the multinational AKI-EPI study. Intensive care medicine, 41, pp.1411-1423.oannidis M, Oudemans-van Straaten HM. Clinical review: Patency of the circuit in continuous renal replacement therapy. Crit Care. 2007;11(4):218. doi: 10.1186/cc5937. PMID: 17634148; PMCID: PMC2206533.

16 Bellomo R, Ronco C. Anticoagulation during CRRT. In: Bellomo R, Baldwin I, Ronco C, Golper T., editors. Atlas of haemofiltration. Sydney: W.B. Saunders; 2002. pp. 63–68.

17 AKIKI Artificial Kidney Initiation in Kidney Injury Study. Available at: https://www.thebottomline.org.uk/summaries/icm/akiki/. Accessed 12th March 2024.

18 IDEAL (Initiating Dialysis Early and Late) Study. Available at: https://www.menzies.utas.edu.au/research/diseases-and-health-issues/research-projects/ideal-study. Accessed 12th March 2024.

19 STARRT (STandard versus Accelerated Initiation of Renal Replacement Therapy in Acute Kidney Injury trial) Study. Available at: https://www.thebottomline.org.uk/summaries/icm/starrt-aki/. Accessed 12th March 2024.

- VTE prophylaxis after major surgery.
- VTE prophylaxis for hospitalised medically ill patients with prolonged immobilization; but that criteria for management with LMWH be clearly defined using an appropriate risk scoring tool.
- Treatment of VTE (from proximal DVT to pulmonary embolism).
- Acute coronary syndromes (unstable angina or non-ST segment elevation MI).

- In renal impairment the dose of LMWH should be reduced based on locally agreed protocols (see Appendix A which describes dosing issues).

Rationale:

- Compared with UFH, LMWH preparations are at least as effective and as safe as classic intravenous heparin therapy and have the advantage of being more convenient to administer.
- The simplified therapy provided by LMWH may allow patients with uncomplicated proximal deep-vein thrombosis to be cared for in an outpatient setting.
- The LMWH have greater convenience in the ability to administer by subcutaneous injection without laboratory monitoring and the possible associated cost reduction resulting from reduced hospital stay and also a lower incidence of heparin-induced thrombocytopenia (HIT).
- LMWHs appear to be as safe and effective as UFH for the treatment of venous thrombosis and pulmonary embolism and at least as safe and effective as UFH for the treatment of patients with unstable angina.

Level of Evidence: I non-inferiority RCTs and Systematic Reviews

Enoxaparin, SC:[20] *Added*

If LMWH is unavailable or contraindicated:
Unfractionated heparin, SC[21]: *Added*

Dose adjustments are suggested in kidney disease[22] and for increased body mass[23].

Please note that The Adult Hospital Level Standard Treatment Guidelines - Chapter 2: Blood and Blood Forming Organs is currently under review by NEMLC for the 2020-23 review cycle, and any updates to the STG will result in the thromboprophylaxis critical care STG being reconsidered.

[20] Low molecular weight heparin (first line option - prophylaxis): National Department of Health: Affordable Medicines, EDPAdult Hospital Level. Medicine Review LMWH vs. UFH for the prophylaxis and treatment of venous thromboembolism and acute coronary syndromes, April 2018. http://www.health.gov.za/
Low molecular weight heparin (first line option - prophylaxis): Junqueira DR, Zorzela LM, Perini E. Unfractionated heparin versus low molecular weight heparins for avoiding heparin-induced thrombocytopenia in postoperative patients. Cochrane Database Syst Rev. 2017 Apr 21;4:CD007557. https://www.ncbi.nlm.nih.gov/pubmed/28431186
Low molecular weight heparin (first line option - prophylaxis): Wein L, Wein S, Haas SJ, Shaw J, Krum H. Pharmacological venous thromboembolism prophylaxis in hospitalized medical patients: a meta-analysis of randomized controlled trials. Arch Intern Med. 2007 Jul 23;167(14):1476-86.https://www.ncbi.nlm.nih.gov/pubmed/17646601
Low molecular weight heparin (first line option - prophylaxis): National Department of Health: Affordable Medicines, EDPAdult

[21] Heparin, SC: Collins R, Scrimgeour A, Yusuf S, Peto R. Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of subcutaneous heparin. Overview of results of randomized trials in general, orthopedic, and urologic surgery. N Engl J Med. 1988 May 5;318(18):1162-73. https://www.ncbi.nlm.nih.gov/pubmed/3283548

[22] Low molecular weight heparin (renal impairment): South African Medicines Formulary. 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

[23] Low molecular weight heparin (morbid obesity): Lalama JT, Feeney ME, Vandiver JW, Beavers KD, Walter LN, McClintic JR. Assessing an enoxaparin dosing protocol in morbidly obese patients. J Thrombolysis. 2015 May;39(4):516-21. http://www.ncbi.nlm.nih.gov/pubmed/25087072
Low molecular weight heparin (morbid obesity): Spinler SA, Inverso SM, Cohen M, Goodman SG, Stringer KA, Antman EM; ESSENCE and TIMI 11B Investigators. Safety and efficacy of unfractionated heparin versus enoxaparin in patients who are obese and patients with severe renal impairment: analysis from the ESSENCE and TIMI 11B studies. Am Heart J. 2003 Jul;146(1):33-41. http://www.ncbi.nlm.nih.gov/pubmed/12851605
Low molecular weight heparin (morbid obesity): Thompson-Moore NR, Wanat MA, Putney DR, Liebl PH, Chandler WL, Muntz JE. Evaluation and Pharmacokinetics of Treatment Dose Enoxaparin in Hospitalized Patients With Morbid Obesity. Clin Appl Thromb Hemost. 2015 Sep;21(6):513-20. http://www.ncbi.nlm.nih.gov/pubmed/25601898
Low molecular weight heparin (morbid obesity): Freeman A, Horner T, Pendleton RC, Rondina MT. Prospective comparison of three enoxaparin dosing regimens to achieve target anti-factor Xa levels in hospitalized, medically ill patients with extreme obesity. Am J Hematol. 2012 Jul;87(7):740-3. http://www.ncbi.nlm.nih.gov/pubmed/22565589

An external comment to include safety in initiation of chemoprophylaxis at 48hrs in severe traumatic brain injury under the general measure section was not accepted as all scenarios are not being outlined in the STG i.e. one condition not singled out.

Kidney disease and body mass index are noted as examples of where dose modification requirements of enoxaparin are required.

23.5.2 ANAEMIA IN CRITICAL CARE

Red Cell Transfusions[24]: *Added to the STG*. Aligned to *Chapter 2: Blood and Blood Forming Organs*

Broad steps to minimize anaemia in critical care are included. Under general measures transfusion triggers for the non-bleeding and bleeding patient are outlined[25].

Non-transfusion alternatives such as cell-salvage, if available, are recommended to reduce the need for red blood cell transfusions.

Caution is provided regarding intravenous iron and erythropoietin specifically that intravenous iron does not appear to reduce transfusion requirements or improve patient outcomes in the critically ill and should not be used; and that erythropoietin has minimal effect on transfusion requirements, does not improve patient outcomes and may be associated with adverse effects including thrombosis, and should not be used in the general critically ill patient. An external comment to consider adding erythropoietin as an option in the Jehovah Witness patient was not added as the indications for erythropoietin were not provided for all scenarios.

23.5.3 THROMBOCYTOPAENIA AND PLATELET DYSFUNCTION IN CRITICAL CARE

Platelet Transfusions: *Added to the STG*. Aligned to *Chapter 2: Blood and Blood Forming Organs*

A brief description, common causes of thrombocytopenia, general measures and indications[26] for platelet transfusions are provided in the STG. A platelet count (s) of greater than and equal to (≤) 10 x 10^9/L was revised to less than (<) 10 x 10^9/L and listed as an acceptable alternative if the patient is not septic, not bleeding, and has a slow decline in platelet count.

Level of Evidence: RCT: Moderate certainty evidence - IIIb

Special situations including heparin-induced thrombocytopenia and aspirin and clopidogrel induced bleeding are outlined.

Thromboelastography (TEG) is available at regional hospitals and is suggested as an example of viscoelastic testing if available.

[24] Red Cell Transfusions: Wise RD, de Vasconcellos K, Gopalan PD, Ahmed N, Alli A, Joubert I, Kabambi KF, Mathiva LR, Mdladla N, Mer M, Miller M, Mrara B, Omar S, Paruk F, Richards GA, Skinner D, von Rahden R. Critical Care Society of Southern Africa adult patient blood management guidelines: 2019. Round-table meeting, CCSSA Congress, Durban, 2018. South Afr J Crit Care 2020;36(1):2-19. https://doi.org/10.7196/SAJCC.2020.v36i1.440.

[25] Wise RD, de Vasconcellos K, Gopalan PD, Ahmed N, Alli A, Joubert I, Kabambi KF, Mathiva LR, Mdladla N, Mer M, Miller M, Mrara B, Omar S, Paruk F, Richards GA, Skinner D, von Rahden R. Critical Care Society of Southern Africa adult patient blood management guidelines: 2019. Round-table meeting, CCSSA Congress, Durban, 2018. South Afr J Crit Care 2020;36(1):2-19. https://doi.org/10.7196/SAJCC.2020.v36i1.440.

[26] van Baarle FLF, van de Weerdt EK, van der Velden WJFM, Ruiterkamp RA, Tuinman PR, Ypma PF, van den Bergh WM, Demandt AMP, Kerver ED, Jansen AJG, Westerweel PE, Arbous SM, Determann RM, van Mook WNKA, Koeman M, Mäkelburg ABU, van Lienden KP, Binnekade JM, Biemond BJ, Vlaar APJ. Platelet Transfusion before CVC Placement in Patients with Thrombocytopenia. N Engl J Med. 2023 May 25;388(21):1956-1965. doi: 10.1056/NEJMoa2214322. PMID: 37224197.

Critical care society of Southern Africa. Guidelines for the provision of critical care in South Africa. July 2022. https://criticalcare.org.za/wp-content/uploads/2022/07/CCSSA-guidelines-final.pdf

23.5.4 PLASMA TRANSFUSION

In practice Freeze Dried Plasma (FDP) and Fresh Frozen Plasma (FFP) are used interchangeably as they are considered to be equivalent, and recommended as such in the Adult Hospital Level Standard Treatment Guidelines - Chapter 2: Blood and Blood Forming Organs Chapter for various bleeding indications. A 2016 NDOH cost summary[27] showed that FDP is less expensive than FFP due to the favourable acquisition cost and logistical advantages. However, at higher doses, FDP is cost neutral when compared to FFP.

Current, 2023 prices, confirm that per unit (ml) FDP is less expensive than FFP.

Product	Price Including VAT	Volume	Price per ml	Reference
Lyophilised Plasma (Bioplasma)*	R1424.05	200ml	R7,12	Medicines Health Product List – June 2023
Fresh Frozen Plasma-Donor Retested	R1903.48	260ml	R7,32	SANBS - State Patients Pricelist – 1 April 2023 – 31 March 2024

*FDP

FDP is recommended as the plasma product of choice, and FFP to appear on the therapeutic interchange database as an alternative for situations of stock shortage.

For prophylaxis or therapy:

- FDP, IV:[28] *Added* to *the STG. Aligned to Chapter 2: Blood and Blood Forming Organs*

Empiric use in large volume blood transfusion:

- FDP, IV:[29] *Added to the STG. Aligned to Chapter 2: Blood and Blood Forming Organs*

23.5.5 COAGULATION FACTORS

In the Adult Hospital Level Standard Treatment Guidelines - Chapter 2: Blood and Blood Forming Organs Chapter Cryoprecipitate, IV is recommended for the management of hypofibrinogenaemia (Section 2.7: Acquired Coagulation Defects); and added as a coagulation option in the adult critical care chapter.

Cryoprecipitate, IV: *Added*

A collaborative project between the South African National Blood Service and Western Cape Blood Services has resulted in the publication of a single guideline[30], which recommends 1 unit per 10 kg total body weight.
For all other coagulation factors; the chapter is aligned with a cross reference to the Adult Hospital Level Standard Treatment Guidelines - Chapter 2: Blood And Blood Forming Organs.

27 National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Fresh frozen plasma (FFP) vs lyophilized plasma (FDP), 21 January 2016. http://www.health.gov.za/. https://accessmedicine.mhmedical.com/content.aspx?bookid=1944&sectionid=143516493

28 Plasma: Wise RD, de Vasconcellos K, Gopalan PD, Ahmed N, Alli A, Joubert I, Kabambi KF, Mathiva LR, Mdladla N, Mer M, Miller M, Mrara B, Omar S, Paruk F, Richards GA, Skinner D, von Rahden R. Critical Care Society of Southern Africa adult patient blood management guidelines: 2019. Round-table meeting, CCSSA Congress, Durban, 2018. South Afr J Crit Care 2020;36(1):2-19. https://doi.org/10.7196/SAJCC.2020.v36i1.440.

29 Plasma: Wise RD, de Vasconcellos K, Gopalan PD, Ahmed N, Alli A, Joubert I, Kabambi KF, Mathiva LR, Mdladla N, Mer M, Miller M, Mrara B, Omar S, Paruk F, Richards GA, Skinner D, von Rahden R. Critical Care Society of Southern Africa adult patient blood management guidelines: 2019. Round-table meeting, CCSSA Congress, Durban, 2018. South Afr J Crit Care 2020;36(1):2-19. https://doi.org/10.7196/SAJCC.2020.v36i1.440.

30 WCBS. Clinical guidelines - Western Cape Blood Service [Internet]. Western Cape Blood Service - Do something remarkable. 2020 [cited 2023 Nov 22]. Available from: https://www.wcbs.org.za/clinical-information/clinical-guidelines/

For Warfarin Poisoning a cross reference is provided to Section 19.9 Anticoagulant (Warfarin And Rodenticide Superwarfarin) Poisoning in the Adult Hospital Level – Chapter 19: Poisonings.

23.5.6 ANTIFIBRINOLYTIC MEDICATION

Severe trauma: (Give within 3 hours of the injury)
Tranexamic acid, IVI[31]: *Added*

The section on antifibrinolytic medication is aligned to the Adult Hospital Level Standard Treatment Guidelines - Chapter 20: Emergencies and Injuries where Tranexamic acid IV, 1gram is infused over 10 minutes for massive transfusion followed with IV infusion, 1 g, over 8 hours. Because the benefit is greatest if initiated in the 1st hour and initiation of tranexamic acid more than 3 hours after the initial insult may be harmful instruction to give tranexamic acid within 3 hours of injury is also provided in the adult critical care chapter. Following external comment, the word trauma under the note section of the STG was replaced with "insult" as tranexamic acid is not only indicated in bleeding due to traumatic events.

Bleeding postpartum obstetric patients
Tranexamic acid, IVI: *Added*

If bleeding persists (after 30 minutes)
Tranexamic acid, IVI: *Added*

Medicine treatment for Bleeding postpartum obstetric patients in the adult critical chapter is aligned to the Adult Hospital Level Standard Treatment Guidelines - Chapter 6: Obstetrics (for postpartum bleeding) where it is used for the indication[32,33]

23.5.7 MASSIVE TRANSFUSION PROTOCOL (MTP)

Major hemorrhage is a common problem in critical care. Therefore, to close off this subchapter in the STG a massive transfusion protocol is outlined. A definition, aspects of a protocol and a standard protype example of a protocol approach is provided. Following external comment, the timing in the definition of massive transfusion as replacement of >50% of blood volume in 3 hours (>5 units in 3 hours) was confirmed and referenced[34].

The section is aligned to the Adult Hospital Level Standard Treatment Guidelines – Chapter 20: Emergencies and injuries for the massive transfusion pack to include 1 mega-unit of platelets - equivalent to 6 pooled donor units.

23.6 NEURO-PSYCHOLOGICAL SUPPORT

Specific areas of neuropsychological support are covered in the chapter. A brief introductory statement related to pain management is provided in this section.

31 Tranexamic acid, IV: CRASH-2 trial collaborators: Shakur H et al. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebocontrolled trial. Lancet. 2010; 376:23-32. https://www.ncbi.nlm.nih.gov/pubmed/20554319 Tranexamic acid: Roberts I et al. The importance of early treatment with tranexamic acid in bleedingtrauma patients: an exploratory analysis of the CRASH-2 randomised controlled trial. Lancet. 2011; 377:1096-1101.
Tranexamic acid: Ker K, Roberts I, Shakur H, Coats TJ. Antifibrinolytic drugs for acute traumatic injury. Cochrane Database Syst Rev. 2015 May 9;(5):CD004896.
Ker K, Roberts I, Shakur H, Coats TJ. Antifibrinolytic drugs for acute traumatic injury. Cochrane Database Syst Rev. 2015 May 9;(5):CD004896. https://www.ncbi.nlm.nih.gov/pubmed/25956410
32 Tranexamic acid, IV: WOMAN Trial Collaborators. Effect of early tranexamic acid administration on mortality, hysterectomy, and other morbidities in women with post-partum haemorrhage (WOMAN): an international, randomised, double-blind, placebo-controlled trial. Lancet 2017; 6736(17)30638-4. https://www.ncbi.nlm.nih.gov/pubmed/28456509
33 Tranexamic acid, IV: National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Tranexamic acid, IV, for management of post partum haemmhorhage in pregnant women, 11 October 2017. http://www.health.gov.za/
34 Shah A, Kerner V, Stanworth SJ, Agarwal S. Major haemorrhage: past, present and future. Anaesthesia. 2023 Jan;78(1):93-104. doi: 10.1111/anae.15866. Epub 2022 Sep 12. PMID: 36089857; PMCID: PMC10087440

23.6.1 PAIN MANAGEMENT

A description of pain management and an example of a pain assessment tool, specific to intensive care, is provided. The Behavioural Pain Scale[35] tool includes compliance with mechanical ventilation specific to ICU care.

Paracetamol IV: *Added*

In July 2015, intravenous (IV) paracetamol was reviewed by the Adult Hospital Level (AHL) Expert Review Committee (ERC) for the indication "Analgesia during the perioperative period"[36]. The purpose of this review was to update the previous reviews on IV paracetamol in order to provide additional evidence to confirm the efficacy and safety of IV paracetamol in the selected indications described above and in comparison, to NSAIDs and opioids. In summary, the review concluded that IV paracetamol can provide safe and efficacious analgesia in trauma patients, the perioperative period and for patients with renal colic, with a safety profile superior to NSAIDs and opioids[36].
The review was presented to the National Essential Medicines List Committee (NEMLC) in October 2015. NEMLC did not recommend paracetamol IV for this indication due to affordability of paracetamol.[37]

In June 2022, the Paediatric Hospital Level ERC also concluded a medicine review for Intravenous Paracetamol for the treatment of peri-operative pain in children where oral route cannot be used.[38] NEMLC recommended that paracetamol IV be included at paediatric hospital level for the management of pain reserved for paediatric patients who cannot receive oral paracetamol, i.e. those with gastrointestinal pathology causing poor absorption or not allowing for feeding.[39] Intravenous paracetamol was found to be less costly than the listed alternative (rectal paracetamol). Paracetamol IV was also approved for the Paediatric Hospital Level Pain Chapter in situations where oral cannot be used.[40]

In July 2023, NEMLC aligned to the paediatric hospital standard treatment guidelines approving paracetamol IV for adult hospital level critical care use in special circumstances as follows:

NEMLC Recommendation: 20 July 2023
NEMLC recommended IV paracetamol for a maximum treatment period of 24 hours; for adult intensive care unit (ICU)/high care ward (HCW) patients, who are nil per mouth. The prescription to be initiated by a specialist; and any extension of treatment to be motivated for and authorised by a medical doctor. The approved indication is recommended specifically for adult ICU/HCW patients who cannot take oral medicines; and safely receive perioperative opioids and/or NSAIDS.

Post-meeting electronic discussion
To ensure equitable access NEMLC recommends the approved indication be expanded to include patients who are candidates for or awaiting admission to ICU/HCW.

NEMLC Recommendation: 10 August 2023 (accepted electronically)
NEMLC recommends IV paracetamol for an initial treatment period of 24 hours only in adult intensive care unit (ICU)/ high care ward (HCW) patients, or those who are candidates for, or awaiting admission to ICU/HCW, who are nil per mouth. The prescription is to be initiated by a specialist, and any extension of IV paracetamol treatment beyond 24 hours is to be authorised by a specialist. The approved indication is specifically for adults who cannot take oral medicines or safely receive perioperative parenteral opioids and/or NSAIDS.

Commonly used analgesics in the ICU
Morphine, IV: *Added*

35 Sessler CN, Gosnell MS, Grap MJ, Brophy GM, O'Neal PV, Keane KA, et al. The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients. Am J Respir Crit Care Med. 2002 Nov 15;166(10):1338–44
36 National Department of Health: Affordable Medicines, EDP- Adult. Medicine Review: Intravenous Paracetamol, Analgesia during the perioperative period, 18 July 2015. http://www.health.gov.za/
37 National Essential Medicines List Committee (NEMLC). Minutes of the meeting. 8 October 2015.
38 National Department of Health: Affordable Medicines, EDP- Paediatric. Medicine Review: Intravenous Paracetamol for the treatment of peri-operative pain in children where oral route cannot be used, June 2022. http://www.health.gov.za/
39 NDOH. Paediatric Hospital Level Standard Treatment Guidelines and Essential Medicines List. 2022. Chapter 20. Pain Control.
40 NDOH. Paediatric Hospital Level Standard Treatment Guidelines and Essential Medicines List. 2022. Chapter 22. Anaesthetics.

Fentanyl, IV: *Added*
Tramadol, IV: *Added*
Ketamine, IV: *Added*

Aligned to the Adult Hospital Level Standard Treatment Guidelines Chapter 12 Anesthesiology and Intensive Care[41] and previous Chapter 13 sedation [42], morphine[43], fentanyl[44,45], ketamine IV[46,47,48] and tramadol IV[49,50] were added to the STG as commonly used IV analgesics in the ICU. The lower dosage range for ketamine of 0.05-0.4 mg/kg/hour was accepted specifically for the ICU setting compared to the higher dosage recommended for emergency care (0.5–1 mg/kg/hour). However, an external comment that higher doses of ketamine IV may be required in polytrauma and traumatic brain injury was accepted and included in the example table described on commonly used analgesics in the ICU (see regional anesthesia).

A brief section on regional anaesthesia is provided and an example of table on commonly used analgesics in the ICU included.

To promote rational prescribing, and reduce the risk for drug interactions, toxicity, and unnecessary resource expenditure with irrational prescribing, the pain medicines were categorised as simple analgesic, weak opioids, strong opioids and adjunctive analgesia and a simple guidance statement provided for prescribing in combination.

An external comment based on more recent clinical experience to administer paracetamol IV as an infusion over 30min to avoid hypotensive reaction was not accepted for inclusion as the current recommendation is aligned to standardized standard treatment guideline dosing.

23.6.2 SEDATION

Adult critical care replaces the previous sedation chapter. A brief introduction and ICU specific Richmond agitation sedation scale (RASS)[51] is provided as an example. A note to exclude delirium before commencing with routine sedation is in included in the STG.

The treatment section is designed not to be stipulative but allow clinicians to be guided by the situation they are treating.

Commonly used sedation medicines in the ICU
Haloperidol, IM: *Not added*

Haloperidol injection supply has been erratic in South Africa.

Propofol, IV: *Added*
Midazolam, IV: *Added*
Lorazepam, IV: *Added*

41 National Department of Health: National Department of Health: Essential Drugs Programme. Adult Hospital level STGs and EML. Chapter 12: Anaesthesiology And Intensive Care..
42 National Department of Health: National Department of Health: Essential Drugs Programme. Adult Hospital level STGs and EML. Chapter 23: Sedation.
43 Morphine, IV (dosing): South African Medicines Formulary. 12th Edition. Division of Clinical Pharmacology. University of Cape Town, 2016.
44 Fentanyl, IV: The South African Society of Anaesthesiologists. South African Acute Pain Guidelines. SAJAA 2009;15(6):1-120. http://www.sasaweb.com/content/images/SASA_Pain_Guidelines.pdf
45 Fentanyl, IV: Scholz J, Steinfath M, Schulz M. Clinical pharmacokinetics of alfentanil, fentanyl and sufentanil. An update. Clin Pharmacokinet. 1996 Oct;31(4):275-92. http://www.ncbi.nlm.nih.gov/pubmed/8896944
46 Ketamine, IV: McNicol ED, Schumann R, Haroutounian S. A systematic review and meta-analysis of ketamine for the prevention of persistent post-surgical pain. Acta Anaesthesiol Scand. 2014 Nov;58(10):1199-213. http://www.ncbi.nlm.nih.gov/pubmed/25060512
47 Ketamine, IV: Brinck EC, Tiippana E, Heesen M, Bell RF, Straube S, Moore RA, Kontinen V. Perioperative intravenous ketamine for acute postoperative pain in adults. Cochrane Database Syst Rev. 2018 Dec 20;12:CD012033. https://www.ncbi.nlm.nih.gov/pubmed/30570761
48 Ketamine, IV: Brinck EC, Tiippana E, Heesen M, Bell RF, Straube S, Moore RA, Kontinen V. Perioperative intravenous ketamine for acute postoperative pain in adults. Cochrane Database Syst Rev. 2018 Dec 20;12:CD012033. https://www.ncbi.nlm.nih.gov/pubmed/30570761
49 Tramadol, IV: Houmes RJ, Voets MA, Verkaaik A, Erdmann W, Lachmann B. Efficacy and safety of tramadol versus morphine for moderate and severe postoperative pain with special regard to respiratory depression. Anesth Analg. 1992 Apr;74(4):510-4. http://www.ncbi.nlm.nih.gov/pubmed/1554117
50 Tramadol, IV: National Department of Health, Essential Drugs Programme. Medicine review: Tramadolol, IV July 2015. http://health.gov.za/
51 Khan BA, Perkins AJ, Gao S, Hui SL, Campbell NL, Farber MO, et al. The CAM-ICU-7 Delirium Severity Scale: A Novel Delirium Severity Instrument for Use in the Intensive Care Unit. Crit Care Med. 2017 May;45(5):851–7.

Propofol IV[52], midazolam IV and lorazepam IV added as commonly used sedation medicines in the ICU as per previous sedation chapter[53].

An external comment to consider outlining a stepwise approach instead of providing the commonly used sedatives in the ICU in a table format was not accepted as a formal stepwise approach does not exist and any of the sedative options listed could be used to initiate sedation.

It was raised through external comment that the South African Medicines Formulary (SAMF) recommends higher maintenance doses of 4-12 mg/kg/h for propofol. The lower dose of propofol was retained; and following external comment, the units for the low maintenance dose of propofol as a commonly used sedative in the ICU was corrected from ug/kg/min to mg/kg/min and referenced[54].

23.6.3 DELIRIUM IN CRITICAL CARE

Delirium in critical care is a specific entity but finalized ensuring alignment to the Adult Hospital Level Standard Treatment Guidelines - Chapter 15: Mental Health Care.

The STG covers the types of delirium, risk factors, clinical presentation and an ICU specific tool, the Confusion assessment method (CAM)-ICU-7 screening tool[55], and general management strategies to reduce delirium.

Following external comment, blood transfusions was moved from the precipitating factors for delirium to the risk factor list as blood transfusions may not necessarily precipitate delirium but rather be associated with delirium due to underlying severity of illness.

For medicine management cross references are provided to the Emergencies and Injuries section 20.8: Delirium, Substance Use section: 15.1 Aggressive Disruptive Behaviour in Adults and for alcohol withdrawal 15.8.1: Alcohol Withdrawal Delirium (Delirium Tremens).

23.6.4 MOOD DISORDERS

For completeness, for neuropsychological, mood disorders in ICU are included. A cross reference to Adult Hospital Level Standard Treatment Guidelines - Chapter 15: Mental Health Care; section 15.3: Mood Disorders is provided.

23.6.5 SEIZURES

For seizures a cross reference to the Adult Hospital Level Standard Treatment Guidelines - Chapter 14: Neurological Disorders; section 14.4: Epilepsy is provided.

23.6.6 INTRACRANIAL PRESSURE MANAGEMENT

For intracranial pressure management a cross reference to the Adult Hospital Level Standard Treatment Guidelines - Chapter 14: Neurological Disorders; section 14.12.2: Brain Oedema Due to Traumatic Injury is provided.

52 The South African Society of Anaesthesiologists. South African Society of Anaesthesiologists Sedation Guidelines, 2015. South Afr J AnaesthAnalg 2015;21(2)S1-S36.http://www.sasaweb.com/content/images/SAJAA_V21N2_1665_Sedation_Guideline.pdf
South African Medicines Formulary. 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.
Ostermann ME, Keenan SP, Seiferling RA, Sibbald WJ. Sedation in the intensive care unit: asystematic review. JAMA. 2000 Mar 15;283(11):1451-9. http://www.ncbi.nlm.nih.gov/pubmed/10732935
53 National Department of Health: National Department of Health: Essential Drugs Programme. Adult Hospital level STGs and EML. Chapter 23: Sedation.
54 Propofol. https://www.drugs.com/dosage/propofol.html
55 Khan BA, Perkins AJ, Gao S, Hui SL, Campbell NL, Farber MO, Chlan LL, Boustani MA. The Confusion Assessment Method for the ICU-7 Delirium Severity Scale: A Novel Delirium Severity Instrument for Use in the ICU. Crit Care Med. 2017 May;45(5):851-857. doi: 10.1097/CCM.0000000000002368. PMID: 28263192; PMCID: PMC5392153.

23.7 GASTRO-INTESTINAL SUPPORT

Gastro-intestinal support includes common critical care issues of nutrition, stress ulcer prophylaxis, regurgitation and aspiration, diarrhoea, liver support and specific pathologies including acute severe pancreatitis, acute cholecystitis, and abdominal compartment syndrome.

23.7.1 NUTRITION

In a brief section on nutrition the STG outlines that critically ill patients are catabolic and need careful management of their nutritional requirements including commencement of timely nutritional support. Oral, enteral and parenteral routes for feeding are suggested depending on the clinical context. The STG also reiterates that the choice of feed should meet the patient's-specific fluid need and caloric, and protein requirements. Support from a dietitian is suggested.

An external comment was noted that TPN is used in ICU and therefore guidance should be provided. Referral criteria included in the STG states that a dietician should be consulted. Specific indications for which a dietician should be consulted were not included as it is outside the scope of the STGs but the referral to a dietitian would include guidance on when to initiate TPN, how to titrate TPN, monitor and wean the patient off TPN.

Following external comment, links to the NDOH enteral[56] and parenteral[57] nutrition practice guidelines for adults was added and referenced. Additionally, a cross reference is provided to section 12.13.1: Nutritional support and a statement added to promote oral feed initiation once safe to do so as risk of adverse outcomes increases with overuse of enteral/parenteral feeding.

23.7.2 STRESS ULCER PROPHYLAXIS

Pantoprazole, IV: *Added*

An intravenous proton pump inhibitor (PPI), pantoprazole, was added for stress ulcer prophylaxis in line with the paediatric hospital level NEMLC approved decision for use of intravenous PPIs in patients where oral medication cannot be taken (Chapter 1: Emergencies and Trauma)[58]. This recommendation is in line with the Tertiary[59] inclusion of intravenous PPIs in cases where oral cannot be taken.

Following external comment, a description of stress related mucosal injury/stress ulcers is provided. [60]

An external comment that prolonged PPI use adds to the risk of hospital acquired pneumonia was accepted.

23.7.3 REGURGITATION AND ASPIRATION

Following external comment, a brief description for regurgitation and aspiration was added.

General advice and measures are provided for the ICU setting including cautions regarding regurgitation of gastric contents leading to ventilation associated pneumonia, need for patients to be nursed at 30-45 degrees with their heads up, reminder for use of nasogastric tubes and the importance of maintaining oropharyngeal hygiene.

Under general measures an external comment to consider removing pH analysis if no longer used commonly in clinical practice, was not accepted as it is may still be used. However, X-ray to confirm placement of nasogastric tube

56 National Department of Health. Directorate: Nutrition. National Enteral Nutrition Practice. Guidelines for Adults. 2016. http://www.health.gov.za/.
57 National Department of Health. Directorate: Nutrition. National Parenteral Nutrition Practice. Guidelines for Adults. 2016. http://www.health.gov.za/.
58 NDOH. Paediatric Hospital Level Standard Treatment Guidelines and Essential Medicines List. 2022. Chapter 1: Emergencies and Trauma.
59 Tertiary and Quaternary Committee Intravenous Proton Pump Inhibitors (IV PPIs) recommendation. March 2023
60 Stress Ulcer Prophylaxis: Mohebbi L, Hesch K. Stress ulcer prophylaxis in the intensive care unit. Proc (Bayl Univ Med Cent). 2009 Oct;22(4):373-6. doi: 10.1080/08998280.2009.11928562. PMID: 21240306; PMCID: PMC2760176.
Bardou, M., Quenot, JP. & Barkun, A. Stress-related mucosal disease in the critically ill patient. Nat Rev Gastroenterol Hepatol 12, 98–107 (2015). https://doi.org/10.1038/nrgastro.2014.235

is now listed before PH analysis. A comment to consider adding guidance on imaging to confirm suspected aspiration was accepted and instruction on obtaining Chest X-ray to confirm suspected aspiration provided.

23.7.4 DIARRHOEA

The STG on diarrhoea is aligned with a cross reference to Section 1.3 (Diarrhoea) in the Adult Hospital Level Standard Treatment Guidelines - Chapter 1: Alimentary tract.

Furthermore, a cross reference is provided to section 1.3.4 (Clostridium difficile diarrhoea in the Adult Hospital Level Standard Treatment Guidelines - Chapter 1: Alimentary tract.

Following external comment, a description of diarrhoea, with specific contextualization to a critically ill population was added[61.]

Following external comment, the term Clostridium difficile diarrhoea was revised to Clostridium (Clostridioides) difficile diarrhoea.

23.7.5 LIVER SUPPORT

Advanced liver support is usually treated at a higher level of care in terms of for example potential for liver transplants, therefore for this STG general supportive measures are ensured with a cross reference to the existing general supportive measures provided in section 1.2.2: Liver Failure, Acute in the Adult Hospital Level Standard Treatment Guidelines - Chapter 1: Alimentary tract.

23.7.6. ACUTE SEVERE PANCREATITIS

The STG on acute severe pancreatitis is aligned with a cross reference to section 1.16: pancreatitis, acute in the Adult Hospital Level Standard Treatment Guidelines - Chapter 1: Alimentary tract.

Following external comment, a brief description of acute, severe pancreatitis was added[62,63].

23.7.7 ACUTE CHOLECYSTITIS

The STG on acute cholecystitis is aligned with a cross reference to section 1.27 Cholecystitis, acute, and cholangitis, acute in the Adult Hospital Level Standard Treatment Guidelines - Chapter 1: Alimentary tract.

23.7.8 ABDOMINAL COMPARTMENT SYNDROME

In the STG methods to relieve intra-abdominal pressure in abdominal compartment syndrome associated with severe critical illness and multi-organ failure are provided. The methods to relieve intra-abdominal pressure include nasogastric tube, urinary catheter, drainage of intra-abdominal collections, appropriate positioning, sedation, analgesia, muscle relaxation (if ventilated), and to consider surgical consult for decompression.

61 Dionne JC, Mbuagbaw L. Diarrhea in the critically ill: definitions, epidemiology, risk factors and outcomes. Curr Opin Crit Care. 2023 Apr 1;29(2):138-144. doi: 10.1097/MCC.0000000000001024. Epub 2023 Feb 22. PMID: 36825593.

62 Finkenstedt, A., Jaber, S. & Joannidis, M. Ten tips to manage severe acute pancreatitis in an intensive care unit. Intensive Care Med 49, 1127–1130 (2023). https://doi.org/10.1007/s00134-023-07121-9

63 Leppäniemi A, Tolonen M, Tarasconi A, Segovia-Lohse H, Gamberini E, Kirkpatrick AW, Ball CG, Parry N, Sartelli M, Wolbrink D, van Goor H, Baiocchi G, Ansaloni L, Biffl W, Coccolini F, Di Saverio S, Kluger Y, Moore E, Catena F. 2019 WSES guidelines for the management of severe acute pancreatitis. World J Emerg Surg. 2019 Jun 13;14:27. doi: 10.1186/s13017-019-0247-0. PMID: 31210778; PMCID: PMC6567462

Following external comment, a description of abdominal compartment syndrome was added.[64,65,66]

23.8 METABOLIC AND ENDOCRINE SUPPORT

The committee acknowledge the challenge in defining the subsection on metabolic and endocrine support. Ultimately the STGs were restricted to a few common endocrine dysfunctions including thyroid disorders, adrenal issues, hypoglycaemia and hyperglycaemia.

23.8.1 THYROID DISORDERS IN CRITICALLY ILL PATIENTS

The introduction to thyroid disorders covers general comments related to thyroid disorders in the critically ill patient and thereafter focuses on specific thyroid problems e.g., sick euthyroid syndrome and hyperthyroidism.

Following external comment, the statement that thyroid function assessment is not routinely recommended and should be guided by clinical history and evaluation is now included in a caution box.

23.8.1.1 SICK EUTHYROID SYNDROME

A brief description of sick euthyroid syndrome is provided in the STG.

23.8.1.2 HYPERTHYROIDISM

The STG on hyperthyroidism is aligned with a cross reference to section 8.18: Hyperthyroidism in the Adult Hospital Level Standard Treatment Guidelines - Chapter 8: Endocrine System.

23.8.1.3 THYROID CRISIS

As an emergency thyroid crisis is covered in detail as follows"

Supportive measures: Hemodynamic
Atenolol, oral (administered via nasogastric tube): *Added*

Historically, Atenolol, oral was retained as the example of the beta-blocker group aligned with section 8.18.1: Graves' hyperthyroidism.[67]
Oral atenolol is not a suitable option in an emergency situation for the treatment of a thyroid crisis in a patient who cannot swallow. Labetalol IV is commercially available in SA, however due to the undesirable alpha1-receptor antagonistic activity it is considered unsuitable for the critical care environment. It was further noted that IV esmolol (SAHPRA registered but non EML), which is a short acting titratable, is a viable option to stabilize patients until oral atenolol can be used. However, the Committee recommended a medicine review regarding use of a pure IV beta blocker (not an alpha and beta agent) in thyroid crisis, as the chapter remains a work in progress and is developed further.

In the absence of an IV formulation of atenolol, the Committee recommended oral atenolol via a nasogastric tube.

Hyperthermia:
Balanced Salt Solution, IV: *Added as per therapeutic interchange database*

[64] Harris, H. & Smith, C. J. (2013). Understanding abdominal compartment syndrome. Nursing Critical Care, 8 (3), 45-47. doi: 10.1097/01.CCN.0000429385.10473.7f.

[65] Rajasurya V, Surani S. Abdominal compartment syndrome: Often overlooked conditions in medical intensive care units. World J Gastroenterol. 2020 Jan 21;26(3):266-278. doi: 10.3748/wjg.v26.i3.266. PMID: 31988588; PMCID: PMC6969886.

[66] Bailey, J., Shapiro, M.J. Abdominal compartment syndrome . Crit Care 4, 23 (2000). https://doi.org/10.1186/cc646

67 NEMLC 2019 Report. South African Adult Hospital Level Essential Medicines List Chapter 8: Endocrine Disorders NEMLC Recommendations For Medicine Amendments (2017 - 2019)

Paracetamol, oral: *Added*

Balanced salt solutions, IV, and paracetamol, oral, added as antipyretic management for hyperthermia.

A cross reference is provided to the Adult Hospital Level Chapter 8: Endocrine System: Section 8.18.5: Thyroid Crisis.

23.8.1.4 HYPOTHYROIDISM

The STG on hypothyroidism is aligned with a cross reference to section 8.11: Hypothyroidism in the Adult Hospital Level Standard Treatment Guidelines - Chapter 8: Endocrine System.

23.8.1.5 MYXOEDEMA COMA

Following external comment, a description of myxoedema coma was added.[68,69]

Hydrocortisone IV: *Added*

Levo-thyroxine IV: *Not Added*

Levothyroxine (T4), oral (administered via nasogastric tube): *Added*

Levo-thyroxine IV is commercially not available in the country. Historically, Levothyroxine, oral, 100 mcg daily is recommended on the Adult Hospital Level Standard Treatment Guidelines for Hypothyroidism[70]. In the absence of Levo-thyroxine IV, the Committee recommended as pragmatic guidance oral thyroxine for administration through nasogastric tube for the management of myxoedema coma. A lower dose for maintenance therapy (100 mcg daily) is usually suggested. Lower doses may also be beneficial for older patients and those at risk of cardiac complications. The dosing was aligned to the South African Medicines Formulary[71]. In light of higher doses being used in clinical practice a recommendation was made to consider a prioritization for review of levothyroxine dosing in myxoedema coma in the next review cycle.

Hydrocortisone added in line with expert opinion and guidelines[72].

23.8.2 ADRENAL INSUFFICIENCY

The STG on adrenal insufficiency management is aligned with a cross reference to section 8.2: Adrenal Insufficiency (Addison Disease) in the Adult Hospital Level Standard Treatment Guidelines - Chapter 8: Endocrine System.

Following external comment, a description of adrenal insufficiency was added.

23.8.2.1 RELATIVE ADRENAL INSUFFICIENCY (RAI)

The STG provides a description of the transient disproportionate reduction of glucocorticoids in relation to the severity of stress in relative adrenal insufficiency (RAI) with a cross reference to septic shock STG in the chapter where RAI prevalence is high.

68 Acharya R, Cheng C, Bourgeois M, Masoud J, McCray E. Myxedema Coma: A Forgotten Medical Emergency With a Precipitous Onset. Cureus. 2020 Sep 16;12(9):e10478. doi: 10.7759/cureus.10478. PMID: 33083180; PMCID: PMC7567317..
69 Mohsen. Myxedema Coma or Crisis: Practice Essentials, Pathophysiology, Epidemiology [Internet]. Medscape.com. Medscape; 2023 [cited 2023 Nov 17]. Available from: https://emedicine.medscape.com/article/123577-overview.
70 National Department of Health: National Department of Health: Essential Drugs Programme. Adult Hospital level STGs and EML. Chapter 8: Endocrine System.
71 South African Medicines Formulary. 14th Edition. Division of Clinical Pharmacology. University of Cape Town. 2022
72 Jonklaas J, Bianco AC, Bauer AJ, Burman KD, Cappol AR, Celi FS, Cooper DS, Kim BW, Peeters RP, Rosenthal MS, Sawka AM; American Thyroid Association Task Force on Thyroid Hormone Replacement. Guidelines for the treatment of hypothyroidism: prepared by the American thyroid association task force on thyroid hormone replacement. Thyroid. 2014 Dec;24(12):1670-751. doi: 10.1089/thy.2014.0028. PMID: 25266247; PMCID: PMC4267409.

23.8.2.2 ADDISONIAN CRISIS

Steroid replacement[73]

Hydrocortisone, IV:[74] *Added*

Steroid replacement for Addisonian crisis is recommended in line with Adrenal Insufficiency (Addison disease), section 8.2 in the Adult Hospital Level Standard Treatment Guidelines - Chapter 8: Endocrine System where hydrocortisone is recommended for acute crisis, for chronic maintenance therapy and during times of severe "stress" i.e., acute illness, surgery, trauma, etc. The recommendation in the STG is an adaptation of the European Society of Endocrinology Guidelines, adapted for pragmatic purposes.

Level of Evidence: IV Guidelines

23.8.3 HYPOGLYCEMIA

If awake and alert:

Glucose, oral: *Added*

If obtunded:

Glucagon[75], SC: *Added*

Glucagon, IM was previously deleted from the EML for management of hypoglycaemia at secondary level of care. A systematic review and meta-analysis by Boido et al (2015)76 showed that in comparison to IV dextrose, glucagon had frequent reports of being inefficacious; OR 0.53 (95% CI 0.20 to 1.42) favouring the use of dextrose. The authors concluded that a second dose should be administered if no other remedies are available and if the patient does not respond within 15 minutes. Furthermore, if glycogen levels are depleted as might be the case in severe starvation, adrenal insufficiency or alcoholic hypoglycaemia, glucagon might not be effective in raising blood glucose levels.
Level of evidence: I Systematic review, Guidelines

However, Glucagon hypoglycaemia kits are recommended, as emergency therapy, on the EML for people with type 1 diabetes, who are found to be at high risk of hypoglycaemia because of recurrent episodes (Chapter 8: Endocrine System). For secondary level adult critical care hospital level for the management of hypoglycemia; glucose (oral) and glucagon (SC)) recommended.

Following external comment, a description of hypoglycemia was added.

Following external comment, the target for glucose concentration was revised from 7-10mmol/L to 6-10 mmol/L.[77] Although lower starting targets are recognized (e.g. 4.5 to 10mmol/L) as appropriate; a conservative target range of 6-10 mmol/L was selected from a safety point of view.

23.8.4 HYPERGLYCEMIA

The STG on hyperglycemia is aligned with a cross reference to section 8.6.2: Diabetic Ketoacidosis (DKA) And Hyperosmolar Hyperglycaemic State (HHS) in the Adult Hospital Level Standard Treatment Guidelines - Chapter 8: Endocrine System.

73 South African Medicines Formulary. 14th Edition. Division of Clinical Pharmacology. University of Cape Town. 2022.
74 Hydrocortisone, IV: Bornstein SR, Allolio B, Arlt W, Barthel A, Don-Wauchope A, Hammer GD, Husebye ES, Merke DP, Murad MH, Stratakis CA, Torpy DJ. Diagnosis and Treatment of Primary Adrenal Insufficiency: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2016 Feb;101(2):364-89. https://www.ncbi.nlm.nih.gov/pubmed/2676004
75 South African Medicines Formulary. 14th Edition. Division of Clinical Pharmacology. University of Cape Town. 2022..
76 Boido A, Ceriani V, Pontiroli AE. Glucagon for hypoglycemic episodes in insulin-treated diabetic patients: a systematic review and meta-analysis with a comparison of glucagon with dextrose and of different glucagon formulations. Acta Diabetol. 2015 Apr;52(2):405-12. https://www.ncbi.nlm.nih.gov/pubmed/25323325
77 Johan Mårtensson, Moritoki Egi, Rinaldo Bellomo, Chapter 79 - Blood Glucose Control in Critical Care, Editor(s): Claudio Ronco, Rinaldo Bellomo, John A. Kellum, Zaccaria Ricci, Critical Care Nephrology (Third Edition), Elsevier, 2019, Pages 464-469.e2, ISBN 9780323449427, https://doi.org/10.1016/B978-0-323-44942-7.00079-0.

Following external comment, a description of hyperglycaemia was added.[78]

Following external comment, insulin sliding scales were removed from the STG because evidence for efficacy of insulin sliding scale strategies is poor, as the variability in glucose levels associated with this strategy may even increase risk of harm. [79,80] Only continuous insulin infusions are now stated in this STG.

23.9 TOXICOLOGY IN ICU

The toxicology in ICU section was summarized substantially from original drafts of the STG, now providing only general measures with a cross reference to the Adult Hospital Level Standard Treatment Guidelines - Chapter 19: Poisonings.

In future iterations of this chapter more details of specific poisonings in the ICU setting will be explored.

23.10 SEPSIS IN ICU

Sepsis as a major challenge in ICU warranted an STG as a topic and is outlined in terms of the following components: definitions, initial resuscitation, hemodynamic support and antimicrobial therapy.

Following external comment; in Table 23.6: Sequential organ failure assessment (SOFA) score a decimal point correction was made for Serum creatinine in µmol/L (mg/dl) from < 12 to < 1.2.

23.10.1 SEPSIS IN ICU: INITIAL RESUSCITATION

The following referenced definition[81] of Sepsis is provided: "Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. Organ dysfunction is defined as an acute increase in SOFA (Sequential Organ Failure Assessment) score of at least 2 points. Patients with sepsis have a significantly higher mortality than those with an infection without sepsis."

The sequential (sepsis-related) organ failure assessment (SOFA score)[82] tool was modified for use in the STG.

An external comment was received suggesting a comment be added to the STG advising avoidance of starch-based infusion products in septic shock. A caution box with the statement to: "Avoid colloids for shock resuscitation in patients with sepsis and acute kidney injury", is now included as stated earlier in the chapter under fluid therapy for shock.

23.10.2 INITIAL RESUSCITATION: HAEMODYNAMIC SUPPORT

Balanced Salt Solution, IV: *Added as per therapeutic interchange database*
Adrenaline, IV: *Added*
Dobutamine, IV: *Added*

The South African standard treatment guidelines (STGs) for Adult Hospital Level, 2019 edition (Section 20.11.2.2 Septic Shock), have previously recommended adrenaline for the treatment of septic shock that is unresponsive to a fluid challenge[83].

78 Chawla, Rajeev; Gangopadhyay, Kalyan Kumar1; Lathia, Tejal Bipin2; Punyani, Hitesh3; Kanungo, Alok4; Sahoo, Abhay Kumar5; Seshadri, Krishna G.6. Management of Hyperglycemia in Critical Care. Journal of Diabetology 13(1):p 33-42, Jan–Mar 2022. | DOI: 10.4103/jod.jod_69_21
79 Hirsch IB. Sliding scale insulin--time to stop sliding. JAMA. 2009 Jan 14;301(2):213-4. doi: 10.1001/jama.2008.943. PMID: 19141770.
80 Du Toit, L., Biesman-Simons, T., Levy, N., Dave, J.A., 2018. A practical approach to managing diabetes in the perioperative period. South African Medical Journal 108, 369.. https://doi.org/10.7196/samj.2018.v108i5.13311
81 Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche JD, Coopersmith CM, Hotchkiss RS, Levy MM, Marshall JC, Martin GS, Opal SM, Rubenfeld GD, van der Poll T, Vincent JL, Angus DC. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016 Feb 23;315(8):801-10. doi: 10.1001/jama.2016.0287. PMID: 26903338; PMCID: PMC4968574
82 Adapted From: Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. Intensive Care Med. 1996;22:707–710
83 National Department of Health: National Department of Health: Essential Drugs Programme. Adult Hospital level STGs and EML. Chapter 20: Emergencies and Injuries.

A medicine review showed that there is no outcome benefit of either adrenaline or noradrenaline compared to the other. Additionally, routine use of noradrenaline IV is not recommended due to cost and availability concerns; even though now SAHPRA registered.

Refer to the medicine review - Vasopressors, inotropes as monotherapy or in combination, 24 April 2023 [84] (Updated: 6 October 2023), below:

AHL_Ch23_Adult CriticalCare_Vasopres

Recommendation: The PHC/Adult Hospital Level Committee suggests not to use the option of noradrenaline for management of septic shock.

Rationale: There is limited evidence that noradrenaline (norepinephrine), with/without other catecholamines results in improved clinical outcomes (mortality, haemodynamic stability) or improved safety (dysrhythmias and lactate concentrations) compared to adrenaline (epinephrine). Furthermore, noradrenaline (norepinephrine) is cost-prohibitive compared to adrenaline at present, and is unlikely to have generic agents available for the foreseeable future.

Level of Evidence: Low to very low certainty evidence
Review indicator: Price reduction, availability of cost-effective noradrenaline products, or any new evidence of efficacy or harm.

NEMLC RECOMMENDATION (MEETING OF 12 OCTOBER 2023):
Although the available evidence was of low to very low certainty, NEMLC did not recommend noradrenaline over adrenaline for the initial management of septic shock that is unresponsive to a fluid challenge, due to the absence of clinically significant advantages in mortality or safety.

Following external comment, the upper range on the adrenaline dosing was revised to 1.0mcg/kg/min. The units for adrenaline dosing were standardized to mcg/kg/min from ug/kg/min throughout the chapter. [85]

A higher dosage of adrenaline is provided for the emergency setting in Chapter 20: Emergencies and injuries (e.g., Dilute 10 mg (10 ampoules) of adrenaline 1:1000 in 1 L sodium chloride 0.9%) versus a wider range which falls within the emergency dosing range for adrenaline in the adult critical care chapter for the intensive care setting (Adrenaline, IV infusion, 0.01-1.0 mcg/kg/min, aiming to achieve a target MAP > 65mmHg within 30 minutes). The context for adrenaline IV use in the critical care and the emergency setting are different, for example, prior to admission to the ICU there might have been a degree of adrenaline therapy which would have occurred. While unambiguity in the interpretation of the STGs is important, the infusion dose range and target as included in the adult critical care chapter for adrenaline IV of 0.01-1.0 mcg/kg/min is unlikely to cause any confusion considering the ICU context in which it is required. A cross-reference to the Adult Hospital Level - Chapter 20: Emergencies and injuries was not included as the doses do not need to be aligned
The committee has recommended a medicine review of noradrenaline and/or other vasopressors as a second line alternative treatment for various types of shock in consideration of historical use in the EML in the case of adrenaline contra-indication, unavailability or ineffectiveness. Noradrenaline (norepinephrine) is now SAHPRA registered. Section 23.3.7.5 (vasoactive medicines for shock) which refers to additional treatment if target with adrenaline is not achieved will remain unfinalized until the recommended review is concluded.

84 National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Vasopressors, inotropes as monotherapy or in combination, April 2023. http://www.health.gov.za/. https://accessmedicine.mhmedical.com/content.aspx?bookid=1944&sectionid=143516493
85 Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, Machado FR, Mcintyre L, Ostermann M, Prescott HC, Schorr C, Simpson S, Wiersinga WJ, Alshamsi F, Angus DC, Arabi Y, Azevedo L, Beale R, Beilman G, Belley-Cote E, Burry L, Cecconi M, Centofanti J, Coz Yataco A, De Waele J, Dellinger RP, Doi K, Du B, Estenssoro E, Ferrer R, Gomersall C, Hodgson C, Hylander Møller M, Iwashyna T, Jacob S, Kleinpell R, Klompas M, Koh Y, Kumar A, Kwizera A, Lobo S, Masur H, McGloughlin S, Mehta S, Mehta Y, Mer M, Nunnally M, Oczkowski S, Osborn T, Papathanassoglou E, Perner A, Puskarich M, Roberts J, Schweickert W, Seckel M, Sevransky J, Sprung CL, Welte T, Zimmerman J, Levy M. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock 2021. Crit Care Med. 2021 Nov 1;49(11):e1063-e1143. doi: 10.1097/CCM.0000000000005337. PMID: 34605781.

Dobutamine is usually added only if no response to adrenalin[86]; in patients with significant left ventricular dysfunction. The evidence for combinations is poor; in practice, most would add dobutamine if patient is a known cardiac patient. SAMF[87] recommends initial infusion at 5mcg/kg/min, increasing by 2.5mcg/kg/min to target. The recommendation for dobutamine was aligned to SAMF to start infusion at 5 ml/hr. Check MAP regularly (every 10-30 minutes until target is reached) and titrate infusion rate by 2.5 ml/hr to reach target MAP. It is stated in the STG that infusion rates exceeding 20 ml/hr are usually not required."

Following external comment, a reference made to vasopressin in the narrative of the STG was deleted as vasopressin is a non-EML item.

23.10.4 SEPSIS IN ICU: ANTIMICROBIAL THERAPY

The antimicrobial therapy STG has been aligned to the Adult Hospital Level Standard Treatment Guideline recommendations for Systemic and Healthcare-Associated Infections.

Guidance is provided on choice of antibiotic, timing, dosing, duration of therapy and source control. Additional special considerations are provided as additional antimicrobials as part of empiric therapy to address atypical and anaerobic organisms, Methicillin-resistant Staphylococcus aureus (MRSA) and invasive fungal infections that would need to be carefully considered.

Examples of possible continuous infusion dosing regimens are provided and include:

- Amoxycillin/Clavulanate: 1.2g loading dose IV over 30 minutes followed by maintenance of 1.2g six-hourly, with each dose by extended infusion over 4 hours.
- Piperacillin/Tazobactam: 4.5g loading dose over 30 minutes IV followed by maintenance of 4.5g six-hourly, with each dose by extended infusion over 4 hours
- Meropenem: 1g loading dose over 30 minutes IV followed by maintenance of 1g six-hourly, with each dose by extended infusion over 4 hours.

Amoxicillin/clavulanic acid IV is historically recommended in the Adult Hospital Level Standard Treatment Guideline for acute cholecystitis and acute cholangitis, diverticulosis: cannot take oral medicines, Pancreatitis acute: abscess of the pancreas, Liver Abscess, pyogenic, Bacterial peritonitis, Septic miscarriage, Postpartum Fever, Diabetic foot ulcers: severe infection, lung abscess, pneumonia, aspiration, empyema, abscess, peritonsillar.

Following external comment, advice on initiation of antibiotics within 1 hour of the presumptive diagnosis of sepsis or septic shock was added. Additionally, a narrative on appropriate samples for microbiology, ideally prior to commencing or changing antibiotics was added. Also included is advice on not delaying antibiotic administration to collect samples as the risk of mortality increases hourly in untreated sepsis.

Prolonged infusion of co-amoxiclav was retained and referenced[88].

Piperacillin/Tazobactam IV is historically recommended in the Adult Hospital Level Standard Treatment Guideline for febrile neutropenia: surgical wound infections, hospital- acquired pneumonia (hap), with risk factors, ventilator associated pneumonia (VAP), and CNS infections/seizures.

[86] Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, Machado FR, Mcintyre L, Ostermann M, Prescott HC, Schorr C, Simpson S, Wiersinga WJ, Alshamsi F, Angus DC, Arabi Y, Azevedo L, Beale R, Beilman G, Belley-Cote E, Burry L, Cecconi M, Centofanti J, Coz Yataco A, De Waele J, Dellinger RP, Doi K, Du B, Estenssoro E, Ferrer R, Gomersall C, Hodgson C, Hylander Møller M, Iwashyna T, Jacob S, Kleinpell R, Klompas M, Koh Y, Kumar A, Kwizera A, Lobo S, Masur H, McGloughlin S, Mehta S, Mehta Y, Mer M, Nunnally M, Oczkowski S, Osborn T, Papathanassoglou E, Perner A, Puskarich M, Roberts J, Schweickert W, Seckel M, Sevransky J, Sprung CL, Welte T, Zimmerman J, Levy M. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock 2021. Crit Care Med. 2021 Nov 1;49(11):e1063-e1143. doi: 10.1097/CCM.0000000000005337. PMID: 34605781

[87] South African Medicines Formulary. 14th Edition. Division of Clinical Pharmacology. University of Cape Town. 2022.

[88] 88 Amoxicillin-Clavulanic Acid (Prolonged Infusions): Fawaz S, Dixon B, Barton S, Mohamed A, Nabhani-Gebara S. Suitability of Amoxicillin-Clavulanic Acid for Administration via Prolonged Infusion. Drug Des Devel Ther. 2020 Jan 10;14:103-109

Meropenem IV is historically recommended in the Adult Hospital Level Standard Treatment Guideline for febrile neutropenia, meningitis: hospital-acquired pneumonia (hap), with risk factors, VAP, and CNS infections/seizures. Meropenem dosing was retained as 6 hourly[89] for the ICU setting and not revised to 8 hourly as requested in external comment.

Extended infusion strategies for antimicrobial therapy are not employed in other chapters in the adult hospital level STGs. Extended infusion for the antimicrobial therapy STG in the critical care chapter was deliberated for an ICU context. Due to the available monitoring at the ICU level the benefits of extended infusion are more likely to be seen in the ICU setting as compared to a medical ward, therefore this strategy was considered justifiable in the ICU context.

Chronic wound care was retained as a factor for choice of appropriate broad-spectrum empiric antimicrobial therapy.

An external comment regarding de-escalation being crucial in reducing selective pressure and combatting antimicrobial resistance was accepted and included.

The following statements on source control were accepted through external comment: Source control is essential in managing infections in all patients, including those in ICU. Effective source control should be achieved as soon as possible.

A table has been incorporated as an example of an ICU Empiric Antimicrobial Guideline in line with the Adult Hospital Level Standard Treatment Guideline recommendations for Systemic and Healthcare-Associated Infections. Several comments on the example table were received during the external comment phase of the chapter. It is noted that recommendations included in the example ICU empiric antimicrobial guideline table may require modifications subject to local resistance patterns. The examples provided are aligned to evidence-based guidance provided in the STGs.

Following publication for comment of the chapter, for infected pancreatic necrosis (suspected) meropenem was removed as an option for community-acquired infection due to expert opinion that prophylactic antibiotics are not indicated, and if infected necrosis occurs, it is usually 2-4 weeks after the pancreatitis, and there would be concern for healthcare-associated infection or multi drug resistant (MDR) organisms. Gentamicin has been removed for community acquired infection for pneumonia in HIV negative patients; as there is no role or gentamicin for this indication. Example for management of Community acquired infection for Infective endocarditis is in line with the cardiovascular chapter recommendations.

LOE: Expert Opinion (IVb)

Table 23.8: Example of an ICU Empiric Antimicrobial Guideline

Infection	Community Acquired Infection	Healthcare Associated Infection	Suspected Multidrug-resistance
Upper Gastro-intestinal tract (GIT)	Amoxicillin/clavulanic acid ± Gentamycin[#] + Fluconazole	Piperacillin-tazobactam ± Amikacin[#] + Fluconazole	Meropenem[*] + Fluconazole
Lower GIT *Urological* *Gynaecological*	Amoxicillin/clavulanic acid ± Gentamycin[#]	Piperacillin-tazobactam ± Amikacin[#]	Meropenem[*]
	For pelvic inflammatory disease, add: Metronidazole		
Infected pancreatic necrosis (suspected)		Piperacillin-tazobactam ± amikacin	Meropenem

[89] Lertwattanachai, T., Montakantikul, P., Tangsujaritvijit, V. et al. Clinical outcomes of empirical high-dose meropenem in critically ill patients with sepsis and septic shock: a randomized controlled trial. j intensive care 8, 26 (2020). https://doi.org/10.1186/s40560-020-00442-7

Infection	Community Acquired Infection	Healthcare Associated Infection	Suspected Multidrug-resistance
Pneumonia in HIV negative patient	Amoxicillin/clavulanic acid + Azithromycin	Piperacillin-tazobactam ± Amikacin[#] ± Vancomycin[^]	Meropenem[*] ± Vancomycin[^]
Pneumonia in HIV positive patient (with bilateral infiltrates)	+Cotrimoxazole + Anti-TB Rx[*]		
Meningitis	Ceftriaxone	Meropenem	
Skin and soft tissue	Amoxicillin/clavulanic acid	Piperacillin-tazobactam ± Vancomycin[^]	Meropenem[*] ± Vancomycin[^]
	For necrotizing fasciitis, add: Clindamycin ± Gentamycin[#]	+ Clindamycin + Amikacin[#]	+ Clindamycin
Catheter-related bloodstream infection		Piperacillin-tazobactam ± Amikacin[#] ± Vancomycin[^]	Meropenem ± Vancomycin[^]
Infective endocarditis	Ampicillin + Cloxacillin + Gentamicin	Meropenem ± Vancomycin[^]	
Tetanus	Metronidazole		
Suspected Clostridium Difficile Enterocolitis	Enteral Vancomycin (IV prep via NGT)		

^ If from unit with high rate of MRSA (methicillin resistant staphylococcus aureus) or recent MRSA within ICU.
# Decision to embark on dual therapy with an aminoglycoside should be based on assessment of potential benefits of expanded antibiotic coverage based on local susceptibility patterns.

For patients with AKI (acute kidney injury) an external comment to discontinue aminoglycoside if serious gram-negative sepsis suspected was not accepted; as the recommendation for continued use of the aminoglycosides are with therapeutic drug monitoring,

Carbapenem-resistant Enterobacterales (CRE) bacteraemia

Ceftazidime-avibactam, IV: *Added*

A medicine review showed that ceftazidime-avibactam-containing therapy is associated with a reduction in mortality (NNT 5 – 7) and nephrotoxicity (NNT 12), and improved clinical cure when compared to other appropriate antibiotic regimens in populations with high proportions of Klebsiella pneumoniae CRE infections that produce KPC and OXA-48 carbapenemases. Recent NICD surveillance suggests comparable CRE epidemiology in South Africa, with the largest proportion of CRE bacteraemia being caused by Klebsiella pneumonia producing OXA-48. However, based on this local data, a significant proportion of CRE isolates (almost 25%) are still unlikely to be susceptible to ceftazidime-avibactam therapy (metallo-beta-lactamases) and thus culture and sensitivity must be used to guide its usage.

Refer to the medicine review - **Ceftazidime-avibactam for the treatment of carbapenem-resistant Enterobacterales (CRE) bacteraemia**, 6 July 2023 (Updated September 2023)[90], below:

AHL_Ch23_Adult CriticalCare_Ceftazidi

Recommendation: The PHC Adult Hospital Level ERC suggests using ceftazidime-avibactam in selected patients with bacteraemia due to carbapenem resistant organisms. In view of the cost and antibiotic stewardship concerns the decision to use this agent should not be based solely on sensitivity of the cultured organism to ceftazidime-avibactam. The decision should be made in consultation with a multidisciplinary antibiotic stewardship team and use should be avoided in patients with a very poor prognosis.

90 National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Ceftazidime-avibactam for the treatment of carbapenem-resistant Enterobacterales (CRE) bacteraemia, July2023 (Updated September 2023). http://www.health.gov.za/. https://accessmedicine.mhmedical.com/content.aspx?bookid=1944&sectionid=143516493

Rationale: Systematic reviews and meta-analyses of observational data suggest a large reduction in mortality associated with treatment with ceftazidime-avibactam. At the current price, the incremental cost-effectiveness ratio suggests an additional cost of ZAR 109 786.21 to prevent one death (when compared to a regimen of tigecycline with amikacin), and an additional cost of ZAR 84 613.32 to prevent one death (when compared to a regimen of tigecycline and colistin). A formal pharmacoeconomic analysis is recommended to guide further decision-making.

Level of Evidence: *Systematic reviews of observational trials.* **(Low Certainty Evidence)**

Review indicator: Evidence of harm and new cost data

NEMLC RECOMMENDATION (MEETING OF 12 OCTOBER 2023):
NEMLC supported the PHC Adult Hospital Level ERC recommendation to use ceftazidime-avibactam in selected patients with bacteraemia due to carbapenem resistant organisms. Use must be based on sensitivity of the cultured organism to ceftazidime-avibactam in consultation with a multidisciplinary antibiotic stewardship team (for example microbiologists or infectious disease specialists). Use of ceftazidime-avibactam should be avoided in patients with a very poor prognosis.

NEMLC did not recommend a full pharmacoeconomic evaluation at this time.

The STG recommends Ceftazidime-avibactam to treat patients with CRE bacteraemia, in consultation with a specialist and antibiotic stewardship team, where the infecting organism is proven to be sensitive to ceftazidime-avibactam on bacterial culture. Duration of treatment is dependent on indication for treatment and clinical response.

For suspected fungal infections, examples of empiric antifungal therapy are provided in line with previous NEMLC approved systemic and health care associated infections including:

- Amphotericin B, OR
- Fluconazole

Following external comment, dose and duration of amphotericin B and fluconazole was included.

An external comment was received regarding the availability of micafungin. Micafungin was not included as it is EML for tertiary level use only. The adult critical care chapter includes secondary level care.

The following detail was added under duration of antimicrobial therapy based on external comment from a specialist microbiologist:

- Duration of antibiotic therapy may be individualised by the use of clinical response and biomarkers.
- Antibiotics may be stopped 48 hours after clinical response or if procalcitonin levels drop below 0.5ng/l or 80% of peak.
- The failure to respond to a short course of antibiotics should prompt consideration of antibiotic resistance or inadequate source control.

23.10.5 SEPSIS IN ICU: ADJUNCTIVE THERAPY

Following clinical editing, adjunctive therapy, in antimicrobial therapy, has been reformatted into a standalone STG.

Adjunctive therapy

Corticosteroids
Hydrocortisone, IV:[91] *Added*

91 Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, Machado FR, Mcintyre L, Ostermann M, Prescott HC, Schorr C, Simpson S, Wiersinga WJ, Alshamsi F, Angus DC, Arabi Y, Azevedo L, Beale R, Beilman G, Belley-Cote E, Burry L, Cecconi M, Centofanti J, Coz Yataco A, De Waele J, Dellinger RP, Doi K, Du B, Estenssoro E, Ferrer R, Gomersall C, Hodgson C, Hylander Møller M, Iwashyna T, Jacob S, Kleinpell R,

Level of Evidence: IV: Guidelines

Corticosteroids as adjunctive therapy in sepsis management was added in line with guidelines, and it was confirmed following external comment that hydrocortisone IV should be continued until resolution of shock.

An external comment to add fludrocortisone as adjunctive therapy to hydrocortisone for patients with shock due to emerging evidence of efficacy was not supported; and. deferred to the next review cycle for prioritization for review. Similarly inhaled antimicrobials for pneumonia were also raised through external comment for consideration as it was mentioned that tracheal aspirates often grow organisms that are sensitive only to drugs that do not penetrate the lung parenchyma well; and felt that this is where inhaled antimicrobials have a role. Commentator also raised that recent literature has not found an increase in antibiotic resistance due to this strategy. The review of inhaled antimicrobials for this indication was also deferred to the next review cycle for prioritization for review, depending on SAHPRA registration status.

23.11 SAFETY IN ICU

To ensure comprehensive guidance a "safety in ICU" STG is provided including concepts of patient safety and patient transfer and handover.

23.11.1 PATIENT SAFETY

Important patient safety issues in critical care including proper patient identification, timely response to critical tests, appropriate and safe use of clinical alarms, improvement of staff communication, appropriate and safe use of medicines and infection prevention and control

Health care providers are reminded that all patient safety incidents (PSI) are to be reported on the South African National Patient Safety Incident Reporting and Learning (NPSIRL) System and acted upon appropriately as per the processes of the system. (https://www.knowledgehub.org.za/elibrary/national-guideline-patient-safety-incident-reporting-and-learning-health-sector-south).

23.11.2 PATIENT TRANSFER AND HANDOVER

The STG provides considerations for the transfer of critically ill patients including:

- Decision to transfer is made by the responsible senior
- Adequate and appropriate communication between referring and receiving teams
- Experienced and well-trained transfer team capable of managing any deterioration
- Patient to be stabilized as far as possible with on-going organ support provided for duration of transfer.
- Appropriately secured airway for transfer
- Appropriate monitoring with sufficient battery back-up
- Appropriate level of sedation and pain control
- Adequate oxygen for transfer duration
- Adequate volumes of medications and fluids for duration of transfer
- Prevention of pressure damage and adequate wounds and fractures management
- Emergency medications and equipment
- Appropriate and detailed documentation to accompany patient

Strategies to improve ICU handovers are also provided as follows:

Klompas M, Koh Y, Kumar A, Kwizera A, Lobo S, Masur H, McGloughlin S, Mehta S, Mehta Y, Mer M, Nunnally M, Oczkowski S, Osborn T, Papathanassoglou E, Perner A, Puskarich M, Roberts J, Schweickert W, Seckel M, Sevransky J, Sprung CL, Welte T, Zimmerman J, Levy M. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock 2021. Crit Care Med. 2021 Nov 1;49(11):e1063-e1143. doi: 10.1097/CCM.0000000000005337. PMID: 34605781.

- Standardize the process, for example into specific phases:
    - Pre-handover preparation
    - Equipment and technology handover
    - Information handover
    - Discussion and plan
- Complete urgent clinical tasks before the information transfer.
- Allow only patient-specific discussions during verbal handovers.
- Require that all relevant team members be present.
- Provide training in team skills and communication.

23.12 END OF LIFE CARE

The STG on End-of-Life Care is aligned with a cross reference to the Adult Hospital Level Standard Treatment Guidelines - Chapter 24: Medicines used in Palliative Care.

The STG advises palliative and end of life care processes when therapy is considered non-beneficial. A Family Meeting Form is provided as an appendix to ensure appropriate documentation of the discussion with patient and family, including signatures for the treating doctor, patient/family member and witness. An external comment to add a component of a "Living Will" as per the HPCSA Ethics booklet (Updated 20 October 2023), was accepted as this is an ethical requirement that must now be adhered to as part of end-of-life care. Following external comment, a section on the determination of death[92] has been added to the end-of-life care STG including a table which presents a summary of the clinical assessment process.

[92] Thomson D, Joubert I, K De Vasconcellos, F Paruk, S Mokogong, R Mathivha, et al. South African Guidelines on the Determination of Death. South African Medical Journal [Internet]. 2014 [cited 2023 Nov 21];111(4b):367–80. Available from: http://www.samj.org.za/index.php/samj/article/view/13264/9746

South African National Essential Medicine List
Adult Hospital Medication Review Process
Component: Critical care

MEDICINE REVIEW

1. Executive Summary

Date: 24 April 2023 (Updated: 6 October 2023)
Medicine (INN): Vasopressors, inotropes as monotherapy or in combination
Medicine (ATC): H01BA, C01CA
Indication (ICD10 code): Septic shock
Patient population: Adult patients
Prevalence of condition: 677.5 (535.7 to 876.1) cases of sepsis per 100 000 in 2017 globally (Rudd, 2017). Septic shock prevalence in Europe and North America among those diagnosed at any time was 6.5% (95% CI 5.6 to 7.5%) using sepsis-3 criteria (Vincent, 2019).
Prescriber Level: Hospital level
Motivator/reviewer name(s): R Mpofu, TD Leong, S Dadan, R Griesel
PTC affiliation: Red Cross War Memorial Children's Hospital pharmacy therapeutics committee (RM)

Key findings

- Internationally, noradrenaline is recommended as a first-line vasopressor for the management of septic shock. This review assessed the evidence for vasopressor agents in the treatment of adults with septic shock. The quality of evidence included in the current, Surviving Sepsis 2021, guidelines were assessed to be low, and adaptation/adolopment approach was therefore not appropriate.
- We sourced and appraised systematic reviews, of which one was assessed as good quality (Gamper, 2016) using the AMSTAR 2 tool. We also reviewed historical Surviving Sepsis guidelines to identify additional studies of relevance. Five relevant primary RCTs were extracted from the systematic review and risk-of-bias appraised and synthesised with meta-analysis of homogenous data as appropriate.
- Noradrenaline (norepinephrine), with/without other catecholamines, probably does not reduce mortality compared to adrenaline in the management of septic shock: 131/289 (45.3%) vs 124/271 (45.8%), with a relative risk (RR) of 0.99 (95% CI 0.83 to 1.18; I^2 = 0%), *low certainty evidence.*
- It is uncertain whether noradrenaline (norepinephrine), with/without other catecholamines, may have an effect on time to mean arterial pressure goal (24 hours without vasopressor use), time to MAP stabilisation (MAP 70 to 80 mmHg) or effect on vasopressor free days (28 days), compared to adrenaline (epinephrine), very *low certainty evidence.*
- Noradrenaline (norepinephrine), with/without other catecholamines, may not reduce mean change in lactate concentration from baseline, at 24 hours, compared to adrenaline (epinephrine), *very low certainty evidence.* The mean difference was MD - 0.16 mmol/l (95% CI -1.14 fewer to 0.82 more). This change is not considered clinically significant.
- There was no difference in supra- or ventricular-tachyarrhythmias between the adrenaline (epinephrine) [31/176 (17.6%)] vs noradrenaline (norepinephrine) + dobutamine combination treatment group [30/184(16.3%)], RR 0.92 (95% CI 0.59 to 1.45), *very low certainty evidence.*
- In conclusion, this review found that adrenaline (epinephrine) monotherapy is associated with similar clinical outcomes as noradrenaline (norepinephrine) when used as monotherapy or in combination with other vasopressors.

PHC/ADULT HOSPITAL LEVEL EXPERT REVIEW COMMITTEE RECOMMENDATION:					
Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
		X			

PHC/ADULT HOSPITAL LEVEL EXPERT REVIEW RECOMMENDATION (Updated Electronically: 6 OCTOBER 2023):

Recommendation: The PHC/Adult Hospital Level Committee suggests not to use the option of noradrenaline for management of septic shock.

Rationale:. Furthermore, noradrenaline (norepinephrine) is cost-prohibitive compared to adrenaline at present, and is unlikely to have generic agents available for the foreseeable future.

Level of Evidence: Low to very low certainty evidence
Review indicator: Price reduction, availability of cost-effective noradrenaline products, or any new evidence of efficacy or harm.

NEMLC RECOMMENDATION (MEETING OF 12 OCTOBER 2023):

Although the available evidence was of low to very low certainty, NEMLC did not recommend noradrenaline over adrenaline for the initial management of septic shock that is unresponsive to a fluid challenge, due to the absence of clinically significant advantages in mortality or safety.

Monitoring and evaluation considerations

Research priorities

Prospero registration: CRD42022368373

2. **Name of author(s)/motivator(s):** R Mpofu, TD Leong, S Dadan, R Griesel

3. **Author affiliation and conflict of interest details**

RM (Division of Clinical Pharmacology, University of Cape Town), TDL (South African Medical Research Council), SD (University of Cape Town), RG (South African Medical Research Council) and have no interests related to vasopressors or inotropes.

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4. **Introduction/ Background**

Sepsis is a global, public health problem with a risk of mortality greater than 20% (Rudd, 2020). Sepsis is defined as life threatening organ dysfunction due to a dysregulated host response to infection (Singer, 2016). This condition is frequently complicated by septic shock, characterized by a failure to maintain mean arterial pressures (MAP) ≥65 mmHg without the use of vasopressor agents and a serum lactate concentration greater than 2 mmol/L (Singer, 2016). Septic shock is associated with an in-hospital mortality risk greater than 40%. Treatment principles for septic shock include early diagnosis and recognition, fluid resuscitation, antibiotic administration in addition to infection source control, and vasopressor therapy (Surviving sepsis, 2021).

Various drugs with vasopressor activity have been recommended for the treatment of septic shock, but adrenaline (also known as epinephrine), noradrenaline (also known as norepinephrine), dopamine, and vasopressin agonists are commonly used. Adrenaline, noradrenaline, and dopamine are endogenous catecholamines that act on α, ß, and dopamine (D) receptors to varying degrees, with clinical effects that are mediated by relative stimulatory effects on these receptors. Adrenaline is a non-selective α-adrenergic and ß-adrenergic receptor agonist that increases cardiac rate, contractility, and systemic vascular resistance, particularly at doses used in the treatment of septic shock (Shields, 2016). However, high doses and prolonged use have been associated with potentially significant arrhythmias and splanchnic vasoconstriction due to $ß_1$-adrenergic receptor stimulation (Overgaard, 2008). Noradrenaline, a more selective catecholamine compared to adrenaline, predominantly stimulates α-adrenergic receptors and results in peripheral vasoconstriction with reduced arrhythmogenic potential due to decreased ß-adrenergic receptor effects (Overgaard, 2008). Dopamine is an endogenous, centrally acting neurotransmitter that also serves as a precursor in the synthesis of noradrenaline. At low doses (0.5 to 3 $mg.kg^{-1}.min^{-1}$), dopamine stimulates postsynaptic, dopaminergic D_1 receptors in the coronary, renal, mesenteric, and cerebral beds, while also stimulating presynaptic D_2 receptors in the vasculature and renal tissues to promote vasodilation and improve organ perfusion. Effects at higher infusion rates (10 to 20 $mg.kg^{-1}.min^{-1}$) are largely mediated by α_1-adrenergic receptor vasoconstriction (Overgaard, 2008). Dopamine has fallen out of favour as a first-line vasopressor agent in the treatment of septic shock based on data demonstrating an increased risk of arrhythmias and mortality compared with other vasopressors like noradrenaline. However, it may still have utility in a select group of patients, e.g., low risk of tachyarrhythmias or absolute/relative bradycardia (Shields, 2016). Vasopressin is an endogenous, non-adrenergic vasopressor that exerts its circulatory effects through V_{1a} receptor mediated vascular smooth muscle constriction and V_2 receptor mediated water reabsorption by enhancing renal collecting duct permeability (Overgaard, 2008). Vasopressin has minimal inotropic or chronotropic effects on the heart (Shields, 2016).

The South African standard treatment guidelines (STGs) for Adult Hospital Level, 2019 edition, have previously recommended adrenaline for the treatment of septic shock that is unresponsive to a fluid challenge, however, most international guidelines consider noradrenaline as first-choice for vasopressor therapy, followed by other vasopressor agents (which are sometimes recommended in combination) that have not previously been considered for the South African Essential Medicines List (EML). This review assessed the evidence for vasopressor agents in the treatment of adults with septic shock.

5. Methods:

We conducted a review of clinical practice guidelines (CPGs), systematic reviews of randomised controlled trials (RCTs) and RCTs that compared noradrenaline (norepinephrine), with/without other catecholamines to adrenaline (current standard of care) for management of septic shock in adults in the Adult Hospital Level Standard Treatment Guidelines and Essential Medicine List, 2019 edition (NDoH, 2019). Review characteristics are included in **Table 1**.

Table 1: Purpose/Objective i.e., PICO

Population	Critically ill adult patients (age ≥18) with septic shock
Intervention	Noradrenaline (norepinephrine) as monotherapy, or in combination with Dopamine OR Vasopressin
Control	Adrenaline (epinephrine)
Outcomes	1. Clinical cure – time to shock reversal 2. Mortality 3. Safety: adverse effects, including ischaemic complications and dysrhythmias
Study designs	Systematic reviews of RCTs or RCTs. Observational studies will only be sourced if the latter are unavailable.

A stepwise methodological approach was used: appraising current good quality guidelines for adaptation/adolopment to local context, followed by screening and selection of systematic reviews and health technological assessments (HTAs) for data extraction and analysis and then extraction of RCTs from systematic reviews as appropriate.

a. **Data sources**: Clinical Practice Guidelines were searched on the Guidelines International Network (GIN) Library database and google scholar. Health Technology Assessments (HTAs) were sought on Nice Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Scottish Medicines Consortium (SMC), International HTA Database and the European network for Health Technology Assessment (EUnetHTA). Systematic reviews and randomised controlled trials were searched in Epistemonikos, Cochrane Library, PubMed. To identify planned and ongoing studies, World Health Organization's International Clinicals Trials Registry Platform (ICTRP) as well as ClinicalTrials.gov were also searched.

b. **Search strategy:**
Search strategies were developed for PubMed and Epistemonikos (

Appendix 1). Search terms used for other databases were adapted from the above listed strategies.

c. Screening, data extraction and analysis, evidence synthesis:

Guidelines: Eligible clinical guidelines were sourced (RM) and appraised in duplicate, using the AGREE II tool (Brouwers, 2010) (RG, RM, TL, SD). To minimise duplication of efforts, where up-to-date guidelines that answers the review question are assessed to be of sufficient quality, the guidelines will be adapted using the GRADE-ADOLOPMENT approach, proposed by the GRADE working group (Schünemann, 2017). This approach considers the populated GRADE Evidence-To-Decision table (Moberg, 2018) for the specific clinical guideline on the GRADEPro website, and the categories are then contextualized for South Africa.

Health Technology Assessments: Eligible HTAs were sourced (TL) with appraisal in duplicate, using the AMSTAR 2 checklist (RM, TL, SD), as required.

Systematic reviews: A stepwise approach was taken, first screening and selecting systematic reviews and HTAs for data extraction and analysis. Records were uploaded into the reference management software, COVIDENCE (Covidence, 2023). Titles and abstracts were screened independently and in duplicate (RG, RM, SD, TDL). Thereafter, full text screening was done by two reviewers (RG, RM, SD, TDL) with conflicts resolved by a third reviewer. Eligible systematic reviews were appraised using the AMSTAR 2 Checklist (Shea, 2017) (TDL, RM, SD) and the most relevant studies was identified through consensus for data extraction. Reasons for excluding full texts at full-text stage were agreed in duplicate with a third reviewer finalizing any disputes. The PRISMA flowchart provides an overview of the review process (see **Appendix 2**).

Randomised controlled trials: Following the selection of the relevant systematic review(s), eligible RCTs were extracted from the systematic review(s). We screened for any additional RCTs that were not included in the eligible systematic review(s). Eligible RCTs were assessed for Risk of Bias using the Cochrane's RoB 2.0 Tool (Higgins, 2019), with data extraction. For dichotomous outcomes, we reported relative risk (RR) with 95% confidence intervals (95% CI) and results from the review or trial where possible. The mean difference (MD) with 95% CI were reported where the standard deviations (SDs) of outcomes were observed in two groups. SDs were calculated for normally distributed interquartile ranges using the formula proposed by Wan et al (2014) and described by Higgins et al (2019). Where available, we reported on the GRADE (level of certainty) of the evidence, considering various factors that may decrease our confidence in the trial finding including risk of bias, inconsistency, imprecision, publication bias and indirectness.

Data from multiple studies (considered to be sufficiently homogenous in terms of design, population, interventions and comparators reporting the same outcome) were combined and summarized through a meta-analysis using the Mantel-Haenzel method and a random-effects model to account for further between-study heterogeneity. The data was analysed using RevMan 5 (Review Manager version 5.4). Estimates were summarized using risk ratios (RR) and 95% CIs for dichotomous data, and mean differences and standard deviations for continuous data. Where appropriate, absolute effects with numbers needed to treat (NNT) have been calculated and reported. For any outcomes where insufficient data were found for a meta-analysis, a narrative synthesis has been presented.

Ongoing clinical trials: Clinical registries were screened (SD) to identify any relevant planned or ongoing clinical trials.

6. Results

a. Guidelines

We identified 3 guidelines, the Surviving Sepsis guidelines (2021), Japanese Clinical Practice Guidelines for Management of Sepsis and Septic Shock (2020) and the clinical practice guidelines for sepsis and septic shock in adults in the Philippines

(2020). These guidelines were all assessed using the AGREE II tool to be of moderate quality (see **Table 2** and **Appendix 3**).

Table 2. AGREE II assessments of the sepsis guidelines

Guideline citation and website	Recommendations	AGREE II Appraisal
Surviving Sepsis Guidelines, 2021	**Recommendation:** For adults with septic shock, we recommend using noradrenaline (norepinephrine) as the first-line agent over other vasopressors. *Strong* • Dopamine: *High-quality evidence* • Vasopressin. *Moderate-quality evidence* • Epinephrine. *Low quality of evidence* • Selepressin. *Low quality of evidence* • Angiotensin II. *Very low-quality evidence* **Recommendation:** For adults with septic shock on norepinephrine with inadequate MAP levels, we suggest adding vasopressin instead of escalating the dose of norepinephrine. *Weak, moderate quality evidence* **Recommendation:** For adults with septic shock and inadequate MAP levels despite norepinephrine and vasopressin, we suggest adding epinephrine. *Weak, low quality of evidence* **Recommendation:** For adults with septic shock and cardiac dysfunction with persistent hypoperfusion despite adequate volume status and arterial blood pressure, we suggest either adding dobutamine to norepinephrine or using epinephrine alone. *Weak, low quality of evidence*	Overall assessment 67% See Appendix 3.
The Japanese Clinical Practice Guidelines for Management of Sepsis and Septic Shock, 2020	**Recommendation:** Between noradrenaline and dopamine, we suggest administering noradrenaline as a first-line vasopressor in adult patients with sepsis *(GRADE 2D: certainty of evidence = "very low")* **Recommendation:** We suggest against using adrenaline as a second-line vasopressor in patients with sepsis/septic shock (*GRADE 2D: certainty of evidence = "very low").* **Recommendation:** We suggest using vasopressin as a second-line vasopressor in patients with sepsis/septic shock *(GRADE 2D: certainty of evidence = "very low").* **Recommendation:** We suggest administering inotropes (adrenaline, dobutamine) in adult patients with septic shock accompanied by cardiac dysfunction *(expert consensus: insufficient evidence).*	Overall assessment 67% See Appendix 3
Clinical practice guidelines for sepsis and septic shock in adults in the Philippines, 2020	**Question 15.** In patients with septic shock requiring vasopressors, should we use norepinephrine over other agents?	Overall assessment 58% See Appendix 3.

	Recommendation: We recommend norepinephrine as a first–line agent in septic shock requiring vasopressors (*strong recommendation, high quality of evidence*). **Question 16.** In patients with septic shock requiring a second vasopressor, which agent should be added to norepinephrine? **Recommendation:** We recommend the use of vasopressin (titrated up to 0.03 U/min) as the second vasopressor of choice on top of norepinephrine in patients with septic shock, with the intent of raising MAP to target or decreasing norepinephrine dosage *(conditional recommendation, low quality of evidence).*	

As the current international guidelines recommend noradrenaline (norepinephrine) as the vasopressor of choice and not adrenaline (epinephrine), noting the low quality, the GRADE-ADOLOPMENT approach was not relevant. To identify additional studies that may have been eligible for inclusion, historic Surviving Sepsis Guidelines (2001, 2004, 2008, 2012, 2016 and 2021) were also reviewed (see **Appendix 4**). However, no additional studies were identified.

b. Health technology assessments

We did not identify any health technology assessments relevant to the review.

c. Systematic reviews and randomised controlled trials

Description of included studies:

Ten systematic reviews were eligible and were critically appraised. Using the AMSTAR 2 tool, only one study (Gamper, 2016) was assessed to be of sufficient quality and the rest were of low to critically low quality (see **Appendix 5**). Five primary RCTs (Annane 2007; Myburgh 2008; Levy 2011; Seguin 2002, Seguin 2006) that compared adrenaline (epinephrine) to other vasopressors, included in the systematic review, were then further reviewed. One RCT which was included in the systematic review (Levy 2011) enrolled participants with cardiogenic shock rather than septic shock, and the population and disease differences in this indication may have important implications in the analysis and interpretation of results. Therefore, we excluded this study in the meta-analysis to minimize the potential effect of selection bias.

- ***Systematic review:***

Gamper 2016: Systematic review of 28 RCTs (n=3497) that compared the effect of one vasopressor regimen (vasopressor alone, or in combination) versus another vasopressor regimen on mortality amongst the critically ill with hypotensive shock. Six vasopressors (alone or in combination) were studied in 12 different comparisons.

For adrenaline (epinephrine) compared with noradrenaline (norepinephrine), as monotherapy or combination therapy (six RCTs; n=703 participants), 298 deaths were observed among the 703 participants (see **Figure 1**). No significant difference was found in either comparison. Participants had septic shock (Annane 2007; Levy 1997; Seguin 2002; Seguin 2006), cardiogenic shock (Levy 2011) or were categorized as critically ill patients (Myburgh 2008).

For the comparison of noradrenaline (norepinephrine) and adrenaline (epinephrine) monotherapy, one moderately large RCT of critically ill patients (n=269) showed a 90-day mortality rate of 380 per 1000 compared to 334 per 1000, respectively with a RR 0.88 (0.63 to 1.25), graded as low certainty evidence as the effect is from a single RCT (Myburgh 2008)
The systematic review was assessed as high quality using the AMSTAR 2 tool (see **Table 3** and **Appendix 5**).

Table 3. AMSTAR 2 assessment of the systematic review by Gamper et al, 2016.

Systematic review	Recommendation	AMSTAR 2 appraisal
Gamper, 2016: Vasopressors for hypotensive shock. Gamper G, Havel C, Arrich J, Losert H, Pace NL, Müllner M, Herkner H. Vasopressors for hypotensive shock. Cochrane Database Syst Rev. 2016 Feb 15;2(2):CD003709.	No differences in total mortality in any comparisons of different vasopressors or combinations in any of the pre‐defined analyses (evidence quality ranging from high to very low). More arrhythmias were observed in participants treated with dopamine than in those treated with norepinephrine (high-quality evidence). Authors suggest that major changes in clinical practice are not needed, but that selection of vasopressors could be better individualised and could be based on clinical variables reflecting hypoperfusion.	High Quality Review. See **Appendix 5**.

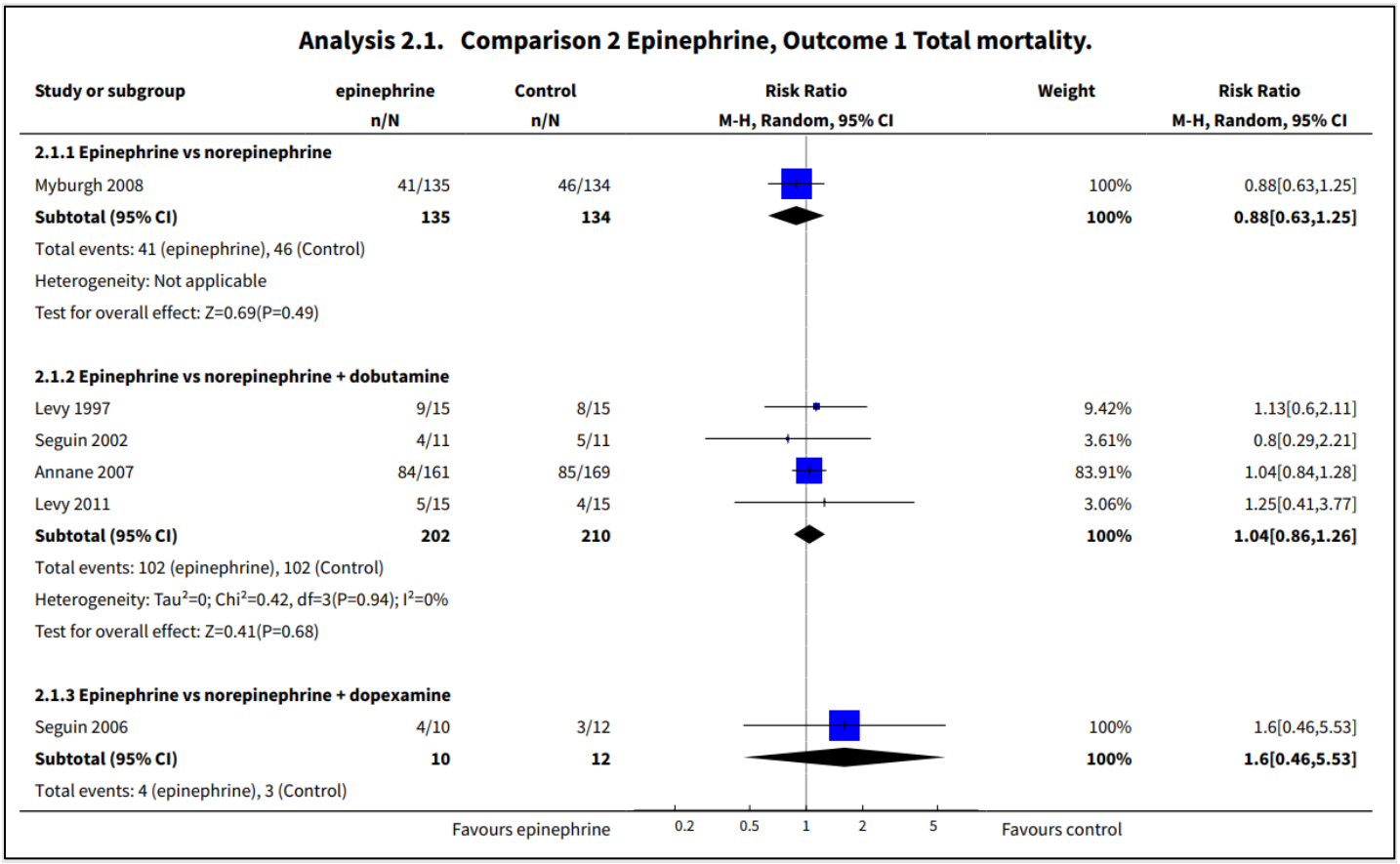

Figure 1. Forest plot comparing epinephrine (adrenaline) to other vasopressors (alone or in combination) amongst critically ill patients with hypotensive shock, including cardiogenic and septic shock (Gamper, 2016)

- ***Randomised controlled trials:***

We further reviewed the primary RCTs that informed the Gamper *et al*. (2016) systematic review that included adrenaline (epinephrine) as a study drug specifically for the management of septic shock. These RCTs were appraised using the Cochrane risk of bias tool (RoB 2) (Higgins, 2019) to independently assess the risk of bias in duplicate (RM, TL) for each outcome in the included studies, resolving any disagreements through discussion (See **Figure 2 and Table 5**).

Monotherapy

Adrenaline (epinephrine) vs noradrenaline (norepinephrine)

One double-blind RCT (Myburgh 2008) conducted at 4 Australian university hospital ICUs of critically ill, adult patients (n=280) with an Acute Physiology and Chronic Health Evaluation II (APACHE II) score of 22 at study entry who required

vasopressors compared adrenaline (epinephrine) as monotherapy to noradrenaline (norepinephrine). Patients were mostly elderly (mean age of 60 years) and presented with either septic shock (n=158) or acute respiratory failure (n=192) randomized to either adrenaline (epinephrine) or noradrenaline (norepinephrine) to achieve a MAP ≥70 mmHg without vasopressors as the primary outcome. Secondary outcomes included 28- and 90-day mortality.

Combination therapy

Adrenaline (epinephrine) vs noradrenaline (norepinephrine) + dobutamine

Three RCTs that compared adrenaline (epinephrine) with noradrenaline (norepinephrine) and dobutamine in septic shock, were reviewed (Annane 2007, Levy 1997, Seguin 2002). Double blinding was conducted in one trial of 330 participants (Annane 2007), but it is uncertain whether investigators, study participants or outcome assessors were blinded in two trials (Levy 1997: n=30, Seguin 2002: n=22). Participants were predominantly male and elderly, with ages ranging from 44 to 83 years. In one trial, participants had a McCabe classification of class 0 (no fatal underlying disease at the time of admission) (Annane 2007) and in the trial by Levy *et al.,* the mean APACHE II scores were 23 and 24 between the two respective treatment groups (Levy 1997). All trials reported on mortality, which was a primary outcome in one RCT (Annane 2007). Primary endpoints for one RCT (Levy 1997) was hemodynamic measures (also measured in the other RCTs) and another RCT was gastric mucosal blood flow (Seguin 2002). Additional outcomes included time to MAP stabilisation (MAP 70 to 80 mmHg), hepatic function and adverse events (including arrythmias and lactate concentrations).

Adrenaline (epinephrine) vs noradrenaline (norepinephrine) + dopexamine

One open-label RCT (n=22) compared adrenaline (epinephrine) to noradrenaline (norepinephrine) with dopexamine combination therapy (Seguin 2006) on gastric mucosal blood flow (GMBF). Mortality rates and haemodynamic parameters (including heart rate, arterial pressures, pulmonary capillary wedge pressure, cardiac output, and others) were also assessed. GMBF and other haemodynamic parameters were measured at various time points: before vasopressor administration, once MAP target had been obtained, 2 hours after attainment of target MAP, and 6 hours after attainment of target MAP. Participants, mostly male, had a mean age of 67 years and 65 years in the respective study arms, with Simplified Acute Physiology Score II (SAPS II) scores of 8 and 9, respectively. Treatment was titrated to maintain a MAP between 70 and 80 mmHg and the time to target MAP was measured.

QUALITY ASSESMENT

Amstar 2 assessment

The quality of nine systematic reviews, critically appraised using the AMSTAR 2 tool, were assessed to be of low to critically low quality (see **Appendix 4**) for the following reasons. There was no explicit statement that the review methods were established a prior or justification for major protocol deviations in four review reports (Cheng 2019, Avni 2015, Zhou 2015, Chen 2019). Ruslan et al did not use a comprehensive literature search strategy (Ruslan 2019). List of excluded studies with the rationale for exclusion was omitted in eight review reports (Oba 2015, Nagendran 2016, Cheng 2019, Raslan 2021, Cheng 2019, Avni 2015, Zhou 2015, Chen 2019). Statistical methods for meta-analysing data were inappropriate in one review (Chen 2019). In six review reports, review authors did not account for RoB in individual RCTs when interpreting/ discussing the results of the review (Cheng 2019, Ruslan 2019, Avni 2015, Zhou 2015, Chen 2019, Jiang 2019). And, lastly, for quantitative synthesis, review authors had not carried out adequate investigation of publication bias (small study bias) and had not discussed its likely impact on the results of the review in three reports (Oba 2015, Nagendran 2016, Zhou 2015).

Only one study (Gamper, 2016) was appraised to be of sufficient quality and five primary RCTs that informed the Gamper *et al* (2016) systematic review that included adrenaline (epinephrine) as a study drug specifically for the management of septic shock was quality assessed using the Cochrane ROB 2 tool.

ROB 2 assessment

We assessed the following domains of risk of bias by using the RoB 2 tool for various outcomes (See **Figure 2**).

Bias arising from the randomisation process

We judged three RCTs as low risk of bias for this domain, as randomisation was performed using a computer-generated list (Annane 2007, Myburgh 2008, Seguin 2006). Two trials did not adequately report allocation concealment (Levy 1997, Seguin 2002).

Bias arising from deviation from the intended interventions

Three RCTs were double blinded (Annane 2007, Myburgh 2008, Seguin 2002). However, only two were judged as low risk as adrenaline-associated lactic acidosis arm may have informed treatment allocation in the trial conducted by Myburgh et al (Myburgh 2008). One trial (Seguin 2006) was open label, whilst three RCTs did not provide adequate information to judge for selection bias (Levy 1997, Seguin 2002, Seguin 2006). Appropriate intention-to-treat analyses were performed to estimate the effect of assignment to intervention in only two RCTs (Annane 2007, Myburgh 2008), and no information was provided for the other three RCTs (Levy 1997, Seguin 2002, Seguin 2006).

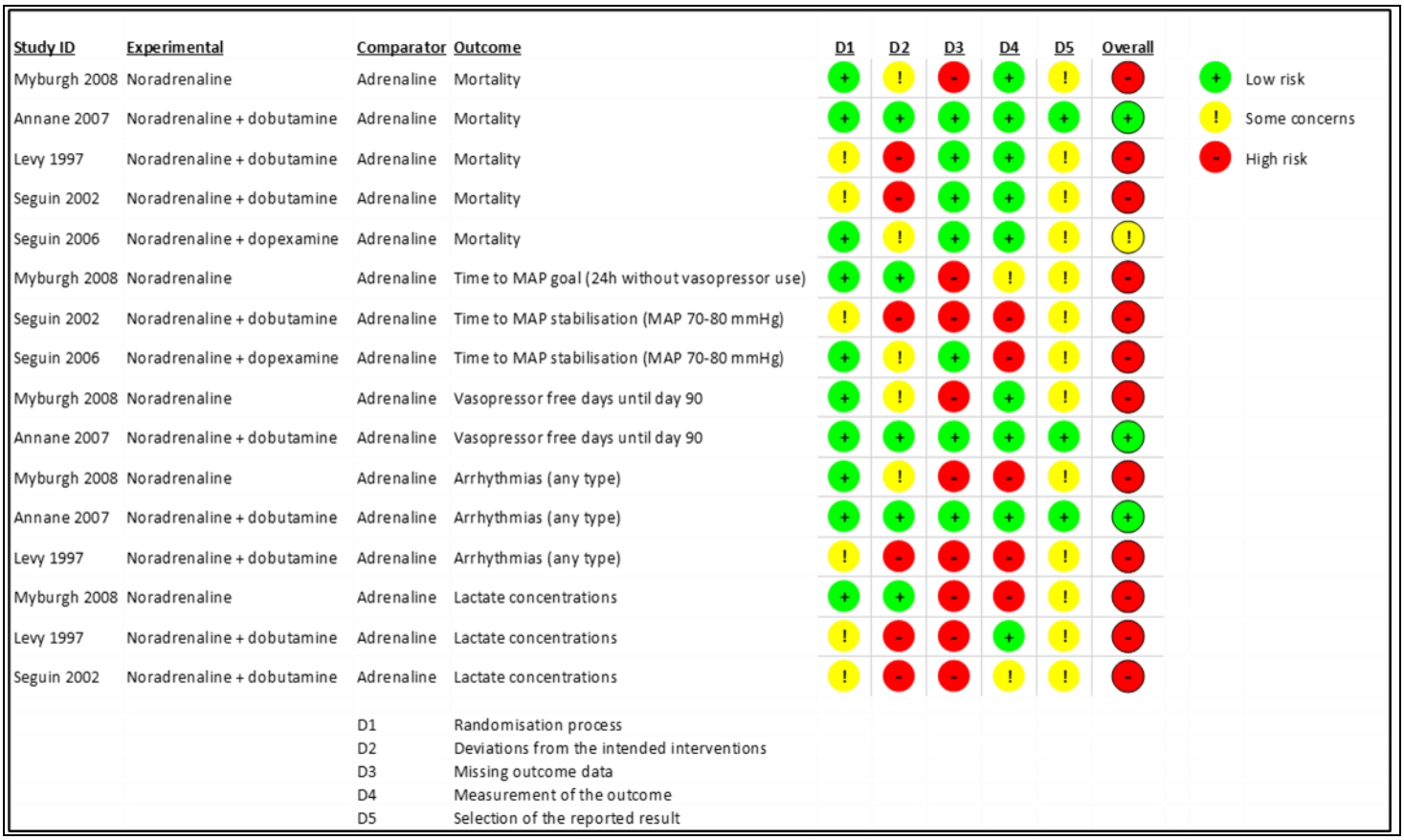

Figure 2: Methodological quality summary - review authors' judgements for each outcome per included study

Bias due to missing outcome data

For most outcomes, it was not reported whether outcome data were available for all, or nearly all participants who underwent randomisation. Only Annane *et al.* reported on availability of outcome data for all outcomes (Annane 2007). Mortality is an observer-reported outcome not involving judgement, assessed as low risk except for RCT by Myburgh *et al*. as there is uncertainty of the time when patients were switched from adrenaline to open-label noradrenaline due to adrenaline-associated lactic acidosis (Myburgh 2008).

Bias in measurement of the outcome

For mortality, we judged all trials as low risk of bias for this domain. For the other outcomes, one trial was open-label (Seguin 2006) and in another two trials there was insufficient information to judge blinding in another (Levy 1997, Seguin 2002). We judged that outcome assessors in one "double-blinded" RCT (Myburgh 2008) were probably aware that adrenaline was received by study participants due to clinically evaluated adrenaline-associated lactic acidosis that caused clinicians to withdraw participants from the adrenaline group, with subsequent receipt of open-labelled noradrenaline. Some concerns were also noted with the Seguin *et al* trials, as there was no clear definition of MAP stabilisation (Seguin 2002, Seguin 2006).

Bias due to selection of the reported result

Only one trial had a protocol registered in a trial registry (Annane 2007). Published protocols, detailing pre-specified outcome(s), and statistical analysis plans were not available for the other four trials.

OUTCOMES

Effectiveness:

- **Mortality (Day 28) – overall (mono- and combination therapy)**

Noradrenaline (norepinephrine), with/without other catecholamines, probably does not increase/reduce mortality compared to adrenaline (epinephrine), in septic shock – evidence assessed as *low certainty* due to serious risk of bias and concerns of blinding of investigators and assessors (refer to **Table 4: GRADE summary of findings**).

Mortality was assessed at an undetermined time point in two RCTs (Levy 1997, Seguin 2002), so we assumed this to be at 28-days, based on other studies with similar study designs involving the same authors (Levy 2011, Seguin 2006). Levy 2011 (performed in participants with cardiogenic shock rather than septic shock) was excluded and five studies were meta-analysed (Levy 1997; Seguin 2002; Seguin 2006; Annane 2007; Myburgh 2008; See

Table 6). Adrenaline (epinephrine) was shown to be comparable to noradrenaline (norepinephrine) monotherapy/combination therapy (with another catecholamine vasopressor), 124/271 (45.8%) vs 131/289 (45.3%), with a relative risk (RR) of 0.99 (95% CI 0.83 to 1.18; I^2 = 0%; **Figure 3**) and an absolute difference of 5 fewer deaths per 1000 patients treated (from 78 fewer to 82 more).

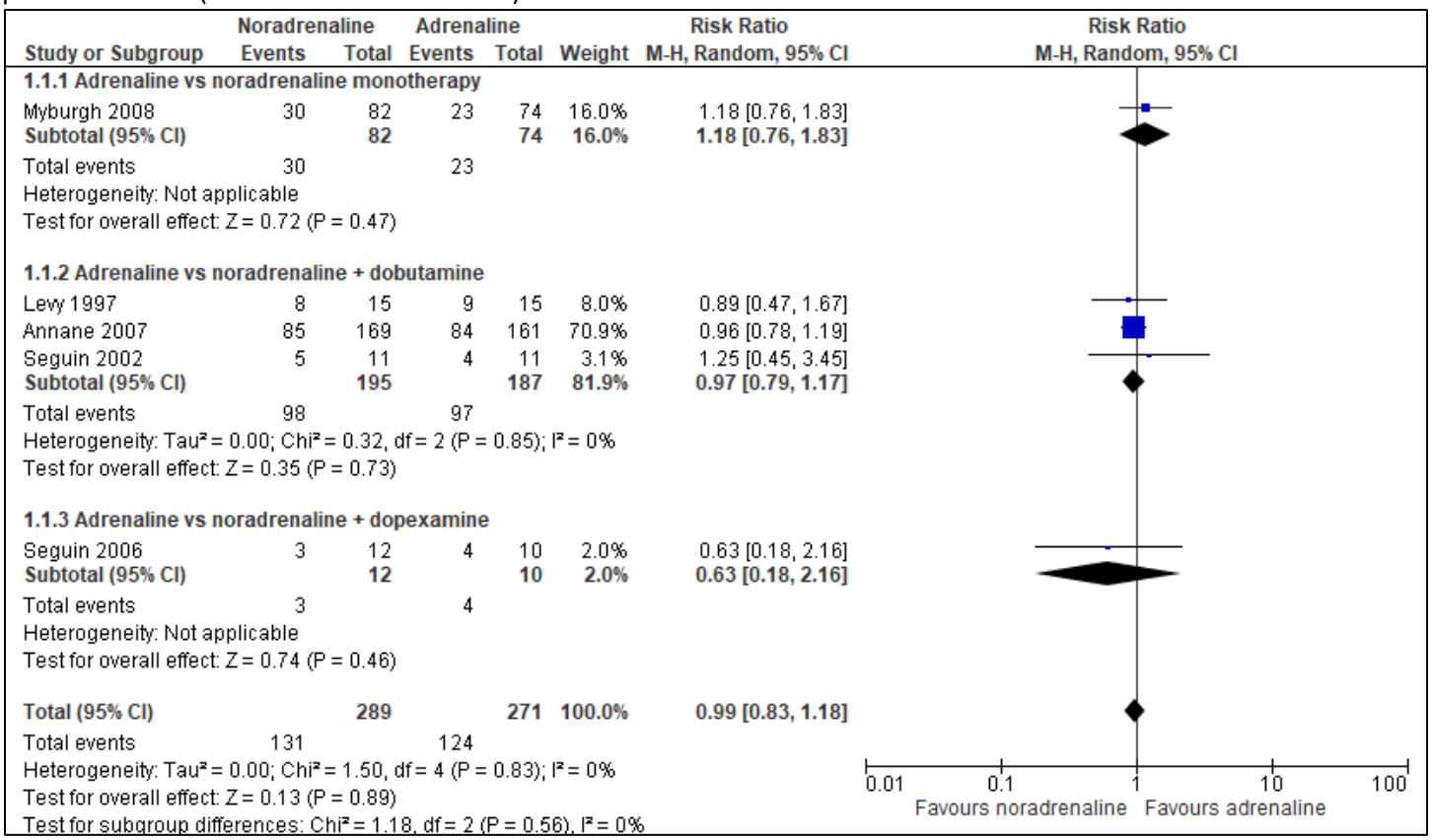

Figure 3. Forest plot comparing adrenaline vs noradrenaline monotherapy or noradrenaline-dopamine derivative (dobutamine or dopexamine) combination therapy in septic shock, for the outcome: mortality.

- **Mortality - monotherapy**

There is probably no difference in mortality between noradrenaline (norepinephrine) [30/82 (36.6%)] compared to adrenaline (epinephrine) [23/74 (31.1%)] RR 1.18 95% CI 0.76 to 1.83 (**Figure 4**). However, 22 patients (12.9%) were withdrawn from their blinded treatment allocation (either adrenaline or noradrenaline) to open-label noradrenaline (norepinephrine) due to associated adverse effects of transient increase in lactate concentrations and heart rate.

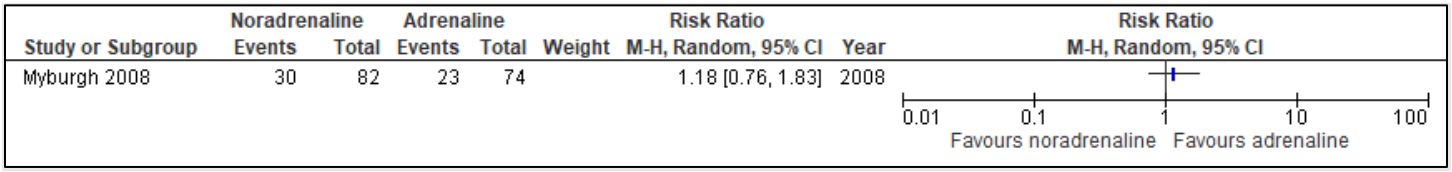

Figure 4. Forest plot comparing adrenaline to noradrenaline in septic shock, for the outcome: mortality.

- **Mortality - combination therapy**

Similarly, there was no mortality difference for noradrenaline (norepinephrine) with dopamine derivative (dobutamine or dopexamine) combination therapy [101/207 (48.8%) compared to adrenaline (epinephrine) monotherapy [101/197 (51.3%)] ,RR 0.96 (95% CI 0.79 to 1.16; I^2=0%; **Figure 5**).

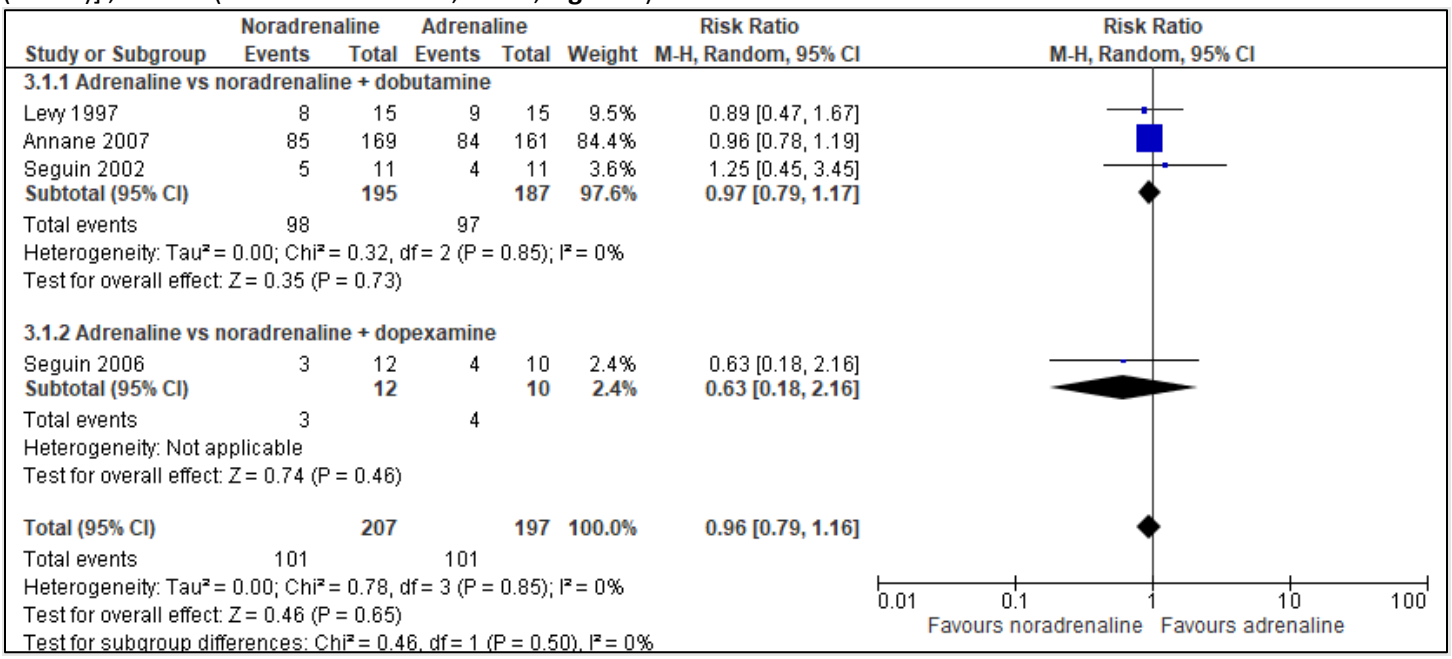

Figure 5. Forest plot comparing adrenaline to noradrenaline + dopamine derivative in septic shock, for the outcome: mortality.

- **Time to MAP goal (24h without vasopressor use)**

Noradrenaline (with/without other catecholamines) may reduce/have little to no effect on time to mean arterial pressure goal (24 hours without vasopressor use) but the evidence is very uncertain – assessed as *very low certainty* due to possible attrition and for serious imprecision in this sub analysis (**Table 4**). In the Myburgh et al (2008) trial, *a priori* severe sepsis subgroup at baseline (158/277), there was no difference in the median time to achieve target MAP between adrenaline (epinephrine) (35.1 h; IQR 16.7 to 75 h; n=76) and noradrenaline (norepinephrine) — 50.0 h(IQR 18.2 to 127.5 h; n=82), with a hazards ratio (HR) of 0.81; 95% CI 0.59 to 1.12; p= 0.18). Based on a probability of 63.9% to achieve the MAP goal by 48 hours with adrenaline (epinephrine), 77 per 1000 fewer patients (from 187 fewer to 82 more) would reach the MAP goal when treated with noradrenaline (norepinephrine) compared to adrenaline (epinephrine) — refer to Kaplan-Meier plot for all critically ill patients in **Figure 6**.

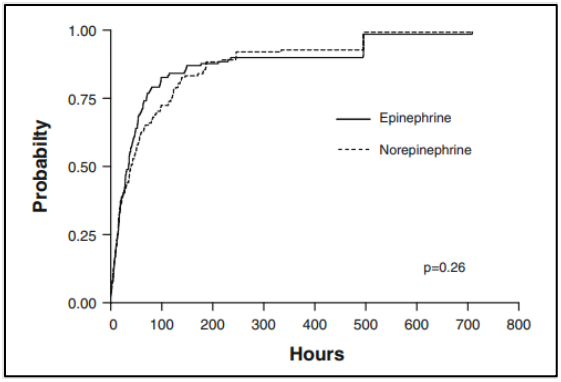

Figure 6. Kaplan-Meier estimates for probability of achieving MAP - adrenaline (epinephrine) vs noradrenaline (norepinephrine) in critically ill adults

- **Time to MAP stabilisation:**

Noradrenaline (with/without other catecholamines) may increase/have little to no effect on time to MAP stabilisation (MAP 70 to 80 mmHg) but the evidence is very uncertain, MD 7.17 minutes (95% CI -16.74 to 31.08; **Figure 7**). Evidence

was judged as *very low certainty* due to serious risk of measurement bias, inconsistency as uncertainty and very serious imprecision (**Table 4**).

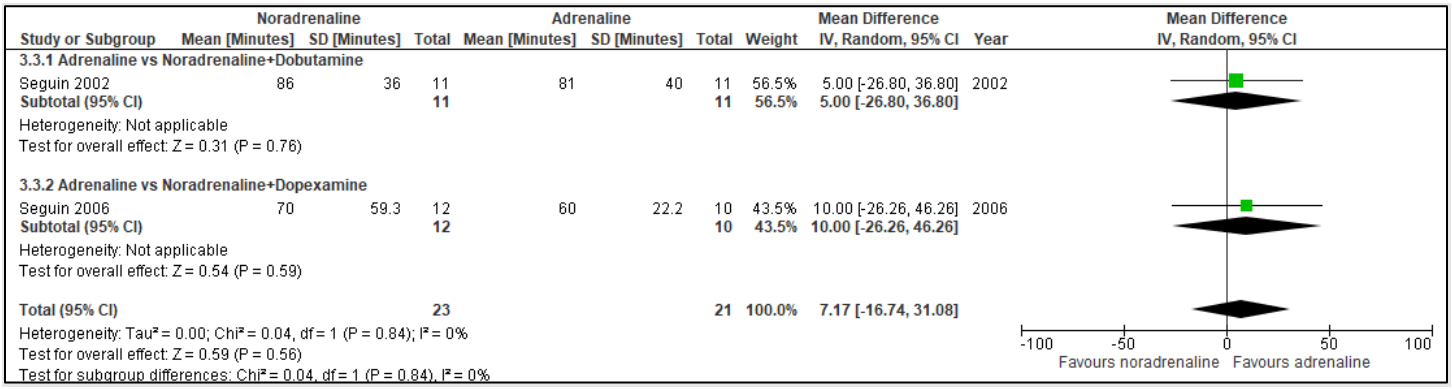

Figure 7. Forest plot comparing adrenaline vs noradrenaline + dopamine derivative in septic shock, for the outcome: Time to MAP stabilisation (70 to 80 mmHg) [minutes].

- **Vasopressor free days (Day 28)**

Noradrenaline (with/without other catecholamines) may reduce/have little to no effect on vasopressor free days (from beginning of treatment to 28 days post treatment initiation) compared to adrenaline (epinephrine), MD of -0.05, 95% CI -4.07 to 3.96; I^2=63% (**Figure 8**), but there was *very low certainty* of evidence due to serious imprecision, possible attrition and inconsistent comparators.

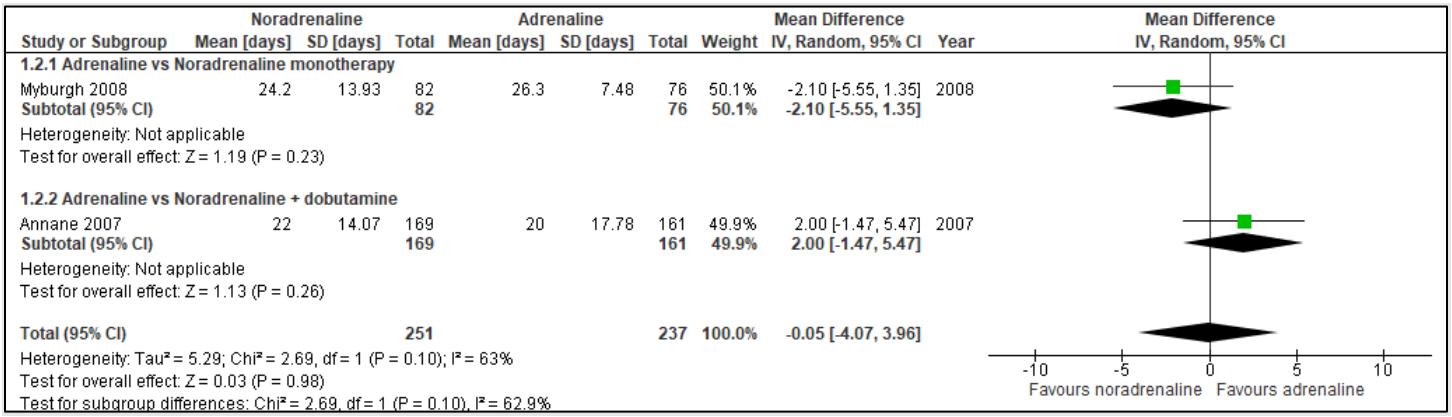

Figure 8: Forest plot comparing adrenaline vs noradrenaline in septic shock, for outcome: vasopressor free days (Day 28)

Safety:

- **Lactate concentrations**

Noradrenaline (norepinephrine), with/without other catecholamines, may not reduce the mean change in lactate concentration, compared to adrenaline (epinephrine). Certainty of evidence was downgraded to *very low certainty* due to serious imprecision and very serious risk of bias (**Table 4**). Two studies (Levy 1997 and Seguin 2002) assessed arterial lactate concentrations during treatment and reported data suitable for inclusion in a meta-analysis. Including 52 patients, the mean difference between the intervention and control groups was -0.16 mmol/L (95% CI -1.14 to 0.82; I^2=4%; **Figure 9**) between the epinephrine monotherapy and the norepinephrine+dobutamine combination therapy groups, which is considered to be clinically insignificant.

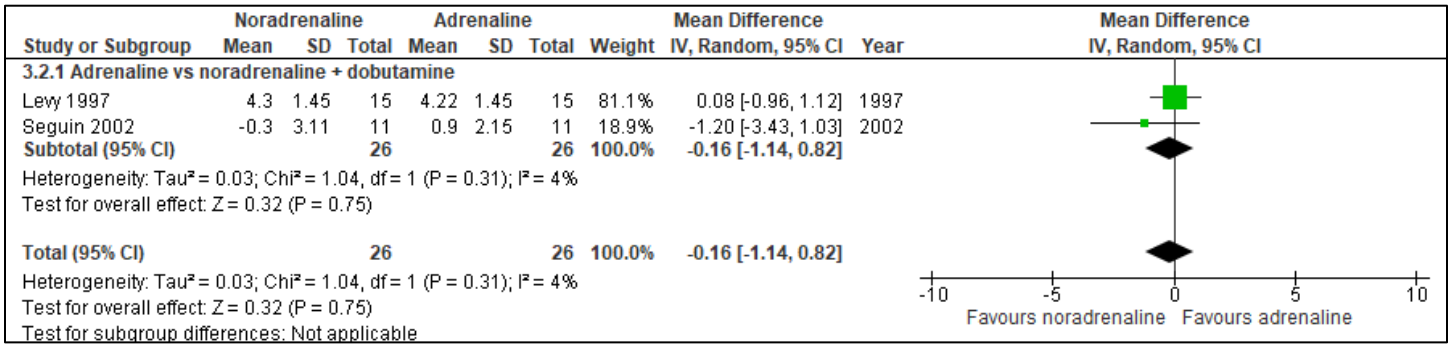

Figure 9. Forest plot comparing adrenaline vs noradrenaline+dobutamine combination in septic shock, on arterial lactate concentrations after 24 hours

- **Arrhythmias (any type)**

Noradrenaline (with/without other catecholamines) may not reduce arrhythmias (any type), certainty of evidence assessed as *very low* due to attrition and very serious imprecision (**Table 4**). Two trials (Levy 1997, Annane 2007) reported on arrhythmias, with no arrythmias reported in either treatment group by Levy *et al.* (1997), whilst Annane *et al.* (2007) reported no difference in supra- or ventricular-tachyarrhythmias between the adrenaline (epinephrine) [31/176 (17.6%)] vs noradrenaline (norepinephrine) + dobutamine combination treatment group [30/184 (16.3%)], RR 0.92 (95% CI 0.59 to 1.45), absolute difference of 14 patients with arrhythmias per 1000 patients treated (from 72 fewer to 79 more; **Figure 10)**.

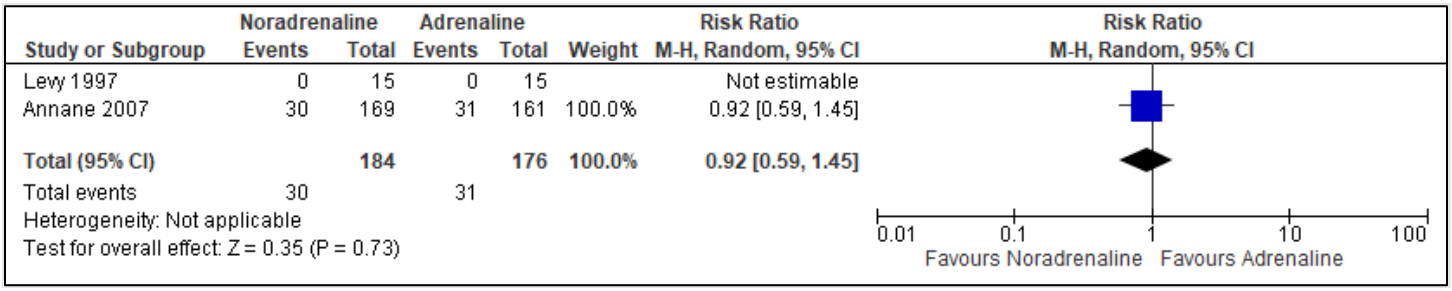

Figure 10. Forest plot of adrenaline compared to noradrenaline + dopamine derivative in septic shock, for the outcome: Arrhythmias.

Table 4. GRADE Summary of findings: Noradrenaline (with/without other catecholamines) compared to adrenaline for septic shock

Patient or population: Septic shock
Setting: Hospital
Intervention: Noradrenaline (with/without other catecholamines)
Comparison: Adrenaline

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty	What happens
		Without Noradrenaline (with/without other catecholamines)	With Noradrenaline (with/without other catecholamines)	Difference		
Mortality follow-up: 28 days n = 560 (5 RCTs)	**RR 0.99** (0.83 to 1.18)	45.8%	**45.3%** (38 to 54)	**0.5% fewer** (7.8 fewer to 8.2 more)	⊕⊕◯◯ Low[a,b]	Noradrenaline (with/without other catecholamines) probably does not increase/reduce mortality.
Time to mean arterial pressure goal (24 hours without vasopressor use) (Time to MAP goal) n = 158 (1 RCT)	**HR 0.81** (0.59 to 1.12) [Time to mean arterial pressure goal (24 hours without vasopressor use)]	**Moderate**			⊕◯◯◯ Very low[c,d]	Noradrenaline (with/without other catecholamines) may reduce/have little to no effect on time to mean arterial pressure goal (24 hours without vasopressor use) but the evidence is very uncertain.
		63.9%	**56.2%** (45.2 to 68.1)	**7.7% fewer** (18.7 fewer to 4.2 more)		
Time to MAP stabilisation (MAP 70 to 80 mmHg) assessed with: minutes n = 44 (2 RCTs)	-	The mean time to MAP stabilisation (MAP 70 to 80 mmHg) was **0**	-	MD **7.17 more** (16.74 fewer to 31.08 more)	⊕◯◯◯ Very low[e,f,g]	Noradrenaline (with/without other catecholamines) may increase/have little to no effect on time to MAP stabilisation (MAP 70 to 80 mmHg) but the evidence is very uncertain.
Vasopressor free days (28 days) n = 488 (2 RCTs)	-	The mean vasopressor free days (28 days) was **0**	-	MD **0.05 fewer** (4.07 fewer to 3.96 more)	⊕◯◯◯ Very low[b,c,h]	Noradrenaline (with/without other catecholamines) may reduce/have little to no effect on vasopressor free days (28 days) but the evidence is very uncertain.
Arrhythmias (any type) n = 360 (2 RCTs)	**RR 0.92** (0.59 to 1.45)	17.6%	**16.2%** (10.4 to 25.5)	**1.4% fewer** (7.2 fewer to 7.9 more)	⊕◯◯◯ Very low[c,g]	Noradrenaline (with/without other catecholamines) may not reduce arrhythmias (any type).
Mean change in lactate concentration assessed with: mmol/l n = 52 (2 RCTs)	-	The mean change in lactate concentration was **0** mmol/l	-	MD **0.16 mmol/l fewer** (1.14 fewer to 0.82 more)	⊕⊕◯◯ Low[b,i]	Noradrenaline (with/without other catecholamines) may not reduce mean change in lactate concentration.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **HR:** hazard Ratio; **MD:** mean difference; **n**: sample size; **RR:** risk ratio

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. Downgraded by one level for serious risk of bias as one trial was open-label (Seguin 2006) and compromised blinding due to adrenaline-specific lactic acidosis toxicity in another trial (Myburgh 2008).
b. Downgraded by one level for serious imprecision as the CI includes appreciable benefit and harm.
c. Downgraded by one level for serious risk of bias due to possible attrition (Myburgh 2008).
d. Downgraded by one level for serious imprecision as OIS criterion in sub-analysis not met.
e. Downgraded by one level for serious risk of measurement bias.
f. Downgraded by one level for serious inconsistency as uncertainty regarding the definition of MAP stabilisation.
g. Downgraded by two levels for very serious imprecision as few events and the CI includes appreciable benefit and harm.
h. Downgraded by one level for serious inconsistency due to different comparators (Annane 2007, Myburgh 2008).
i. Downgraded by one level for serious risk of bias as insufficient information to assess selection and measurement risk (Levy 1997, Seguin 2002).

d. Planned or ongoing clinical trials

A search was conducted on Clinical Trials and WHO ICTRP databases, and we identified no planned or ongoing trials relevant to the PICO of this review.

7. Conclusion:

Our review showed that there is little difference in the effectiveness and safety of noradrenaline (norepinephrine) and adrenaline (epinephrine) for managing septic shock. The latest Surviving Sepsis guidelines recommend noradrenaline (norepinephrine) as first-line therapy, but the evidence cited to support this recommendation is limited and suggests little difference between the two agents (Evans 2021). Our review found that the risk of mortality and the time required to stabilize blood pressure without vasopressors were similar for both agents, although the certainty of the evidence was low or very low.

While adrenaline (epinephrine) has been associated with a potentially higher risk of adverse outcomes, such as arrhythmias, tachycardia, and elevated lactate concentrations, our review found that these risks were similar for both agents. It has been suggested that increased lactate concentrations may be an indicator of increased tissue hypoxia and anaerobic metabolism, but this did not translate to an increase in adverse clinical outcomes in the studies included in this review and meta-analysis. While it is possible that adrenaline (epinephrine) may be associated with elevated lactate concentrations, these changes are likely transient as was shown in one RCT (Myburgh, 2008) and may not negatively impact clinical outcomes (Belletti, 2021). Clinicians should be aware of this potential adverse effect when monitoring patients' clinical progress using blood gas investigations such as arterial blood pH and lactate concentrations.

Thus, it could be inferred that noradrenaline (norepinephrine) can safely be used as an alternative to adrenaline (epinephrine) but may not be affordable. A direct comparison of per-milligram drug prices suggest a seven to twenty fold increase in treatment costs with noradrenaline compared with adrenaline. Therefore, the choice of vasopressor therapy will most likely depend on cost, feasibility, and availability.

In conclusion, this review found that adrenaline (epinephrine) monotherapy is associated with similar clinical outcomes as noradrenaline (norepinephrine) used as monotherapy or in combination with other vasopressors.

Table 5. Characteristics of included studies

AUTHOR, DATE	TYPE OF STUDY	POPULATION (N)	INTERVENTION(S) vs COMPARATOR(S)	OUTCOMES	COMMENTS
A: SYSTEMATIC REVIEW					
Gamper, 2016	Systematic review of 28 RCTs 6 RCTs compared epinephrine to other vasopressors (alone or in combination)	N=3497; critically ill patients with hypotensive shock N=703; epinephrine comparisons, (compared with norepinephrine, norepinephrine + dobutamine and norepinephrine + dopexamine) Participants with septic shock (Annane 2007; Levy 1997; Seguin 2002; Seguin 2006), participants with cardiogenic shock (Levy 2011) and critically ill participants (Myburgh 2008).	Epinephrine Vs Norepinephrine; Norepinephrine + dobutamine; and Norepinephrine + dopexamine	Overall/Total mortality	• Systematic review of high quality (High AMSTAR rating – see **Appendix 4.** • Systematic review reviewed all vasopressors alone or in combination, and only 6 of the 28 RCTs were eligible for review (PICO criteria) • Population included all critically ill patients with hypotensive shock – this review focuses specifically on patients with septic shock
B: RANDOMISED CONTROLLED TRIALS					
Epinephrine vs norepinephrine					
Myburgh 2008	Multi-centre double-blind randomized controlled trial, 4 multi-disciplinary university hospital ICUs; Australia Funding for statistical analysis of this study from the Australian and New Zealand College of Anaesthetists (Project grant: 06/024). Financial contribution from participating institutions that provided substantial support from internal funds Conflict of interest: none declared	N=280 Adult ICU participants requiring vasopressors for any reason Subgroup analysis: septic shock, circulatory failure Mean age = 60 years 39% female APACHE II score = 22	Switch from the vasopressor at inclusion to : Epinephrine (no dosing scheme reported) Or Norepinephrine (no dosing scheme reported) no restriction on other vasopressors except study drugs	• To achieve MAP > 70 mm Hg (or individualized by treating physicians) • Time to achieve MAP goal • Drug-free days from randomization (primary) • Mortality at days 28, 90	• For the mortality analysis: used data on 90-day mortality • Risk of bias assessment – see figure 2
Epinephrine vs norepinephrine + dobutamine					
Annane, 2007	Multi-centre double-blind randomized controlled trial in 19 ICUs (CATS study); France	n=330 Adult participants with septic shock (study authors' definition)	Epinephrine infusion 0.2 µg/kg/min (n = 161) Vs	• 28-day mortality (primary); 7-, 14-, 90-day ICU • Hospital mortality • Duration of vasopressor therapy	• For the mortality analysis, 90-day mortality was used.

AUTHOR, DATE	TYPE OF STUDY	POPULATION (N)	INTERVENTION(S) vs COMPARATOR(S)	OUTCOMES	COMMENTS
	Funding: The French Ministry of Health provided financial support (1997 Clinical Research Hospital Programme PHRC 1997, AOM 97123) *Declarations of interest:* None reported	Mean age = 63 years, 39% female SAPS II score = 53, SOFA score = 11	Norepinephrine infusion 0.2 µg/kg/min and dobutamine 5 µg/kg/min (N = 169) Both adjusted according to MAP, pulmonary arterial wedge pressure, cardiac index and response to fluid challenge	• Time to haemodynamic success • Adverse events	• Risk of bias assessment – see figure 2
Levy, 1997	Single-centre randomized controlled trial, University hospital; France *Funding:* Supported by "Commi-tee of Clinical Research of Nancy Universi-ty Hospital" and by a grant of Lilly France(Saint-Cloud, France) *Declarations of interest:* Not declared	n = 30 Mean age = 54 years (Epinephrine group); 56 years (Norepinephrine/dobutamine group) Predominantly pulmonary infection APACHE II score: epinephrine group = 23; Norepinephrine/dobutamine group = 24 Adult surgical and medical participants with septic shock	Epinephrine and norepinephrine started at 0.3mg/kg per min and titrated to MAP > 80 mmHg Dobutamine was infused at a fixed dose of 5 µg/kg/min	• Mortality • Haemodynamics • Tonometry	• Risk of bias assessment – see figure 2 • Reporting error for arterial pH at 24 hours between groups found. No correction available on journal article webpage.
Seguin 2002	Single-centre randomized controlled trial, University hospital; France *Funding:* Not reported *Declarations of interest:* Not reported	n = 22 Adult participants with septic shock; unclear whether medical or surgical	Goal-directed epinephrine vs norepinephrine + fixed dobutamine (5 mcg/kg/min)	• Death	• For the mortality analysis: used data on undetermined mortality • It is unclear when participants died • Risk of bias assessment – see figure 2
Epinephrine vs norepinephrine + dopexamine					
Seguin 2006	Single-centre randomized controlled trial, University hospital; France *Funding:* Supported by Grant from Rennes University Hospital and Rennes 1 University, 2001 Clinical	n =22 Adult participants with septic shock (study authors' definition) Mean age = 66 years, 23% female SAPS II score = 54 SOFA score = 10	Norepinephrine (NE) infusion 0.2 mcg/kg/min ***plus*** Dopexamine (DX) infusion 0.5 mcg/kg/min • If cardiac index > 3 L/kg/min, NE increased by 0.2 mcg/kg/min every 3 minutes until MAP 70 to 80 mmHg	• Primary: Gastromucosal blood flow • Haemodynamics • 28-day mortality • 90-day mortality	• For the mortality analysis, 90-day mortality was used. • Risk of bias assessment – see figure 2

AUTHOR, DATE	TYPE OF STUDY	POPULATION (N)	INTERVENTION(S) vs COMPARATOR(S)	OUTCOMES	COMMENTS
	Research Program, Rennes, France *Declarations of interest:* Not reported		• If cardiac index < 3 L/kg/min, DX increased by 0.5 mcg/kg/min every 3 minutes until MAP 70 to 80 mmHg vs Epinephrine infusion 0.2 mcg/kg/min. Increased by 0.2 mcg/kg/min every 3 minutes until MAP 70 to 80mm Hg		

Table 6. Excluded studies

Author, date		Title	Study type	Reason for exclusion
1	Zhao, 2012	Dopamine versus norepinephrine for septic shock: A systemic review.	Systematic Review	Wrong comparator
2	Zhou, 2014	Clinical trials comparing norepinephrine with vasopressin in patients with septic shock: a meta-analysis.	Systematic Review	Wrong comparator
3	Lu, 2021	Norepinephrine was superior in death risk reducing and hemodynamics compared to dopamine in treatment of patients with septic shock	Systematic Review	Wrong comparator
4	Yao, 2020	Clinical Efficiency of Vasopressin or Its Analogs in Comparison With Catecholamines Alone on Patients With Septic Shock: A Systematic Review and Meta-Analysis.	Systematic Review	Wrong comparator
5	Kochkin, 2020	Modern vasopressor therapy of septic shock (Review)	Systematic Review	Wrong study design
6	Gordon, 2021	A meta-analysis of early administration of vasopressor in septic shock: Is there mortality benefit?	Systematic Review	Wrong comparator
7	Soong, 2011	Vasopressin and terlipressin in the treatment of vasodilatory septic shock: A systematic review	Systematic Review	Wrong comparator
8	Belletti, 2015	The Effect of inotropes and vasopressors on mortality: a meta-analysis of randomized clinical trials.	Systematic Review	Wrong comparator
9	Tan, 2016	Vasopressin and its analog terlipressin versus norepinephrine in the treatment of septic shock: A meta-analysis.	Systematic Review	Wrong comparator
10	Yin, 2018	Efficacy of norepinephrine, dopamine or vasopressor in the management of septic shock and severe sepsis: A meta-analysis.	Systematic Review	Wrong comparator
11	Serpa Neto, 2012	Vasopressin and terlipressin in adult vasodilatory shock: a systematic review and meta-analysis of nine randomized controlled trials.	Systematic Review	Wrong comparator
12	Vasu, 2012	Norepinephrine or dopamine for septic shock: systematic review of randomized clinical trials.	Systematic Review	Wrong comparator
13	Teja, 2020	Vasopressor Dosing in Septic Shock Clinical Trials: A Systematic Review and Ecologic Study.	Systematic Review	Wrong outcomes
14	Roumpf, 2019	Does the Addition of Vasopressin to Catecholamine Vasopressors Affect Outcomes in Patients With Distributive Shock?	Systematic Review	Wrong comparator
15	Nagendran, 2019	Vasopressin in septic shock: an individual patient data meta-analysis of randomised controlled trials.	Systematic Review	Wrong comparator
16	Sedhai, 2022	Vasopressin versus norepinephrine as the first-line vasopressor in septic shock: A systematic review and meta-analysis.	Systematic Review	Wrong comparator
17	Rudis, 1996	Is it time to reposition vasopressors and inotropes in sepsis?	Pooled data analysis	Wrong study design
18	Li, 2020	Effect of terlipressin on prognosis of adult septic shock patients: a Meta-analysis	Systematic Review	Wrong intervention
19	Zhou, 2013	Effectiveness of norepinephrine versus dopamine for septic shock: a meta analysis	Systematic Review	Wrong comparator
20	Zhu, 2019	Terlipressin for septic shock patients: a meta-analysis of randomized controlled study.	Systematic Review	Wrong intervention
21	Morelli, 2008a	Effects of short-term simultaneous infusion of dobutamine and terlipressin in patients with septic shock: the DOBUPRESS study	RCT in Gamper, 2016	Wrong intervention
22	Morelli, 2008b	Phenylephrine versus norepinephrine for initial hemodynamic support of patients with septic shock: a randomized, controlled trial.	RCT in Gamper, 2016	Wrong intervention
23	Morelli 2009	Continuous terlipressin versus vasopressin infusion in septic shock (TERLIVAP): a randomized, controlled pilot study.	RCT in Gamper, 2016	Wrong intervention
24	Svoboda 2012	Terlipressin in the treatment of late phase catecholamine-resistant septic shock. Hepato-Gastroenterology	RCT in Gamper, 2016	Wrong intervention
25	Yildizdas 2008	Terlipressin as a rescue therapy for catecholamine-resistant septic shock in children. Intensive Care Medicine	RCT in Gamper, 2016	Wrong intervention
26	Hajjar 2019	Vasopressin Versus Norepinephrine for the Management of Septic Shock in Cancer Patients: the VANCS II Randomized Clinical Trial	RCT	Wrong comparator
27	Permpikul 2017	Early norepinephrine administration vs. standard treatment during severe sepsis/septic shock resuscitation: a randomized control trial	RCT	Wrong indication
28	Fe 2017	Vasopressin or epinephrine as a second vasopressor in septic shock: a pilot study	Pilot study	Wrong study design
29	Nadler 2016	Vasopressin as a Single Vasopressor Agent in Patients with Septic Shock	Narrative review	Wrong study design
30	Clem 2016	Norepinephrine and vasopressin vs norepinephrine alone for septic shock: randomized controlled trial	RCT	Wrong comparator
31	Zambolim 2018	Vasopressin versus norepinephrine for the management of septic shock in cancer patients (VANCS II)	RCT	Wrong comparator
32	Roy 2016	Attempting to define and refine vasopressin use in septic shock: the VANISH trial	Narrative review	Wrong study design
33	Du 2015	Comparison of clinical effect of dopamine and norepinephrine in the treatment of septic shock	RCT	Wrong comparator
34	Einav 2021	Vasopressor and inotrope treatment for septic shock: An umbrella review of reviews.	Non-RCT	Wrong study design
35	Young 2019	Vasopressin in septic shock: what we know and where to next?	Non-RCT	Wrong study design
36	Hernández 2019	Norepinephrine in septic shock.	Narrative review	Wrong comparator
37	Ammar 2019	Optimal norepinephrine-equivalent dose to initiate epinephrine in patients with septic shock.	Non-RCT	Wrong study design
38	Teja 2022	First-Line Vasopressor Use in Septic Shock and Route of Administration: An Epidemiologic Study.	Non-RCT	Wrong study design
39	Nguyen 2017	Comparative Effectiveness of Second Vasoactive Agents in Septic Shock Refractory to Norepinephrine.	Non-RCT	Wrong study design
40	Aso 2022	Vasopressin versus epinephrine as adjunct vasopressors for septic shock	Non-RCT	Wrong study design
41	Feldheiser 2021	Vasopressor effects on venous return in septic patients: a review.	Letter	Wrong study design

42	Hammond 2018	Prospective Open-label Trial of Early Concomitant Vasopressin and Norepinephrine Therapy versus Initial Norepinephrine Monotherapy in Septic Shock.	RCT	Wrong comparator
43	Li 2019	How to use vasoactive drugs in septic shock.	Narrative review	Non- English article
44	Annane 2015	Evidence to Practice Gap: The Case of Dopamine.	Narrative review	Wrong study design
45	Russell 2018	Vasopressin versus norepinephrine in septic shock: a propensity score matched efficiency retrospective cohort study in the VASST coordinating center hospital.	Non-RCT	Wrong study design
46	Sedhai 2022	Vasopressin versus norepinephrine as the first-line vasopressor in septic shock: A systematic review and meta-analysis.	Non-RCT	Wrong study design
47	Mazandaran University of Medical Sciences 2020	Comparison Dopamine and Nor-epinephrine on End tidal carbon dioxide pressure in patients with septic shock	RCT	Wrong outcomes
48	Albanese 2005	Terlipressin or norepinephrine in hyperdynamic septic shock: a prospective, randomized study	RCT in Gamper, 2016	Wrong intervention
49	Boccara 2003	Terlipressin versus norepinephrine to correct refractory arterial hypotension after general anesthesia in patients chronically treated with renin-angiotensin system inhibitors	RCT in Gamper, 2016	Wrong intervention
50	Choong 2009	Vasopressin in pediatric vasodilatory shock: a multicenter randomized controlled trial	RCT in Gamper, 2016	Wrong intervention
51	De Backer 2010	Comparison of dopamine and norepinephrine in the treatment of shock	RCT in Gamper, 2016	Wrong intervention
52	Dünser 2003	Arginine vasopressin in advanced vasodilatory shock: a prospective, randomized, controlled study	RCT in Gamper, 2016	Wrong intervention
53	Han 2012	[A clinical study of pituitrin versus norepinephrine in the treatment of patients with septic shock].	RCT in Gamper, 2016	Wrong intervention
54	Han 2013	Terlipressin decreases vascular endothelial growth factor expression and improves oxygenation in patients with acute respiratory distress syndrome and shock	RCT in Gamper, 2016	Wrong intervention
55	Jain 2010	Comparison of phenylephrine and norepinephrine in the management of dopamine-resistant septic shock.	RCT in Gamper, 2016	Wrong intervention
56	Lauzier 2006	Vasopressin or norepinephrine in early hyperdynamic septic shock: a randomized clinical trial	RCT in Gamper, 2016	Wrong intervention
57	Levy 2011	Comparison of norepinephrine-dobutamine to epinephrine for hemodynamics, lactate metabolism, and organ function variables in cardiogenic shock. A prospective, randomized pilot study	RCT in Gamper, 2016	Wrong intervention
58	Luckner 2006	Cutaneous vascular reactivity and flow motion response to vasopressin in advanced vasodilatory shock and severe postoperative multiple organ dysfunction syndrome	RCT in Gamper, 2016	Wrong intervention
59	Malay1999	Low-dose vasopressin in the treatment of vasodilatory septic shock	RCT in Gamper, 2016	Wrong intervention
60	Marik 1994	The contrasting effects of dopamine and norepinephrine on systemic and splanchnic oxygen utilization in hyperdynamic sepsis	RCT in Gamper, 2016	Wrong intervention
61	Martin 1993	Norepinephrine or dopamine for the treatment of hyperdynamic septic shock	RCT in Gamper, 2016	Wrong intervention
62	Mathur 2007	Comparison of norepinephrine and dopamine in the management of septic shock using impedance cardiography	RCT in Gamper, 2016	Wrong intervention
63	Patel 2010	Efficacy and safety of dopamine versus norepinephrine in the management of septic shock	RCT in Gamper, 2016	Wrong intervention
64	Ruokonen 1993	Regional blood flow and oxygen transport in septic shock	RCT in Gamper, 2016	Wrong intervention
65	Russell 2008	Vasopressin versus norepinephrine infusion in patients with septic shock	RCT in Gamper, 2016	Wrong intervention
66	Svoboda 2012	Terlipressin in the treatment of late phase catecholamine-resistant septic shock	RCT in Gamper, 2016	Wrong intervention
67	Yildizdas 2008	Terlipressin as a rescue therapy for catecholamine-resistant septic shock in children	RCT in Gamper, 2016	Wrong intervention

Note: The table lists 48 excluded records described in the PRISMA flow diagram (**Appendix 2**) and 19 RCTs excluded from the 2016 Gamper *et al*. systematic review.

Evidence to decision framework

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE OF BENEFIT	**What is the certainty/quality of evidence?** • **Mortality** High [ ] Moderate [ ] Low [X] Very low [ ] • **Time to MAP goal (24h without vasopressor use)** High [ ] Moderate [ ] Low [ ] Very low [X] • **Time to MAP stabilisation** High [ ] Moderate [ ] Low [ ] Very low [X] • **Vasopressor free days (to day 28):** High [ ] Moderate [ ] Low [ ] Very low [X] *High quality: confident in the evidence* *Moderate quality: mostly confident, but further research may change the effect* *Low quality: some confidence, further research likely to change the effect* *Very low quality: findings indicate uncertain effect*	• **Mortality:** *low certainty evidence due to serious* risk of bias (concerns of blinding of investigators and assessors) and serious imprecision. • **Time to MAP goal** (24 hours without vasopressor use)**:** *very low certainty evidence* due to serious risk of bias (possible attrition) and for serious imprecision. • **Time to MAP stabilisation** (MAP 70 to 80 mmHg or clinician discretion): *very low certainty* due to serious risk of measurement bias, serious inconsistency (uncertainty regarding the definition of MAP stabilisation) and very serious imprecision. • **Vasopressor free days (to day 28):** *very low certainty evidence* due to serious imprecision, serious risk of bias (possible attrition) and serious inconsistency (inconsistent comparators).
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** • **Mortality** Large [ ] Moderate [ ] Small [ ] None [X] • **Time to MAP goal (24h without vasopressor use)** Large [ ] Moderate [ ] Small [X] None [ ] • **Time to MAP stabilisation (70 to 80 mmHg or clinician discretion)** Large [ ] Moderate [ ] Small [X] None [ ] • **Time to MAP goal (24h without vasopressor use)** Large [ ] Moderate [ ] Small [ ] None [X]	• **Mortality:** Noradrenaline (norepinephrine) vs adrenaline (epinephrine) — 131/289 (45.3%) vs 124/171 (45.8%), with a relative risk (RR) of 0.99 (95% CI 0.83 to 1.18; I^2 = 0%; 5 fewer deaths per 1000 patients treated (from 78 fewer to 82 more)), • **Time to MAP goal:** Noradrenaline (norepinephrine) vs adrenaline (epinephrine) — Median 50.0 h vs 35.1 h — HR 0.81; 95% CI 0.59 to 1.12; p= 0.18. Based on a probability of 63.9% to achieve the MAP goal by 48 hours with epinephrine (adrenaline), 77 fewer patients per 1000 (from 187 fewer to 42 more) would achieve MAP goal when comparing noradrenaline (norepinephrine)-treated patients to adrenaline (epinephrine)-treated patients. • **Time to MAP stabilisation (70 to 80 mmHg or clinician discretion):** Noradrenaline may increase/have little to no effect on time to MAP stabilisation — Mean difference (MD) 7.17 minutes (from 16.74 fewer to 31.08 more). • **Vasopressor free days (to day 28):** Noradrenaline may reduce/have little to no effect on vasopressor free days — MD -0.05 days (from 4.07 fewer to 3.96 more)
QUALITY OF EVIDENCE OF HARM	**What is the certainty/quality of evidence?** • **Lactate concentrations** High [ ] Moderate [ ] Low [ ] Very low [X] • **Arrhythmias (any)** High [ ] Moderate [ ] Low [ ] Very low [X] *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	• **Lactate concentrations:** *very low certainty evidence* due to very serious risk of bias and serious imprecision, which is considered to be clinically insignificant. • **Arrhythmias (any type):** *very low certainty evidence* due to serious risk of bias (possible attrition) and very serious imprecision.

<table>
<tr><th></th><th>JUDGEMENT</th><th>EVIDENCE & ADDITIONAL CONSIDERATIONS</th></tr>
<tr><td>EVIDENCE OF HARMS</td><td>What is the size of the effect for harmful outcomes?
• Lactate concentrations
Large [ ] Moderate [ ] Small [ ] None [X]
• Arrhythmias (any)
Large [ ] Moderate [ ] Small [ ] None [X]</td><td>• Lactate concentrations: Noradrenaline may reduce/have no effect on lactate concentration — MD - 0.16 mmol/l (95% CI -1.14 fewer to 0.82 more).
• Arrhythmias (any type): adrenaline (epinephrine) [30/184 (16.3%)] vs noradrenaline (norepinephrine) + dobutamine combination treatment group [31/176 (17.6%)], RR 0.92 (95% CI 0.59 to 1.45).</td></tr>
<tr><td>BENEFITS & HARMS</td><td>Do the desirable effects outweigh the undesirable harms?
Favours intervention [ ] Favours control [ ] Intervention = Control or Uncertain [X]</td><td>There is uncertainty as to whether desirable effects outweigh undesirable effects, noting that increase in lactate concentrations may not be clinically important.</td></tr>
<tr><td>THERAPEUTIC INTERCHANGE</td><td>Therapeutic alternatives available: n/a</td><td></td></tr>
<tr><td>FEASABILITY</td><td>Is implementation of this recommendation feasible?
Yes [ ] No [X] Uncertain [ ]</td><td>Noradrenaline has recently been registered with SAHPRA, however, there are concerns regarding cost.</td></tr>
<tr><td>RESOURCE USE</td><td>How large are the resource requirements?
More intensive [X] Less intensive [ ] Uncertain [ ]</td><td>Price of medicines/ treatment course:
<table>
<tr><th>Medicine</th><th>Tender price *</th><th>SEP 100%</th><th>SEP 60%</th></tr>
<tr><td>Adrenaline (Pharma-Q Adrenaline 1 Amp 1 mg/ml)*</td><td>R 4.00</td><td>R 36.11 (10 units)</td><td>R 21.67</td></tr>
<tr><td>Noradrenaline (BGM-noradrenaline 10 Amps 2mg/ml; Available through S21 process – private sector price**</td><td>n/a</td><td>R 434.70 (10 units)***</td><td>n/a</td></tr>
<tr><td>Noradrenaline (Sinora – noradrenaline 10 Amps 4mg/4ml)***</td><td>n/a</td><td>R 2564.11</td><td>R 1538.40</td></tr>
</table>
* Contract circular HP06-2021SVP
**S21 private sector price sourced from MediKredit
***Noradrenaline-Sinora Single exit price (14 August 2023)
<table>
<tr><th>Medicine</th><th>Days treated (Median & IQR)¥</th><th>Total treatment dose (mg) (Median & IQR)¥</th><th>Per patient cost (Median & IQR) (Rand)</th></tr>
<tr><td>Adrenaline</td><td>2 (1, 11)</td><td>40.3 (23.0, 86.7)</td><td>R 161.28 (R 92.16, R 346.94)</td></tr>
<tr><td>Noradrenaline (BGM-noradrenaline)</td><td>4 (2, 21)</td><td>56.2 (40.3, 130.4)</td><td>R 1 220.64 (R 876.36, R 2 834.59)</td></tr>
<tr><td>Noradrenaline (Sinora)</td><td>4 (2, 21)</td><td>56.2 (40.3, 130.4)</td><td>R 3 600.01 (R 2 584.62, R 8 360.02)</td></tr>
</table>
¥ Based on data from Myburgh et al (2008)

Other resources: n/a</td></tr>
</table>

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
VALUES, PREFERENCES, ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the options?** Minor [ ] Major [ ] Uncertain [X] **Is the option acceptable to key stakeholders?** Yes [ ] No [ ] Uncertain [X]	There is no local survey data assessing the preferences and acceptability of healthcare workers or patients. However, it was reported that use of noradrenaline is preferred in the private sector.
EQUITY	**Would there be an impact on health inequity?** Yes [ ] No [ ] Uncertain [X]	There is no local survey data assessing equity. Additionally, there are concerns regarding price.

Version	Date	Reviewer(s)	Recommendation and Rationale
Initial	24 April 2023 *(Updated 6 October 2023)*	RM, TDL, SD, RG	The PHC/Adult Hospital Level Committee suggests not to use the option of noradrenaline for the management of septic shock in adults. The evidence is limited and uncertain.

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Appendix 1: Search Strategies

A: PubMed

1) Date: 7 October 2022

Search	Query	Results
#11	Search: #3 AND #6 Filters: Meta-Analysis, Systematic Review	113
#10	Search: #3 AND #6 Filters: Systematic Review	89
#9	Search: #7 AND #8	2,267
#7	Search: #3 AND #6	5,269
#8	Search: (randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]) NOT (animals [mh] NOT humans [mh])	4,844,207
#6	Search: #4 OR #5	383,954
#5	Search: noradrenaline[tiab] OR norepinephrine[tiab] OR levonor[tiab] OR levophed[tiab] OR levarterenol[tiab] OR arterenol[tiab] OR epinephrine[tiab] OR dopamine[tiab] OR intropin[tiab] OR adrenaline[tiab] OR vasopressin*[tiab] OR lypressin[tiab] OR felypressin[tiab] OR ornipressin[tiab] OR terlipressin[tiab] OR vasoconstrictor*[tiab] OR pitressin[tiab] OR vasopressor*[tiab]	306,406
#4	Search: norepinephrine[mh] OR vasoconstrictor agents[mh] OR epinephrine[mh] OR dopamine[mh] OR vasopressins[mh]	237,850
#3	Search: #1 OR #2	167,808
#2	Search: septic shock[tiab] OR toxic shock[tiab] OR endotoxin shock[tiab] OR endotoxic shock[tiab] OR severe sepsis[tiab] OR septicemia*[tiab] OR septiceamia*[tiab] OR blood stream infection*[tiab] OR bloodstream infection*[tiab] OR sepsis syndrome[tiab]	68,896
#1	Search: systematic inflammatory response syndrome[mh] OR sepsis[mh] OR shock, septic[mh]	137,718

PubMed

2) Date: 23 September 2022

Search	Query	Results
#10	Search: #3 AND #6 Filters: Meta-Analysis, Systematic Review	37
#9	Search: #7 AND #8	857
#8	Search: (randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]) NOT (animals [mh] NOT humans [mh])	4,831,580
#7	Search: #3 AND #6	1,774

Search	Query	Results
#6	Search: #4 OR #5	81,014
#5	Search: septic shock[tiab] OR toxic shock[tiab] OR endotoxin shock[tiab] OR endotoxic shock[tiab] OR severe sepsis[tiab] OR septicemia*[tiab] OR blood stream infection*[tiab] OR bloodstream infection*[tiab]	68,122
#4	Search: shock, sepsis[mh]	34,792
#3	Search: #1 OR #2	127,718
#2	Search: noradrenaline[tiab] OR norepinephrine[tiab] OR levonor[tiab] OR levophed[tiab] OR levarterenol[tiab] OR arterenol[tiab]	98,409
#1	Search: norepinephrine[mh]	87,035

B: Epistemonikos

Date: 7 October 2022

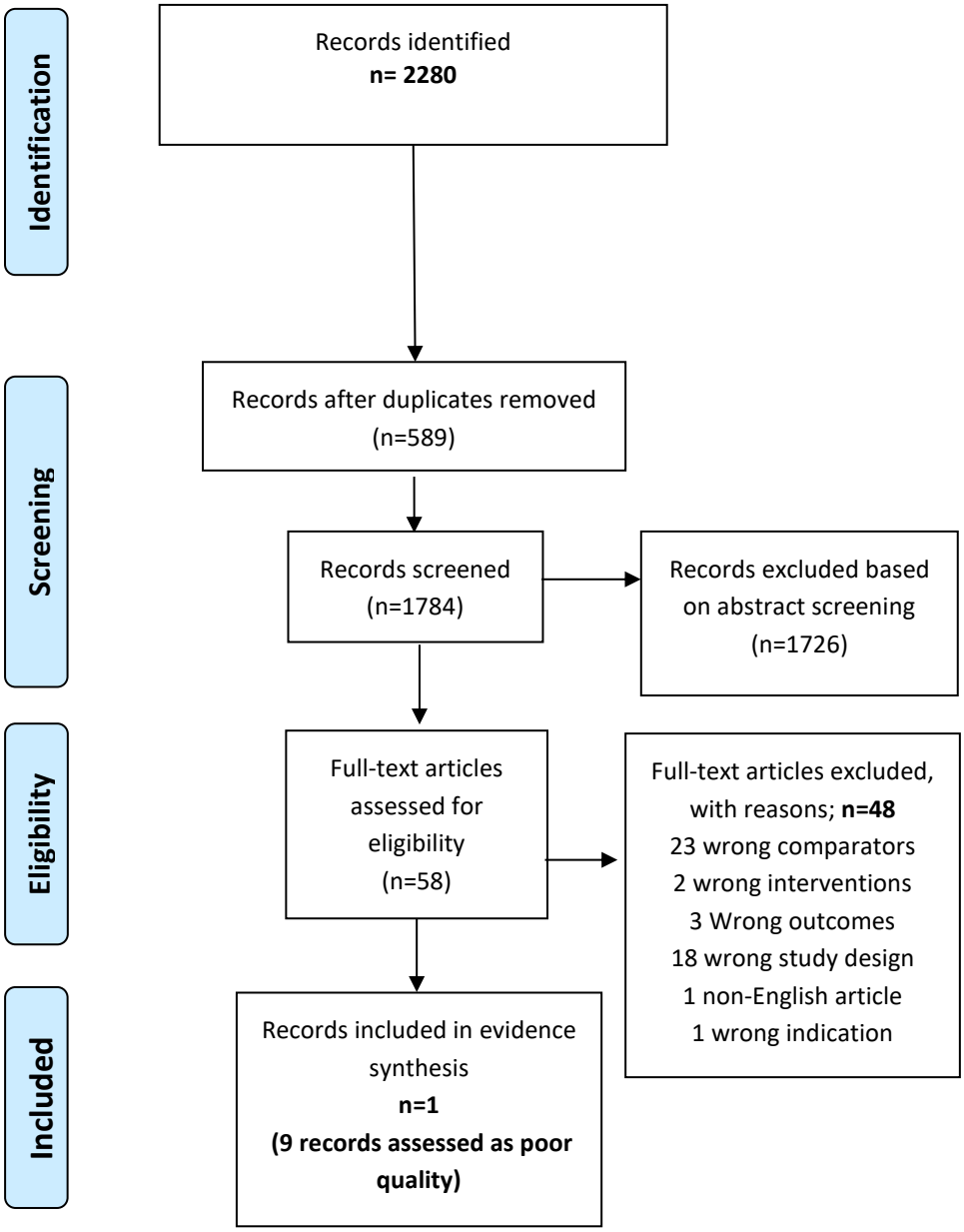
#	Query	Results
5	(title:("septic shock" OR "toxic shock" OR "endotoxin shock" OR "endotoxic shock" OR sepsis OR septicemia* OR septiceamia* OR "blood stream infection" OR "blood stream infections" OR "bloodstream infection" OR "bloodstream infections") OR abstract:("septic shock" OR "toxic shock" OR "endotoxin shock" OR "endotoxic shock" OR sepsis OR septicemia* OR septiceamia* OR "blood stream infection" OR "blood stream infections" OR "bloodstream infection" OR "bloodstream infections")) AND (title:(noradrenaline OR norepinephrine OR levonor OR levophed OR levarterenol OR arterenol OR epinephrine OR dopamine OR intropin OR adrenaline OR vasopressin* OR lypressin OR felypressin OR ornipressin OR terlipressin OR vasoconstrictor* OR pitressin OR vasopressor*) OR abstract:(noradrenaline OR norepinephrine OR levonor OR levophed OR levarterenol OR arterenol OR epinephrine OR dopamine OR intropin OR adrenaline OR vasopressin* OR lypressin OR felypressin OR ornipressin OR terlipressin OR vasoconstrictor* OR pitressin OR vasopressor*)) **Filters: Publication type = Primary Study**	634
4	(title:("septic shock" OR "toxic shock" OR "endotoxin shock" OR "endotoxic shock" OR sepsis OR septicemia* OR septiceamia* OR "blood stream infection" OR "blood stream infections" OR "bloodstream infection" OR "bloodstream infections") OR abstract:("septic shock" OR "toxic shock" OR "endotoxin shock" OR "endotoxic shock" OR sepsis OR septicemia* OR septiceamia* OR "blood stream infection" OR "blood stream infections" OR "bloodstream infection" OR "bloodstream infections")) AND (title:(noradrenaline OR norepinephrine OR levonor OR levophed OR levarterenol OR arterenol OR epinephrine OR dopamine OR intropin OR adrenaline OR vasopressin* OR lypressin OR felypressin OR ornipressin OR terlipressin OR vasoconstrictor* OR pitressin OR vasopressor*) OR abstract:(noradrenaline OR norepinephrine OR levonor OR levophed OR levarterenol OR arterenol OR epinephrine OR dopamine OR intropin OR adrenaline OR vasopressin* OR lypressin OR felypressin OR ornipressin OR terlipressin OR vasoconstrictor* OR pitressin OR vasopressor*)) **Filters: Publication type = Systematic Review**	170
3	(title:("septic shock" OR "toxic shock" OR "endotoxin shock" OR "endotoxic shock" OR sepsis OR septicemia* OR septiceamia* OR "blood stream infection" OR "blood stream infections" OR "bloodstream infection" OR "bloodstream infections") OR abstract:("septic shock" OR "toxic shock" OR "endotoxin shock" OR "endotoxic shock" OR sepsis OR septicemia* OR septiceamia* OR "blood stream infection" OR "blood stream infections" OR "bloodstream infection" OR "bloodstream infections")) AND (title:(noradrenaline OR norepinephrine OR levonor OR levophed OR levarterenol OR arterenol OR epinephrine OR dopamine OR intropin OR adrenaline OR vasopressin* OR lypressin OR felypressin OR ornipressin OR terlipressin OR vasoconstrictor* OR pitressin OR vasopressor*) OR abstract:(noradrenaline OR norepinephrine OR levonor OR levophed OR levarterenol OR	823

	arterenol OR epinephrine OR dopamine OR intropin OR adrenaline OR vasopressin* OR lypressin OR felypressin OR ornipressin OR terlipressin OR vasoconstrictor* OR pitressin OR vasopressor*))	
2	(title:(noradrenaline OR norepinephrine OR levonor OR levophed OR levarterenol OR arterenol OR epinephrine OR dopamine OR intropin OR adrenaline OR vasopressin* OR lypressin OR felypressin OR ornipressin OR terlipressin OR vasoconstrictor* OR pitressin OR vasopressor*) OR abstract:(noradrenaline OR norepinephrine OR levonor OR levophed OR levarterenol OR arterenol OR epinephrine OR dopamine OR intropin OR adrenaline OR vasopressin* OR lypressin OR felypressin OR ornipressin OR terlipressin OR vasoconstrictor* OR pitressin OR vasopressor*))	16,934
1	(title:("septic shock" OR "toxic shock" OR "endotoxin shock" OR "endotoxic shock" OR sepsis OR septicemia* OR septiceamia* OR "blood stream infection" OR "blood stream infections" OR "bloodstream infection" OR "bloodstream infections") OR abstract:("septic shock" OR "toxic shock" OR "endotoxin shock" OR "endotoxic shock" OR sepsis OR septicemia* OR septiceamia* OR "blood stream infection" OR "blood stream infections" OR "bloodstream infection" OR "bloodstream infections"))	22,555

C: Health technology assessment databases

Databases that were searched included NICE, Canada HTA, EUNETHTA and INATHTA, Google scholar.

Appendix 2: PRISMA flowchart



Modified From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

Appendix 3: AGREE II appraisal summaries

Guideline	Domain 1	Domain 2	Domain 3	Domain 4	Domain 5	Domain 6	Overall Assessment
Surviving Sepsis Guidelines, 2021	83%	58%	56%	75%	21%	54%	67%
The Japanese Clinical Practice Guidelines for Management of Sepsis and Septic Shock, 2020	92%	89%	83%	75%	44%	92%	67%
Clinical practice guidelines for sepsis and septic shock in adults in the Philippines, 2020	72%	56%	39%	78%	60%	38%	58%

Domain 1: Scope and purpose
Domain 2: Stakeholder involvement
Domain 3: Rigour of development
Domain 4: Clarity of presentation
Domain 5: Applicability
Domain 6: Editorial independence
OA: overall assessment

Appendix 4: Appraisal of previous surviving sepsis campaign guidelines that recommend norepinephrine vs. epinephrine therapy in patients with septic shock

Surviving sepsis guideline title (year published)	Recommendations	Cited evidence	Comment
Hemodynamic support in septic shock (2001)	• "Norepinephrine and dopamine preferred over epinephrine to correct hypotension in septic shock (grade E evidence)".	• "Norepinephrine markedly improves MAP and glomerular filtration. This is particularly true in the high output-low resistance state of many septic shock patients." • "A few studies have used norepinephrine as the only adrenergic agent to correct sepsis-induced hemodynamic abnormalities" – Fukuoka, 1989; Martin, 1990a; Martin, 1993; Ruokonen, 1993; Marik, 1994 • "Renal ischemia observed during hyperdynamic septic shock is not worsened by norepinephrine infusion and even suggests that this drug may effectively optimize renal blood flow and renal vascular resistance" - Redl-Wenzl, 1993; Winslow, 1973; Marik, 1994 • "Norepinephrine is probably more effective than dopamine at reversing hypotension in septic shock patients" - Martin, 1993 • "Other studies, however, have observed no significant changes in either cardiac output or stroke volume index after the use of norepinephrine in the presence of a significant increase in vascular resistance, suggesting that norepinephrine is exerting α_1-receptor agonist effects." - Desjars, 1987; Meadows, 1988; 1989; Hesselvik, 1989; Martin, 1990; Martin, 1994 • "Epinephrine has detrimental effects on splanchnic blood flow and causes transient decreases in pH and increases in the pCO2 gap" - Levy, 1997; Meier-Hellmann, 1997 • "Epinephrine administration has been associated with increases in systemic and regional lactate concentrations." - Levy, 1997; Wilson, 1992; Meier-Hellman, 1997 • "Because of its negative effects on gastric blood flow and blood lactate concentrations its use should be limited."	• Imbalanced presentation of evidence justifying preferred use of norepinephrine over epinephrine. • Low quality evidence informed preferred use of norepinephrine over epinephrine: Grade E evidence = Level IV or V evidence; Non-randomized studies, historical control studies, uncontrolled studies, case series, and expert opinion evidence
Surviving sepsis campaign guidelines (2004)	• "Either norepinephrine or dopamine (through a central line as soon as available) is the first-	• "Although there is no high-quality primary evidence to recommend one catecholamine over another, human and animal studies suggest some	• Preference for norepinephrine over epinephrine appears to depend on differences in metabolic effects like

	choice vasopressor agent to correct hypotension in septic shock."	advantages of norepinephrine and dopamine over epinephrine (potential tachycardia, possibly disadvantageous effects on splanchnic circulation) and phenylephrine (decrease in stroke volume)." – Hollenberg, 1999; Regnier, 1977; Martin, 1993; Martin, 2000; De Backer, 2003 • "Dopamine increases MAP and cardiac output, primarily due to an increase in stroke volume and heart rate." – Hollenberg, 1999; Regnier, 1977; Martin, 1993; Martin, 2000; De Backer, 2003 • "Norepinephrine increases MAP due to its vasoconstrictive effects, with little change in heart rate and less increase in stroke volume compared to dopamine." – Hollenberg, 1999; Regnier, 1977; Martin, 1993; Martin, 2000; De Backer, 2003 • "Norepinephrine is more potent than dopamine and may be more effective at reversing hypotension in patients with septic shock. Dopamine may be particularly useful in patients with compromised systolic function, but causes more tachycardia and may be more arrhythmogenic." – Hollenberg, 1999; Regnier, 1977; Martin, 1993; Martin, 2000; De Backer, 2003	lactate, as well as relatively preserved splanchnic circulation in patients with severe shock on norepinephrine compared to those on epinephrine. However, none of the referenced studies showed improvements in clinical outcomes or mortality.
Surviving sepsis campaign guidelines (2008)	• "We recommend either norepinephrine or dopamine as the first choice vasopressor agent to correct hypotension in septic shock (administered through a central catheter as soon as one is available) (grade 1C)." • "We suggest that epinephrine, phenylephrine, or vasopressin should not be administered as the initial vasopressor in septic shock (grade 2C)." • "We suggest that epinephrine be the first chosen alternative agent in septic shock that is poorly responsive to norepinephrine or dopamine (grade 2B)."	• "There is no high-quality primary evidence to recommend one catecholamine over another. Much literature exists that contrasts the physiologic effects of choice of vasopressor and combined inotrope/vasopressors in septic shock." – Martin, 1994; Martin, 2000; De Backer, 2003; Day, 1996; Le Tulzo, 1997; Bollaert, 1990; Zhou, 2002; Mackenzie, 1991; Moran, 1993; Yamazaki, 1982; Gregory, 1991; Annane, 2007 • "Human and animal studies suggest some advantages of norepinephrine and dopamine over epinephrine (the latter with the potential for tachycardia as well as disadvantageous effects on splanchnic circulation and hyperlactemia) and phenylephrine (decrease in stroke volume). There is, however, no clinical evidence that epinephrine results in worse outcomes, and it should be the first chosen alternative to dopamine or norepinephrine." – No references cited	• Recommendation for norepinephrine in preference over epinephrine more nuanced than previous guidelines, and is largely made on theoretical/haemodynamic response data rather than evidence with clinical outcomes. • Strength of recommendation grading: Grade 1 = Strong recommendation, Grade 2 = Weak recommendation. • Quality of evidence grading: High quality = grade A, moderate quality = grade B, low quality = grade C
Surviving sepsis campaign guidelines (2012)	• "We recommend that vasopressor therapy initially target a MAP of 65 mmHg (grade 1C)."	• "Dopamine increases MAP and cardiac output, primarily due to an increase in stroke volume and heart rate. Norepinephrine increases MAP due to	• "Reason for preference of norepinephrine over epinephrine is largely based on theoretical

	• "We recommend norepinephrine as the first-choice vasopressor (grade 1B)." • "We suggest epinephrine (added to and potentially substituted for norepinephrine) when an additional agent is needed to maintain adequate blood pressure (grade 2B)." • "Vasopressin (up to 0.03 U/min) can be added to norepinephrine with the intent of raising MAP to target or decreasing norepinephrine dosage (UG)." • "Low-dose vasopressin is not recommended as the single initial vasopressor for treatment of sepsisinduced hypotension, and vasopressin doses higher than 0.03–0.04 U/min should be reserved for salvage therapy (failure to achieve an adequate MAP with other vasopressor agents) (UG)." • "We suggest dopamine as an alternative vasopressor agent to norepinephrine only in highly selected patients (e.g., patients with low risk of tachyarrhythmias and absolute or relative bradycardia) (grade 2C)."	its vasoconstrictive effects, with little change in heart rate and less increase in stroke volume compared with dopamine. Norepinephrine is more potent than dopamine and may be more effective at reversing hypotension in patients with septic shock." – • "Information from five randomized trials (n = 1,993 patients with septic shock) comparing norepinephrine to dopamine does not support the routine use of dopamine in the management of septic shock." - Martin, 2000; Ruokonen, 1993; Marik, 1994; Patel, 2010; De Backer, 2010 • "Although some human and animal studies suggest epinephrine has deleterious effects on splanchnic circulation and produces hyperlactatemia, no clinical evidence shows that epinephrine results in worse outcomes, and it should be the first alternative to norepinephrine. Indeed, information from 4 randomized trials (n = 540) comparing norepinephrine to epinephrine found no evidence for differences in the risk of dying (RR, 0.96; CI, 0.77–1.21; fixed effect; I^2 = 0%)." - Levy, 1997; Annane, 2007; Seguin, 2002; Myburgh, 2008 • "Epinephrine may increase aerobic lactate production via stimulation of skeletal muscles' β2-adrenergic receptors and thus may prevent the use of lactate clearance to guide resuscitation." - No references cited	considerations." • "Despite making a "soft" recommendation for norepinephrine over other vasopressors, the recommendation is assessed as grade 1B. The referenced clinical outcome data that congruent with this assessment are from norepinephrine vs dopamine studies." • "Four intervention parallel cohort studies failed to show significant differences between norepinephrine and epinephrine, with no difference in mortality shown by an RR of 0.96."
Surviving sepsis campaign guidelines (2016)	• "We recommend norepinephrine as the firstchoice vasopressor (strong recommendation, moderate quality of evidence)." • We suggest adding either vasopressin (up to 0.03 U/min) (weak recommendation, moderate quality of evidence) or epinephrine (weak recommendation, low quality of evidence) to norepinephrine with the intent of raising MAP to target, or adding vasopressin (up to 0.03 U/min)	• "Human and animal studies suggest that the infusion of epinephrine may have deleterious effects on the splanchnic circulation and produces hyperlactatemia. However, clinical trials do not demonstrate worsening of clinical outcomes. One RCT comparing norepinephrine to epinephrine demonstrated no difference in mortality but an increase in adverse drug-related events with epinephrine." - Myburgh, 2008 • "A meta-analysis of four randomized trials (n = 540) comparing norepinephrine to epinephrine found no significant difference in mortality (RR 0.96; CI 0.77–1.21; low-quality evidence)." - Avni, 2015	• Blinding in cited RCT by Myburgh, 2008 may have been at risk of compromise: Epinephrine was already thought to increase heart rate and lactic acidosis compared to norepinephrine prior to study, & these were the two commonest reasons for relative withdrawal from study, after which patients would receive open-label norepinephrine which was preferred and recommended by 3 previous editions of SSC guidelines.

	(weak recommendation, moderate quality of evidence) to decrease norepinephrine dosage."	• "Epinephrine may increase aerobic lactate production via stimulation of skeletal muscle β2-adrenergic receptors and thus may preclude the use of lactate clearance to guide resuscitation." - No reference cited	
Surviving sepsis campaign guidelines (2021)	• For adults with septic shock, we recommend using norepinephrine as the first-line agent over other vasopressors (Strong recommendation)." • "For adults with septic shock and inadequate MAP levels despite norepinephrine and vasopressin, we suggest adding epinephrine (Weak recommendation, low-quality evidence)."	• "Quality of evidence used to make recommendation by drug: Dopamine - High quality evidence; Epinephrine - Low quality evidence; Vasopressin - Moderate-quality evidence" • "In settings where norepinephrine is not available, epinephrine or dopamine can be used as an alternative, but we encourage efforts to improve the availability of norepinephrine. Special attention should be given to patients at risk for arrhythmias when using dopamine and epinephrine." - No references cited • "Potential adverse effects of epinephrine include arrhythmias and impaired splanchnic circulation." - De Backer, 2003 • "Epinephrine may increase aerobic lactate production via stimulation of skeletal muscle β-2 adrenergic receptors, making the use of serum lactate to guide resuscitation challenging." - Presumably Myburgh, 2008 (see comment). • "A randomized blinded study comparing epinephrine with norepinephrine in patients with shock showed no difference in 90-day mortality (HR, 0.88; 95% CI, 0.63–1.25) and vasopressor-free days (Myburgh, 2008). The panel issued a strong recommendation for norepinephrine as the first-line agent over other vasopressors." • "Epinephrine has been suggested as second or third-line vasopressor for patients with septic shock...With the use of norepinephrine at elevated concentrations, the α_1 receptors may already be saturated and downregulated." - Akinaga, 2013 • "The use of another drug such as epinephrine that targets the same receptors may be of limited utility and vasopressin could be more adequate in patients with shock unresponsive to norepinephrine. In an indirect comparison, a network meta-analysis did not find any significant difference between epinephrine and vasopressin	• Unclear what evidence/rationale was used to make a strong recommendation for norepinephrine in the absence of long-term, clinically relevant differences in efficacy or safety. • There is no clinical data available to corroborate an increased risk of arrhythmias using epinephrine in septic shock. Cited text by De Backer et al (2003) assess effects of epinephrine, norepinephrine, and dopamine on splanchnic circulation. Epinephrine has improved cardiac index compared to other agents in moderate and severe shock, but impaired splanchnic circulation in severe shock compared to norepinephrine.

		in terms of mortality (RR, 0.94; 95% CI, 0.47–1.88). Epinephrine might be useful in refractory septic shock patients with myocardial dysfunction.” - Belletti, 2017	

Appendix 5: AMSTAR assessment of systematic reviews

No.	Criteria	Yes (Y)/ Partial Yes (PY)/ No (N)									
		Belletti 2017	Oba 2015	Nagendran 2016	Cheng 2019	Ruslan 2021	Gamper 2016	Avni 2015	Zhou 2015	Chen 2019	Jiang 2019
1	Research questions and inclusion criteria for the review included the components of PICO	PY	PY	Y	Y	Y	Y	Y	Y	N	Y
2*	Report of the review contained an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol	PY	PY	PY	N	PY	PY	N	N	N	Y
3	Review authors explained selection of the study designs for inclusion in the review	N	N	N	N	N	N	N	N	N	N
4*	Review authors used a comprehensive literature search strategy	PY	PY	PY	PY	N	Y	PY	PY	PY	Y
5	Review authors perform study selection in duplicate	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
6	Review authors perform data extraction in duplicate	Y	N	Y	N	Y	Y	Y	Y	N	Y
7*	Review authors provided a list of excluded studies and justify the exclusions	Y	N	N	N	N	Y	N	N	N	Y
8	Review authors described the included studies in adequate detail	Y	y	PY	Y	Y	Y	Y	PY	N	Y
9*	Review authors used a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review	Y	PY	Y	Y	Y	Y	Y	PY	PY	Y
10	Review authors reported on the sources of funding for the studies included in the review.	N	N	Y	N	N	Y	N	N	N	N
11*	For meta-analyses, review authors used appropriate methods for statistical combination of results	Y	Y	Y	Y	Y	Y	Y	Y	N	Y
12	For meta-analyses, review authors assessed the potential impact of RoB in individual RCTs on the results of the meta-analysis or other evidence synthesis	N	N	Y	N	N	Y	N	N	N	N
13*	Review authors accounted for RoB in individual RCTs when interpreting/ discussing the results of the review	Y	PY	Y	N	N	Y	N	N	N	N
14	Review authors provided a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review	Y	Y	Y	N	N	Y	N	Y	N	Y
15*	For quantitative synthesis, review authors carried out adequate investigation of publication bias (small study bias) and discussed its likely impact on the results of the review	Y	N	N	Y	Y	Y	Y	N	Y	Y
16	Review authors reported any potential sources of conflict of interest, including any funding they received for conducting the review	Y	Y	Y	Y	Y	Y	N	Y	Y	Y
	OVERALL QUALITY ASSESMENT:	Low to moderate	Critically low	Critically low	Critically low	Critically low	High	Critically low	Critically low	Critically low	Critically Low
	Rationale and conclusion:	See below for respective rating									

** Critical domains = 2, 4, 7, 9, 11, 13, 15*

Rating overall confidence in the results of the review

- *High:* No or one non-critical weakness: the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest
- *Moderate:* More than one non-critical weakness*: the systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that *were* included in the review
- *Low:* One critical flaw with or without non-critical weaknesses: the review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the *question* of interest
- *Critically low*: More than one critical flaw with or without non-critical weaknesses: the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies

(*Multiple non-critical weaknesses may diminish confidence in the review and it may be appropriate to move the overall appraisal down from moderate to low confidence).

South African National Essential Medicine List
Primary Healthcare and Adult Hospital Level of Care Medication Review Process
Component: Critical care, Antibiotics

MEDICINE REVIEW

Title: Ceftazidime-avibactam for the treatment of carbapenem-resistant Enterobacterales (CRE) bacteraemia
Date: 21 September 2023

EXECUTIVE SUMMARY

Date: 6 July 2023
Medicine (INN): Ceftazidime-avibactam
Medicine (ATC): J01DD52
Indication (ICD10 code): B96.89

Patient population: Adults with CRE bacteraemia
Prevalence of condition:

- In Sub-Saharan African region, 27.3 deaths per 100 000 people associated with antimicrobial resistance. (1)
- In South Africa, NICD surveillance data reports 2 144 patients identified with CRE bacteremia over 24 months across 16 tertiary public hospitals in 4 provinces (2)

Level of Care: Adult Hospital Level
Prescriber Level: Medical Doctor, Specialist
Current standard of Care:

- Various antimicrobials depending on isolate susceptibility and drug availability, alone or in combination. Regimens may include tigecycline, colistin, amikacin and high-dose meropenem.

Efficacy and safety estimates:

- In the treatment of carbapenem-resistant K. pneumoniae bloodstream infections specifically, ceftazidime-avibactam containing treatment regimens are associated with a 61% reduction in odds of 30-day all-cause mortality, compared to other appropriate antimicrobial therapies. (4 studies, n = 493, 28.6% vs. 44.0%; OR 0.39; 95% confidence interval (CI) 0.25, 0.60; $p < 0.0001$; I^2=0%; NNT 7 (NNT 6.46 95% CI 4.16, 14.48))(3)
- In the treatment of carbapenem-resistant Enterobacterales bacteraemia, ceftazidime-avibactam containing treatment regimens are associated with a 45% reduction in risk of 30-day all-cause mortality, compared to other appropriate antimicrobial therapies (11 studies, n = 1205, RR 0.55; 95% CI 0.45, 0.68; $p < 0.00001$; $I^2 = 0\%$; NNT 6 (NNT 5.52 95% CI 4.21, 8.00))(4)
- In the treatment of carbapenem-resistant Enterobacterales bacteraemia, ceftazidime-avibactam containing treatment regimens are associated with a 52% reduction in risk of 30-day all-cause mortality, compared to colistin containing regimens (RR 0.48 95% CI 0.33, 0.69, $I^2 = 36\%$, $p < 0.0001$; NNT 5 (NNT 4.39 95% CI 3.11, 7.47))(4)
- Ceftazidime-avibactam containing regimens are associated with a reduced risk of nephrotoxicity when compared to other appropriate antibiotic regimens for the treatment of carbapenem-resistant Enterobacterales bacteraemia (5 studies; 380 patients; RR 0.41; 95% CI 0.20, 0.84; I^2= 2%; p = 0.02; NNT 13 (NNT 12.20 95% CI 7.17, 40.81)).(4)

Motivator/reviewer name(s): Gayle Tatz, Jessica Taylor, Jeremy Nel, Marc Blockman

Secretariat support: Milli Reddy
PTC affiliation: Marc Blockman (Western Cape provincial pharmacy therapeutics committee)

KEY FINDINGS

- We conducted a systematic review of the evidence for the safety and efficacy of ceftazidime-avibactam-containing therapy in the management of carbapenem-resistant Enterobacterales (CRE) bacteraemia.
- Current standard of care for CRE bacteraemia is dependent on sensitivity testing and may include therapies such as aminoglycosides, colistin, tigecycline and high-dose carbapenems, usually given as a combination regimen comprising two drugs.
- Concerns over poor efficacy, increasing resistance, and serious potential toxicities associated with these agents has driven the development of novel antimicrobials such as ceftazidime-avibactam.
- Due to the nature of the infection being researched, studies identified were largely observational and it is unlikely that interventional data will become available in the future.
- Two systematic reviews with meta-analysis, and 8 primary observational studies were included in the review.
- Ceftazidime-avibactam-containing therapy was associated with a reduction in mortality (NNT 5 – 7) and nephrotoxicity (NNT 13) compared to other appropriate antibiotic regimens in populations with high proportions of *Klebsiella pneumoniae* CRE infections that produce KPC and OXA-48 carbapenemases.
- Recent NICD surveillance suggests comparable CRE epidemiology in South Africa, with the largest proportion of CRE bacteraemia being caused by *Klebsiella pneumoniae* producing OXA-48.
- However, CRE isolates producing metallo-beta-lactamases will not be susceptible to ceftazidime-avibactam. Local data suggest that almost 25% of CRE isolates fall into this category. These isolates can be identified by standard laboratory testing.
- At the current price, the incremental cost effectiveness ratio suggests an additional cost of ZAR 109 786.21 to prevent one death (when compared to a regimen of tigecycline with amikacin), and an additional cost of ZAR 84 613.32 to prevent one death (when compared to a regimen of tigecycline and colistin). A formal pharmacoeconomic analysis is recommended to guide further decision making

PHC/ADULT HOSPITAL LEVEL EXPERT REVIEW COMMITTEE RECOMMENDATION:

	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
Type of recommendation				**x**	

Recommendation: The PHC Adult Hospital Level ERC suggests using ceftazidime-avibactam in selected patients with bacteraemia due to carbapenem resistant organisms. In view of the cost and antibiotic stewardship concerns the decision to use this agent should not be based solely on sensitivity of the cultured organism to ceftazidime-avibactam.

The decision should be made in consultation with a multidisciplinary antibiotic stewardship team and use should be avoided in patients with a very poor prognosis.

(Conditional: Low Certainty Evidence)

Rationale: Systematic reviews and meta-analyses of observational data suggest a large reduction in mortality associated with treatment with ceftazidime-avibactam. At the current price, the incremental cost-effectiveness ratio suggests an additional cost of ZAR 109 786.21 *to prevent one death (when compared to a regimen of tigecycline with amikacin), and an additional cost of ZAR* 84 613.32 *to prevent one death (when compared to a regimen of tigecycline and colistin). A formal pharmacoeconomic analysis is recommended to guide further decision-making.*

Level of Evidence: *Systematic reviews of observational trials.* **(Low Certainty Evidence)**

Review indicator: Evidence of harm and new cost data

NEMLC RECOMMENDATION (MEETING OF 12 OCTOBER 2023):
NEMLC supported the PHC Adult Hospital Level ERC recommendation to use ceftazidime-avibactam in selected patients with bacteraemia due to carbapenem resistant organisms. Use must be based on sensitivity of the cultured organism to ceftazidime-avibactam in consultation with a multidisciplinary antibiotic stewardship team (for example microbiologists or infectious disease specialists). Use of ceftazidime-avibactam should be avoided in patients with a very poor prognosis.

NEMLC did not recommend a full pharmacoeconomic evaluation at this time.

Monitoring and evaluation considerations

Research priorities

NAME OF AUTHOR(S)/MOTIVATOR(S)

Gayle Tatz[1], Jessica Taylor[1], Jeremy Nel[2], Marc Blockman[1]

AUTHOR AFFILIATION AND CONFLICT OF INTEREST DETAILS

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There are no conflicts of interest to declare.

BACKGROUND

Antimicrobial resistance (AMR) is increasingly being recognised as a major threat to public health with the potential for widespread adverse implications in the treatment and prevention of bacterial infections over the next two decades. One review estimated that approximately 4.9 million deaths were associated with AMR in 2019 globally, while the western Sub-Saharan African region was deemed to have the highest rate of death associated with AMR at 27.3 deaths per 100 000 people. (1) The loss of efficacy of antimicrobial agents impacts the security of future healthcare provision, and at worst, could lead to the spread of untreatable pathogens resulting in mortality rates reminiscent of the pre-antibiotic era.

The societal and economic costs of AMR are also significant and require consideration. According to the Centre for Disease Control and Prevention in the United States of America (USA), AMR results in additional direct healthcare costs of USD 20 billion in the USA (ZAR 344 billion). (5) This figure excludes indirect and societal costs, such as loss of productivity. Local data are sparse but likely to echo international literature. As micro-organism resistance to initial treatment options increases, more costly and resource-intensive interventions are required. It is therefore imperative that measures to improve the use of available antimicrobials are formulated, implemented, evaluated, and optimised. Promotion of the appropriate use of antimicrobials is one of the key strategies that has been included in the national framework to slow the development and spread of AMR. This can be achieved with the availability of updated, evidence-based standard treatment guidelines and the South African Essential Medicines List. (6)

Carbapenem-resistant Enterobacterales

Carbapenem-resistant Enterobacterales (CRE) are Gram-negative bacteria not susceptible to at least one of the carbapenem antibiotics, or which produce a carbapenemase, a type of beta-lactamase. Beta-lactamases are categorised as class A, B, C or D using the Ambler classification system. Carbapenemases comprise class A (e.g., Guinea extended-spectrum beta-lactamase (GES) and Klebsiella pneumoniae carbapenemase (KPC)), class B (e.g., imipenem metallo-beta-lactamase (IMP), New Delhi metallo-beta-lactamase (NDM) and Verona integron-encoded metallo-beta-lactamase (VIM)) and class D beta-lactamases (e.g., oxacillinase-48-like (OXA-48)).(7) Infections caused by CRE are associated with increased morbidity and mortality as effective treatment options are severely limited. (3)

South African Perspective

In South Africa, over a 24-month period spanning January 2019 to December 2020, surveillance conducted by the National Institute of Communicable Disease (NICD) identified 2 144 patients with CRE bacteraemia across 16 public sector tertiary academic hospitals.(2). One third of the study population (35.6%) were aged 19 years or younger, 50.1% were adults aged 20 – 59 years, and 14.2% were adults aged 60 years and older. Klebsiella pneumoniae was identified as the causative pathogen in most CRE isolates (79.8%), and the most frequently detected carbapenemase genes identified across isolates was $bla_{OXA\text{-}48\text{-}LIKE}$ (76.8%), followed by bla_{NDM} (21.1%) and bla_{VIM} (1.3%). The in-hospital mortality rate was 36.6% and increasing age, comorbidities and history of previous antimicrobial use were associated with increased odds of death. Approximately 30.6% of CRE isolates in the study were resistant to amikacin, 19.8% of isolates were resistant to tigecycline and 18.6% of isolates were resistant to colistin (an absolute increase of 5.6% from the previous surveillance period). Susceptibility of isolates to the carbapenems was low, with sensitivity to doripenem, imipenem or meropenem ranging from 41.2% to 44.9% and only 11.5% of isolates were sensitive to ertapenem.

Ceftazidime-avibactam

At present, combination antibiotic regimens that include high-dose carbapenems, amikacin, tigecycline and colistin, are employed as last resort treatment options for CRE. However, concerns about poor efficacy, increasing resistance

and serious potential toxicities associated with these agents has driven the development of novel antimicrobials such as ceftazidime-avibactam. (8)

Ceftazidime-avibactam (CAZ-AVI) is an extended-spectrum beta-lactam and beta-lactamase inhibitor antimicrobial. Ceftazidime induces bacterial cell lysis by attaching to penicillin-binding proteins and inhibiting bacterial peptidoglycan synthesis. Avibactam exhibits no clinically relevant antibacterial activity itself but prevents the inactivation of ceftazidime by class A, class C and some class D carbapenemases (such as OXA-48). Avibactam is not active against the class B metallo-beta-lactamase producing bacteria (such as NDM, VIM and IMP). (4, 9) CAZ-AVI is currently registered in South Africa for the treatment of complicated intra-abdominal infections (in combination with metronidazole), hospital- and ventilator-associated bacterial pneumonias (HAP and VAP) and complicated urinary tract infections (cUTIs). (9)

A recent study conducted by Perovic et al. determined in vitro activity of CAZ-AVI against E. Coli and K. pneumoniae isolated from positive blood cultures from sentinel South African hospitals. In 30% of the E. Coli isolates, and 61% of the K. pneumonia isolates, multidrug resistance was detected. However, all isolates were found to be highly susceptible to CAZ-AVI, with a 96% and 100% susceptibility rate reported for E. Coli and K. pneumoniae isolates respectively.(10)

The objective of this review is to appraise and assess the efficacy and safety data for CAZ-AVI-based antimicrobial treatment regimens in the treatment of CRE infections.

RESEARCH QUESTION

"Is ceftazidime-avibactam-based therapy more effective and/or safer than colistin or tigecycline or aminoglycoside-based treatment regimens in the management of carbapenem-resistant Enterobacterales bacteraemia?"

OBJECTIVES

Our PICO framework for the review is outlined in *Table 1.*

Table 1. PICO Framework

Population	• Adults with CRE bacteremia
Intervention	• Ceftazidime-avibactam-based therapy
Comparators	• Colistin-based therapy • Tigecycline-based therapy • Aminoglycoside-based therapy
Outcomes	• Clinical cure • Mortality

	• Safety
Study type	• Systematic reviews with meta-analysis (pairwise or network meta-analysis) of randomised controlled trials or observational studies • Randomised controlled trials • Observational studies (retrospective or prospective) • Health technological assessments

METHODS

Data sources

We searched the following databases for reviews and primary research: MEDLINE, Epistemonikos, and the Cochrane database of systematic reviews. For health technology assessments (HTAs), the following databases were searched: National Institute for Health Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Scottish Medicines Consortium (SMC), and the International HTA Database. All studies from database inception until 17 April 2023 - the date the search was performed - were considered eligible. No search of the grey literature was conducted. However, additional references brought to the reviewers' attention while reviewing reference lists of included studies were considered eligible for inclusion.

Search Strategy

We conducted our search on 17 April 2023.

Database	Search Strategy
PubMed	((carbapenem-resistant) OR (CRE)) AND (ceftazidime) AND (avibactam) AND ((colistin) OR (tigecycline) OR (aminoglycoside)) AND ((clinical cure) OR (mortality) OR (safety))
Epistemonikos	CRE AND ceftazidime AND avibactam AND clinical cure OR mortality OR safety
HTA databases	ceftazidime/avibactam OR ceftazidime-avibactam

We removed duplicates and screened titles and abstracts, followed by full-text screening using Endnote citation manager software. Screening was performed at both stages by two reviewers (GT and JT). Disagreements between reviewers at each stage of the selection process were resolved through discussion until a consensus was reached.

Additional Inclusion and Exclusion Criteria

We included studies conducted in adult patients with CRE bacteraemia that compared CAZ-AVI-based therapy to colistin- or tigecycline- or aminoglycoside-based therapies, which reported on safety and/or clinical efficacy outcomes.

Narrative reviews and systematic reviews without meta-analysis were excluded from the review, but their reference lists were examined to identify studies for inclusion. Language of included studies was restricted to English.

Considering the barriers to performing randomised clinical trials in this field of research, both primary observational studies and systematic reviews with meta-analyses of observational studies were considered eligible for inclusion.

Data Extraction

A tool for data extraction was developed in Excel by JT and GT. (11) We extracted data pertaining to study design, sample size, population, site of infection, organism, effect size and dosing regimens for intervention and comparator.

Assessment of evidence quality

All included studies underwent quality assessment. We assessed the quality of included systematic reviews with meta-analyses using the AGREE II grading tool.(12) We assessed the quality of included randomised controlled trials using the Cochrane risk of bias tool. (13) We assessed the quality of included observational studies using the ROBINS-I assessment tool. (14)

Data Analysis and Presentation

Data are summarised in a tabular format and in a narrative summary with relevant figures and graphs. Numbers needed to treat to benefit (NNT) or harm (NNH) for significant findings are also presented where possible.

RESULTS:

The results of the search and the study selection process are reported in the results section below and presented using the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram (figure 1).(15)

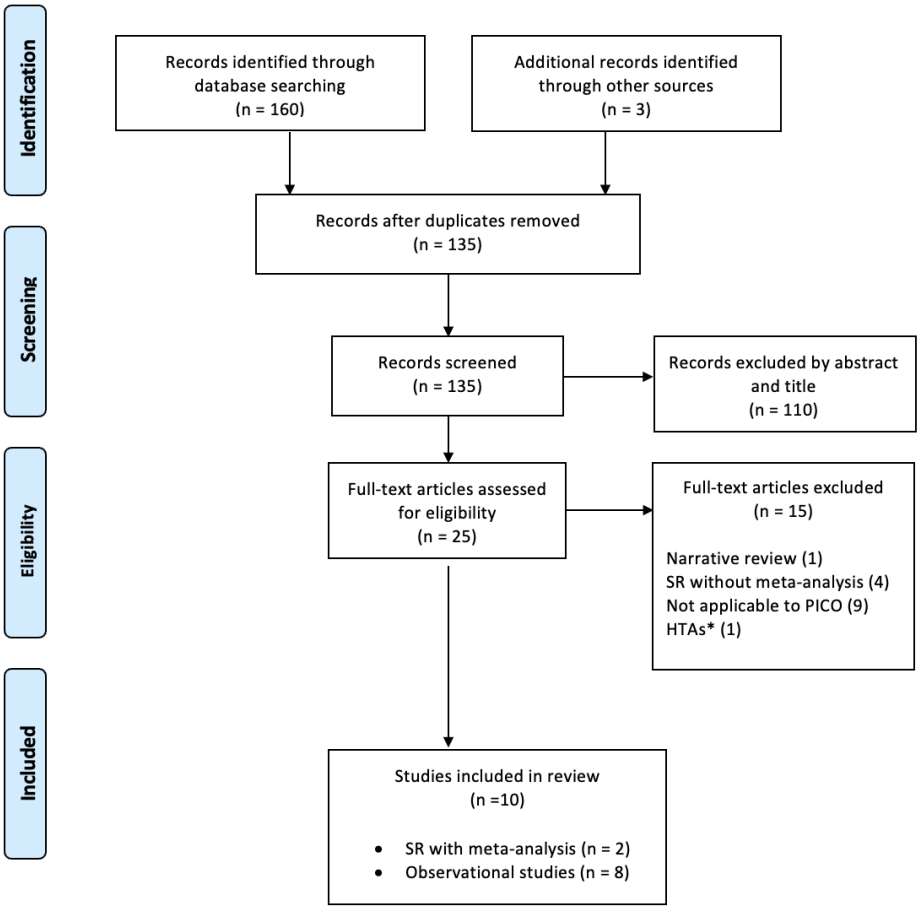


Figure 1. PRISMA flow-diagram detailing study identification, selection, and exclusion

One hundred and sixty studies were identified using the search strategy outlined above, with 3 additional studies identified through other sources. Once 28 duplicates were removed, 135 records were screened by title and abstract. After excluding 110 studies, the remaining 25 studies underwent full text review.

On full text review, a further 15 studies were excluded for reasons as outlined in *Figure 1* and *Table 2*, including the National Institute of Clinical Excellence (NICE) HTA.(16-30) The primary objective of this HTA was to estimate the benefits associated with the use of CAZ-AVI to patients and the UK National Health Service (NHS) over time, to inform delinked compensation to Pfizer (the manufacturer of CAZ-AVI) and to incentivise the development of antimicrobials for drug resistant infections. Considering the delinked system of payment (which is not applicable to South Africa) and the differences in epidemiology of drug resistant infections, the findings of this HTA, including the projected QALYS gained per year, cannot be extrapolated to the South African setting or be included in our review. However, the references were reviewed for primary efficacy studies meeting inclusion criteria.

After full text screening, we included 10 studies: 2 systematic reviews with meta-analyses of observational data, and 8 observational studies.(3, 4, 31-38) Five of the 8 observational studies identified for inclusion were analysed as part of the 2 systematic reviews with meta-analyses and are therefore not discussed or presented separately here.(34-38)

Table 2. Reasons for study exclusion

Study	Reason for exclusion
Hu et al. 2022 (17)	Systematic review without meta-analysis
Chen et al. 2021 (18)	Not applicable to PICO (outcome)
Durante-Mangoni et al. 2019 (19)	Systematic review without meta-analysis
Cultrera et al. 2020 (20)	Not applicable to PICO (population and comparator)
Hsu et al. 2019 (21)	Not applicable to PICO
Kanji et al. 2022 (22)	Systematic review without meta-analysis
Katchanov et al. 2018 (23)	Not applicable to PICO (outcome)
King et al. 2017 (24)	Not applicable to PICO (comparator and study design)
Meng et al. 2022 (25)	Not applicable to PICO (population)
Shen et al. 2021 (26)	Not applicable to PICO (study design)
Shi et al. 2021 (27)	Not applicable to PICO (population)
Soriano et al. 2021 (28)	Systematic review without meta-analysis
Zhen et al. 2022 (29)	Narrative review
Zhong et al. 2018 (30)	Not applicable to PICO (population and comparator)
NICE Health Technology Assessment (16)	See text

Evidence synthesis: Efficacy

Two systematic reviews with meta-analyses were identified for inclusion (*Table 3*). On quality assessment using AMSTAR II, both reviews were assessed as of critically low-quality *(Appendix 1).* There was a 37.5% overlap of primary studies included in the two systematic reviews, calculated using the corrected covered area (CCA) method described by Hennessy and Johnson (*Appendix 3)*.(39) However, since the target populations differed between the systematic reviews, both are discussed below. The 3 observational studies identified in the search that were not included in the

systematic reviews, reported similar findings (*Table 4*). (31-33)The observational study judged to be at the lowest risk of bias is discussed in more detail below.(33)

Chen et al. (4)

Chen et al. conducted a systematic review of 11 observational studies (5 case-control studies and 6 cohort studies) of adults with CRE blood stream infection (BSI) or bacteraemia. Three studies were conducted prospectively, and 8 studies were conducted retrospectively. All 11 studies (n = 1205) reported on the primary study outcome of mortality. Nine of 11 included studies were assessed to be of high quality, with Newcastle Ottawa scores (NOS) ≥ 7. The remaining 2 studies had scores of 6, but were still included in the meta-analysis. No sensitivity analysis with the excluded lower quality studies was performed.

Six studies (n = 567) reported on the secondary outcome of clinical cure, 4 studies (n = 455) on the secondary outcome of relapse and 5 studies (n = 380) on the secondary outcome of nephrotoxicity. The primary sites of infection varied. In 6 studies, all participants were infected with *Klebsiella pneumoniae*. In the remaining 5 studies, multiple organisms were identified, of which the majority (79 – 88%) were *Klebsiella pneumoniae*. In the majority of included studies, most participants were admitted to the intensive care unit. Specifically, 1 study was conducted predominantly in those with haematological malignancies.

The predominant carbapenemase identified was KPC (> 70%) in 6 of the included studies, OXA-48 in 2 studies and metallo-beta-lactamases in 1 study. CAZ-AVI was administered mostly in combination therapy with carbapenems and tigecycline. Control groups received varied regimens but most contained tigecycline or colistin. The most common combination regimen identified in control arms consisted of both tigecycline and colistin.

The primary outcome of the study was 30-day all-cause mortality, which was reported in 11 studies consisting of 1 205 patients. Participants treated with CAZ-AVI-containing regimens had a statistically significant 45% reduction in the relative risk of mortality compared to those treated with other appropriate antibiotics (RR 0.55; 95% confidence interval (CI) 0.45, 0.68; I^2= 0%, p < 0.00001; NNT 6 (NNT 5.52 95% CI 4.21, 8.00)) (*Figure 2*). When specifically compared to colistin-containing treatment regimens, those treated with CAZ-AVI-containing regimens were also found to have a significantly lower relative risk of mortality (RR 0.48; 95% CI 0.33, 0.69; I^2 = 36%; p < 0.0001, NNT 5 (NNT 4.39 95% CI 3.11, 7.47)) (*Figure 3*). Interestingly, when stratified by type of carbapenemase, CAZ-AVI was also associated with reduced mortality risk in those infected with CRE-producing metallo-beta-lactamases (RR 0.44; 95% CI 0.23, 0.83; P = 0.01) (*Figure 4*).

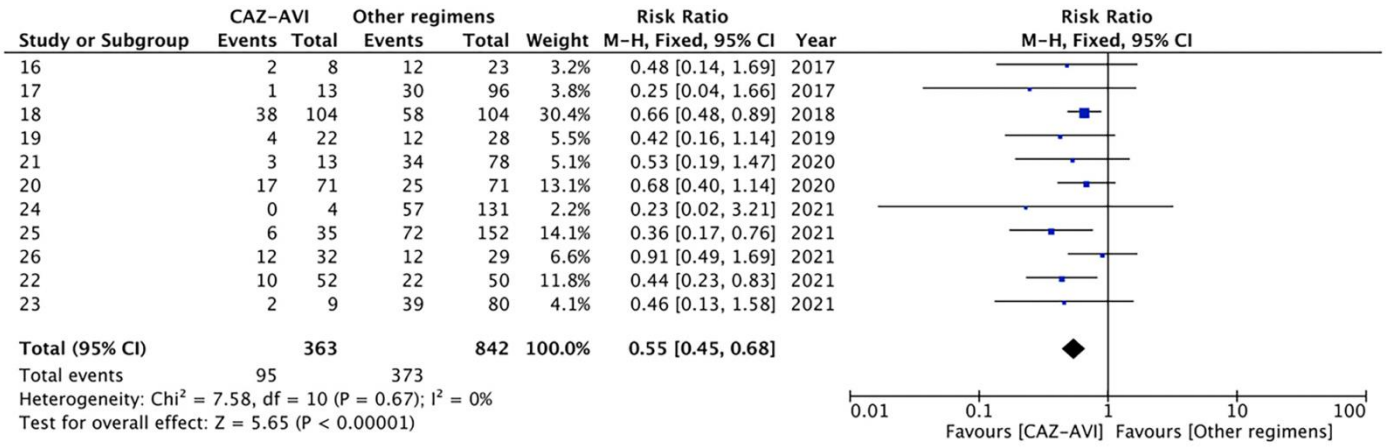


Figure 2. Thirty-day all-cause mortality of ceftazidime-avibactam (CAZ-AVI) regimens compared to other appropriate antibiotic controls in carbapenem-resistant Enterobacterales bloodstream infection from Chen et al. (4)

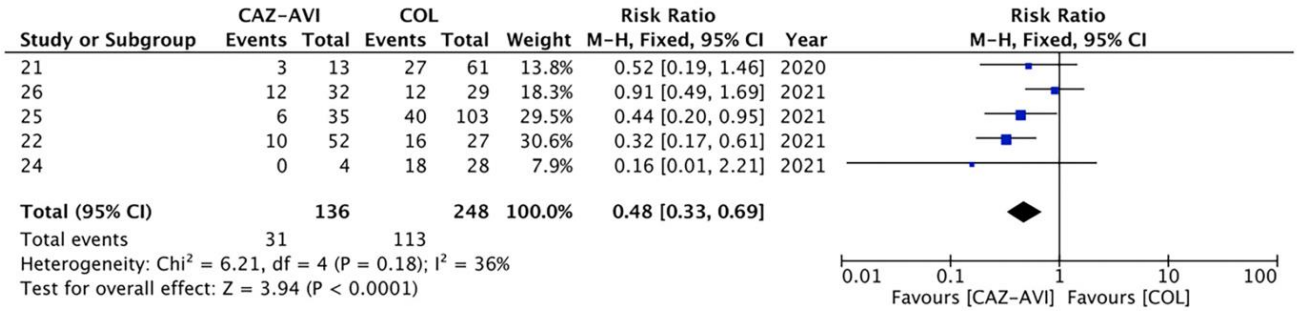


Figure 3. Subgroup analysis of 30-day all-cause mortality in those treated with ceftazidime-avibactam (CAZ-AVI)-based regimens compared to colistin-containing regimens from Chen et al.(4)

A higher rate of clinical cure was associated with CAZ-AVI-containing regimens (RR 1.85; 95% CI 1.57, 2.18; I^2 = 0%, p < 0.00001; NNT 3 (NNT 2.94 95% 2.37, 3.88)). No difference was found in the relapse rate in those treated with CAZ-AVI containing regimens as compared to other appropriate antibiotics, although only 4 studies with 455 contributed to this outcome (RR 0.69; 95% CI 0.29, 1.66; I^2 = 54%; p = 0.86). Additionally, the definitions of relapse varied significantly among included studies. Furthermore, a reduction in nephrotoxicity was reported for the groups receiving CAZ-AVI-containing regimens as compared to other appropriate antibiotic regimens (RR 0.41; 95% CI 0.20, 0.84; I^2= 2%; p = 0.02; NNT 13 (NNT 12.20 95% CI 7.17, 40.81))(*Figure 5*). The studies included in the review included a majority of CRE infections likely to be susceptible to CAZ-AVI (KPC or OXA-48 producing) and a minority of CRE infections unlikely to be susceptible (MBL-producing). If the entire population had been susceptible, CAZ-AVI may have performed even better. The proportion of CRE isolates likely to be susceptible to CAZ-AVI in the review, is comparable to that of South Africa. In the study, KPC dominated, while locally OXA-48 is the most prevalent carbapenemase.

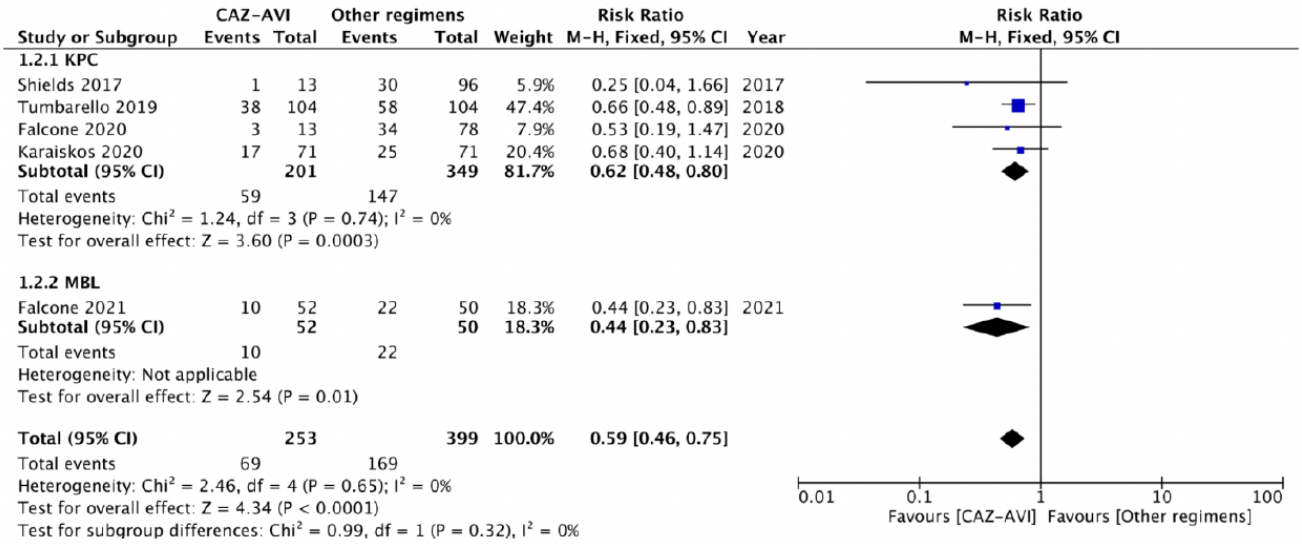


Figure 4. Subgroup analysis by identified carbapenemase of 30-day all-cause mortality in those treated with ceftazidime-avibactam (CAZ-AVI)-based regimens compared to other appropriate antibiotic controls from Chen et al.(4)

Figure 5. Nephrotoxicity of the ceftazidime-avibactam (CAZ-AVI) regimens compared with control in carbapenem-resistant Enterobacterales (CRE) bloodstream infection (BSI) from Chen et al.(4)

Karampatakis et al.(3)

Karampatakis et al. conducted a systematic review and meta-analysis to assess the efficacy and safety of CAZ-AVI containing treatment regimens (monotherapy or combination therapy) compared to other antimicrobials in adults with CRE *K. pneumoniae* infections. Similar to Chen et al., since no randomised controlled data was available, the authors analysed 11 observational studies. The methodological quality of included studies was assessed using the Critical Appraisal Skills Programme (CASP) checklist for observational studies. Three studies were classified as of poor-quality, and the remaining 8 studies were classified as high-quality studies. Eight of the included studies were conducted retrospectively and three were prospectively performed. Comparator regimens varied among included studies and consisted of tigecycline or colistin monotherapy or various treatment combinations of colistin, tigecycline, aminoglycosides, aztreonam or fosfomycin.

For the primary outcome, the CAZ-AVI treatment arms had greater odds of clinical success than treatment arms consisting of other appropriate antibiotics (7 studies; 652 patients; OR 3.55; 95% CI 2.42, 5.19; p < 0.00001; I^2 = 6%) (*Figure 6*). CAZ-AVI treatment was associated with a similar increased odds of clinical success in those patients with bloodstream infections specifically (3 studies; 261 patients; OR 3.96; 95% CI 2.08, 7.54; p < 0.0001, I^2 = 0%). Furthermore, CAZ-AVI treatment was also associated with higher odds of microbiological eradication (5 studies; 430 patients; OR 5.39; 95% CI 2.20, 13.21; p = 0.0002; I^2 = 69%). CAZ-AVI was reportedly associated with a 67% reduction in odds of 30-day mortality (7 studies; 774 patients; OR 0.33; 95% CI 0.23, 0.48; p 0.00001; I^2 = 0%; NNT 6 (NNT 5.32 95% CI 3.94, 8.18)) (*Figure 7*). In those studies that examined bloodstream infections only, a similar reduction in the odds of mortality by day 30 were reported for CAZ-AVI treatment (4 studies; 493 patients; OR 0.39; 95% CI 0.25, 0.60; p < 0.0001; I^2 = 0%, NNT 7 (NNT 6.46 95% CI 4.16, 14.48)). Only 3 studies included reported on prevalence of various carbapenemases per cohort precluding any subgroup analysis and therefore no conclusion can be drawn for effectiveness by carbapenemase produced. No meta-analysis of safety outcomes was able to be performed due to lack of data.

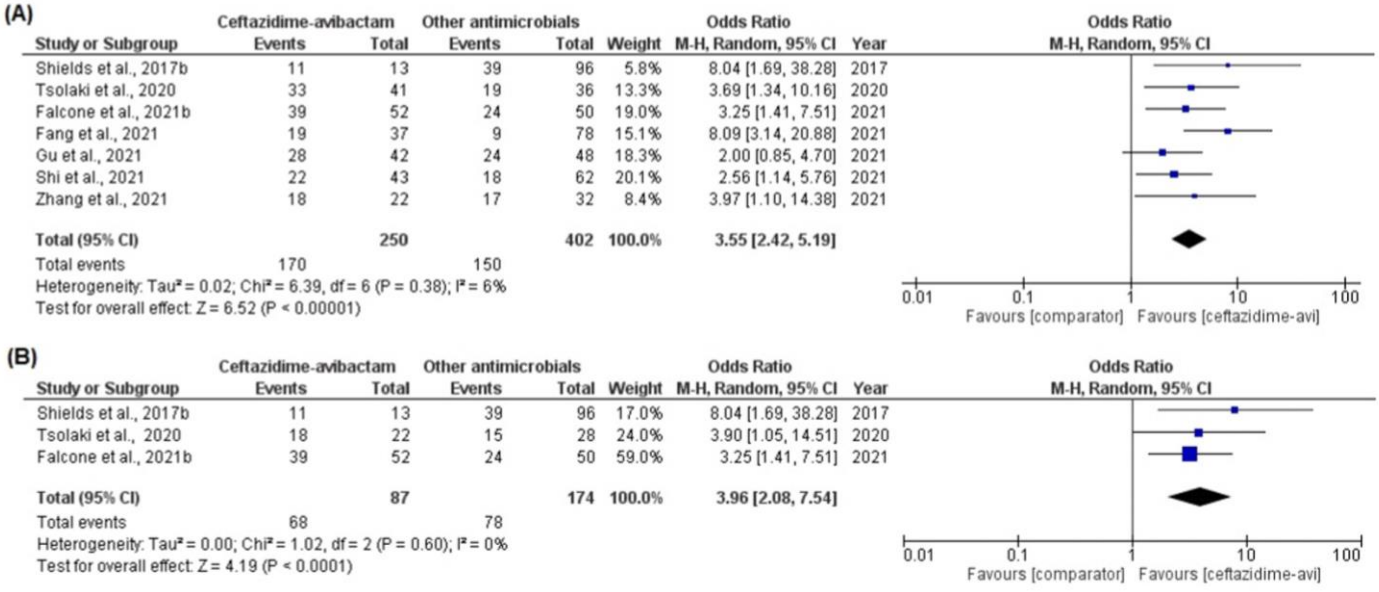


Figure 6. Clinical success of CAZ-AVI vs. comparators in the treatment of CRE K. pneumoniae infections (A) and in CRE K. pneumonia BSIs specifically (B), Karampatakis et al. (3)

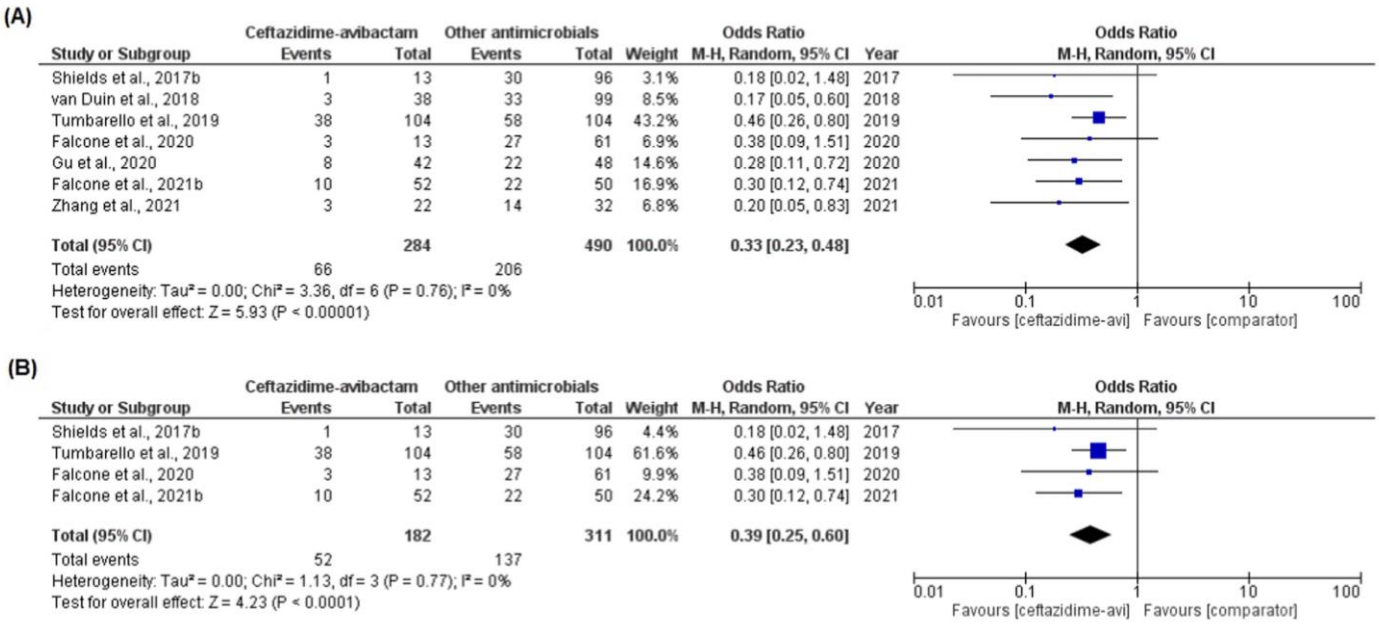


Figure 7. 30-day mortality of CAZ-AVI vs. comparators in the treatment of CRE K. pneumoniae infections (A) and in CRE K. pneumoniae BSIs specifically (B), Karampatakis et al. (3)

Caston et al. (33)

Caston et al. conducted an industry-sponsored multicentred retrospective observational study comparing outcomes in participants with carbapenemase-producing Enterobacterales (CPE) infections treated with CAZ-AVI or best available alternative therapies. The study, conducted in the Spanish Public Healthcare system, enrolled 339 participants and was assessed to be at moderate risk of bias using the ROBINS-I tool. (14) Complicated urinary tract infection (38.1%) and bloodstream infections (32.7%) were the most frequently reported CPE infections. Of the cases with bacterial isolates available (n = 174), the most frequently reported causative organism was *K. pneumoniae (*163), and the most frequent carbapenemase was OXA-48 (109), followed by KPC (62).

CAZ-AVI treatment was used in combination drugs such as amikacin (30.3%), tigecycline (26.8%), colistin (17.9%) , gentamycin (10.7%), fosfomycin (10.7%), tobramycin (1.8%) and aztreonam (1.8%). Various combinations of these antimicrobials made up the regimens in the comparator arm. A multivariate logistic regression model and adjustment for propensity scores were used to control or confounding.

In terms of baseline characteristics between the two groups, at the start of treatment the CAZ-AVI group had significantly greater proportion of participants with diabetes mellitus, acute renal failure, haematological malignancies, septic shock and CPE bloodstream infections. In the multivariate analysis, after adjustment for propensity score, treatment with CAZ-AVI was associated with improved survival (OR 0.41; 95% CI 0.20, 0.80; p = 0.01). Interestingly, this survival benefit was most pronounced in patients with higher risk of morality based on an INCREMENT-CPE score > 7 points (*Figure 8 and 9*). The INCREMENT-CPE score predicts mortality associated with CRE bacteraemia, considering variables such as severe sepsis or septic shock, Pitt score ≥ 6, Charlson comorbidity index ≥

2, source of bacteraemia other than urinary or biliary tract and inappropriate early targeted therapy.(40) CAZ-AVI containing therapy was also identified as an independent predictor of clinical response (OR 2.43; 95% CI 1.16, 5.12; p =0.02). and microbiological response (OR 0.40; 95% CI 0.18; 0.85; p = 0.02).

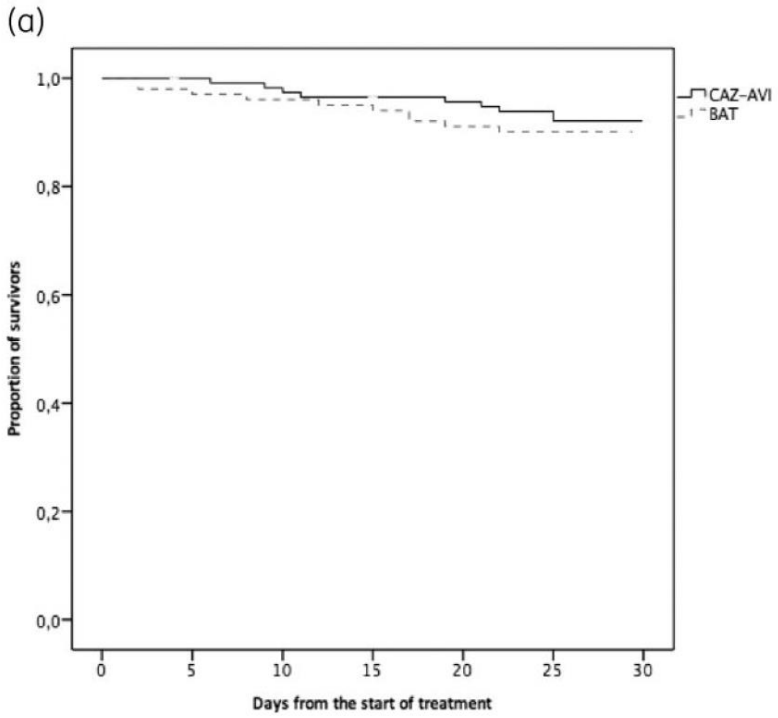


Figure 8. Survival in patients with INCREMENT-CPE score ≤ 7 points treated with ceftazidime-avibactam (CAZ-AVI) (solid line) or best alternative therapy (discontinuous line) for infections caused by carbapenemase-producing Enterobacterales (CPE) (log rank p = 0.73), Caston et al. (32)

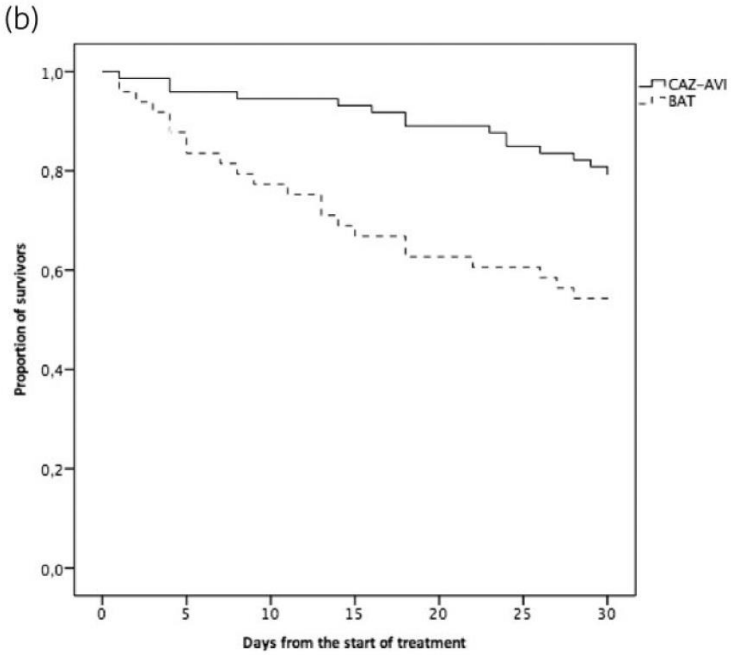


Figure 9. Survival in patients with INCREMENT-CPE score > 7 points treated with CAZ-AVI (solid line) or best alternative therapy (discontinuous line) for infections caused by CPE. (log rank p = 0.004), Caston et al. (32)

Evidence Synthesis: Safety

The most commonly reported adverse reactions associated with CAZ-AVI treatment are nausea, diarrhoea and a positive direct antiglobulin or Coombs tests. This seroconversion to Coombs positivity, while very common, has not yet been associated with the development of haemolysis. (9) Furthermore, in patients with renal impairment, failure to dose adjust ceftazidime has been associated with neurological adverse events such as tremor, convulsions and encephalopathy.(9)

Safety outcomes were not extensively investigated in the included systematic reviews. Karampatakis et al. did not perform meta-analysis of safety outcomes in their study due to lack of data.(3) Chen et al. reported only on nephrotoxicity.(4) CAZ-AVI containing regimens were associated with a reduction in risk of nephrotoxicity as compared to other appropriate antibiotic regimens (5 studies; 380 patients; RR 0.41; 95% CI 0.20, 0.84; I^2= 2%; p = 0.02; NNT 13 (NNT 12.20 95% CI 7.17, 40.81)).(4)

In terms of safety, in the study by Caston et al., treatment with CAZ-AVI was associated with less adverse events (AEs) than alternative antibiotic regimens (5.8% vs. 20%; p < 0.001). (33) Although diarrhoea was more frequently reported in the CAZ-AVI treatment arm, this was not statistically significant (45.4% vs. 13.3%; p = 0.07). Renal failure occurred more frequently in patients receiving comparator regimens (10% vs 1.6%; p ≤ 0.01), despite the higher baseline proportion of participants with acute renal failure in the CAZ-AVI arm. In total 10 participants experienced AEs resulting in treatment discontinuation. Eight participants in the comparator arm discontinued treatment early, 7

as a result of renal failure. Two participants treated with CAZ-AVI discontinued treatment early due to Clostridium difficile colitis.

Table 3. Summary of systematic reviews with meta-analyses										
Name of systematic review	**Primary study sites**	**Population**	Number of primary studies (N) **Total number of participants (n)**	**Site of Infection**	**Organism**	**Intervention**	**Comparator**	**Primary Outcomes**	**Secondary**	AMSTAR II Rating **(see appendices)**
Y Chen et al. 2022**(4)**	USA Europe China	Adults with CRE BSI	N = 11 observational studies (n = 1205)	UTI, respiratory tract, IAI, catheter-related	K. pneumoniae (6 studies) Multiple pathogens of which 79 – 88% K. pneumoniae (5 studies)	CAZ-AVI-based combination therapy.	OAA (Most common combination regimen in control group was colistin + tigecycline)	**30-day all-cause mortality:** CAZ-AVI vs. OAA, 11 studies, n=1205 RR 0.55; 95% CI 0.45, 0.68 p < 0.00001; I^2 = 0% NNT 6 CAZ-AVI vs. colistin-containing therapy. RR 0.48 95% CI 0.33, 0.69, I^2 =36%, p<0.0001 NNT 5	**Clinical cure:** CAZ-AVI vs. OAA 6 studies, n = 567 RR 1.85, 95% CI 1.57, 2.18, I^2 = 0%, p < 0.00001 NNT 3 **Relapse rate:** CAZ-AVI vs. OAA 4 studies, n = 455 RR 0.69, 95% CI 0.29, 1.66, I^2 = 54%, p =0.41 **Nephrotoxicity:** CAZ-AVI vs. OAA 5 studies, n = 380 RR 0.41, 95% CI 0.2, 0.84, I^2 = 2%, p =0.02 NNT 13	Critically Low Quality
Karampatakis et al. 2023**(3)**	USA Europe China	Adults with CRE K. pneumonia infection	N = 11 observational studies (n = 1213)	All (4) BSI (3)	CRE K. pneumoniae	CAZ-AVI monotherapy or combination therapy	OAA (Monotherapy or combination therapy)	**Clinical success:** CAZ-AVI vs. OAA, 7 studies, n=652 68% vs. 37.3%; OR 3.55; 95% CI 2.42, 5.19; p < 0.00001, I^2 6% **Clinical success for studies of patients with BSIs only:** CAZ-AVI vs. OAA, 3 studies, n=261 78.2% vs. 44.8%; OR 3.96 95% CI 2.08, 7.54; p < 0.0001; I^2 = 0% NNT 3	**28-day mortality:** CAZ-AVI vs. OAA, 4 studies, n = 439 18.2% vs. 35.2%, OR 0.38; 95% CI 0.21, 0.71; p = 0.002; I^2 =38% **28-day mortality for patients with BSIs only:** CAZ-AVI vs. OAA, 2 studies, n = 192 18.3% vs. 41.4%; OR 0.32; 95% CI 0.16, 0.61; p = 0.0007; I^2 = 0% **30-day mortality:** CAZ-AVI vs. OAA, 7 studies, n = 774 23.2% vs. 42.0%; OR 0.33; 95% CI 0.23, 0.48; p < 0.00001; I^2 = 0%; NNT 6 **30-day mortality for patients with BSIs:** CAZ-AVI vs. OAA, 4 studies, n = 493 28.6% vs. 44.0%; OR 0.39; 95% CI 0.25, 0.60; p < 0.001; I^2=0%; NNT 7	Critically Low Quality

ICU = intensive care unit; CAZ-AVI = ceftazidime-avibactam; OAA = other appropriate antibiotic; UTI – urinary tract infection; IAI = intraabdominal infection; CRE = carbapenem resistant Enterobacterales; BSIs = blood stream infections

Table 4. Summary of primary studies												
Study Name	**Study Type**	**Study Site**	**Population**	**n**	**Site of Infection**	**Microbiology**	**Intervention**	**Comparator**	**Primary Outcome**	**Secondary Outcome**	**Comments**	**ROBINS Quality**
Almangour et al. 2022 (31)	Retrospective cohort	Saudi Arabia	Hospitalised adults with CRE infections. Mean age: 58 years Males: 62% ICU: 65% Mechanically ventilated: 48%	230	HAP (26%), UTI (19%), Wound infection (16%), IAI (13%), VAP (10%), BSIs (26%)	K. Pneumonia (87%). In CAZ-AVI arm 78% of isolates were susceptible to CAZ-AVI. In colistin arm 76% of isolates were susceptible to colistin. Patients were excluded if isolate identified was non-susceptible to the study drug being investigated.	CAZ-AVI (n = 149) 2.5g 8 hourly In combination with: Tigecycline (11%) Aminoglycoside (5%)	Colistin-based regimen (n = 81) 9 MIU as loading dose, followed by at least 9 MIU given in divided doses. * In combination with: Carbapenem (58%) Tigecycline (10%) Aminoglycoside (7%)	**Clinical cure at the end of treatment:** CAZ-AVI 71% vs. colistin 52% OR 2.29; 95% CI 1.31, 4.01; p < 0.004, NNT 5 **In-hospital mortality:** CAZ-AVI 35% vs. colistin 44% OR 0.67; 95% CI 0.39, 1.16; p = 0.156	**Infection-related mortality:** CAZ-AVI 28% vs. colistin 33% OR 0.79; 95% CI 0.44, 1.41; p = 0.418 **AKI:** CAZ-AVI 15% vs. colistin 33% OR 0.37, 95% CI 0.19,0.69; p = 0.002, NNT 6 **Length of hospital stay, ICU stay, duration of mechanical ventilation, 30-day readmission or 30 and 90-day recurrence:** No statistically significant difference	No statistically significant difference in time to active therapy and time to study drug. Combination therapy more commonly used in the colistin arm (70% VS. 23%, P < 0.001). Higher incidence of heart failure and peripheral vascular disease in CAZ-AVI arm. Median comorbidity index higher in CAZ-AVI arm. Higher median baseline creatinine in CAZ-AVI arm. Median APACHE score 15 in CAZ-AVI and 16 Colistin.	Serious risk of bias
Alraddadi et al. 2019 (32)	Retrospective cohort	Saudi Arabia	Adults who received >24 hours CAZ-AVI for clinically established CRE infections. Mean age (CAZ-AVI): 59.5 years Mean age (comparator): 61.5 years Males (CAZ-AVI): 80% Males (comparator): 57.1%	38	BSIs (CAZ-AVI): 70% BSIs (comparator): 53.6%	In CAZ-AVI group: K. Pneumonia 70% E. Coli 30% OXA-48 80% In comparator group: K. Pneumonia (82.1% E. Coli 17.9% OXA-48 68%	CAZ-AVI (n =10) Dosing not specified	OAA (n = 28) 25 of 28 patients received combination therapy: Colistin 75% Carbapenem 75% Tigecycline31.1% Aminoglycoside 28.6% Dosing not specified	**Clinical remission:** CAZ-AVI vs. OAA 80% vs. 53.6%, p = 0.14	**30-day mortality:** CAZ-AVI vs. OAA 50% vs. 57.1%; p = 0.7 **Relapse with same isolate:** CAZ-AVI vs. OAA 20% vs. 3.6%, p = 0.1	Underpowered Risk of chronological bias as CAZ-AVI only available from December 2017. Comparator group selected from those with CRE infections between Jan and Nov. 2017 compared to intervention group selected between Dec. 2017 and Aug. 2018.	Critical risk of bias

Table 4. Summary of primary studies												
Study Name	**Study Type**	**Study Site**	**Population**	**n**	**Site of Infection**	**Microbiology**	**Intervention**	**Comparator**	**Primary Outcome**	**Secondary Outcome**	**Comments**	**ROBINS Quality**
Caston et al. 2022 (33)	Retrospective cohort.	Spain	Adults with cUTI, HAP, IAI or BSI with confirmed CPE, and received ≥ 48 hours of CAZ-AVI. Median age: 70 years Males (CAZ-AVI): 66.1% Males (comparator): 57.3%	339	BSIs (CAZ-AVI): 38.1% BSI (comparator): 26%	In CAZ-AVI group: K. pneumoniae 89.9% OXA-48 73.5% KPC 25.5% In comparator group: K. pneumoniae 94% OXA-48 77.3% KPC 22.7%	CAZ-AVI (n = 189) Monotherapy 70.4% In combination with: Amikacin 30.3% Tigecycline 26.8%, Colistin 17.9% Gentamicin 10.7% Fosfomycin 10.7% Tobramycin 1.8% Aztreonam 1.8% Dosing not specified	OAA (n = 150) Monotherapy 42.6% Dosing not specified	**30-day crude mortality after diagnosis of infection**: CAZ-AVI vs. OAA 13.7% vs. 22%; p = 0.04 **Mortality rate in BSI subgroup:** CAZ-AVI vs. OAA 13.9% vs. 30.8%; p = 0.03 **Mortality rate for CAZ-AVI monotherapy vs. CAZ-AVI combination therapy**: 14.3% vs. 12.5%; p = 0.82 **In multivariate analysis with adjustment for propensity score:** CAZ-AVI was associated with increased survival OR 0.41; 95% CI 0.20, 0.80; p = 0.01	**21-day clinical response:** CAZ-AVI vs. OAA 89.4% vs. 79.3%; p = 0.01 **CAZ-AVI containing therapy was an independent predictor of clinical response on multivariate analysis:** OR 2.43; 95% CI 1.16, 5.12; p = 0.02 **Microbiological eradication:** CAZ-AVI vs. OAA 83.3% vs. 69.4%; p = 0.02. **CAZ-AVI containing therapy was only factor independently associated with microbiological response on multivariate analysis:** OR 0.40; 95% CI 0.18, 0.85; p = 0.02 **Adverse events:** CAZ-AVI vs. OAA 5.8% vs. 20%; p < 0.001 **Renal failure:** CAZ-AVI vs. OAA 1.6% vs. 10%; p ≤ 0.01		Moderate risk of bias Industry sponsored.

*(1 MIU = 80mg of prodrug colisthimethate sodium)

ICU = intensive care unit; CAZ-AVI = ceftazidime-avibactam; OAA = other appropriate antibiotic; UTI – urinary tract infection; cUTI = complicated urinary tract infection; IAI = intraabdominal infection; CRE = carbapenem resistant enterobacterales; BSIs = blood stream infections; OAA = other appropriate antibiotics; CPE = carbapenemase producing Enterobacterales

CONCLUSION

This review suggests that ceftazidime-avibactam-containing therapy is associated with a reduction in mortality (NNT 5 – 7) and nephrotoxicity (NNT 13), and improved clinical cure when compared to other appropriate antibiotic regimens in populations with high proportions of Klebsiella pneumoniae CRE infections that produce KPC and OXA-48 carbapenemases. Recent NICD surveillance suggests comparable CRE epidemiology in South Africa, with the largest proportion of CRE bacteraemia being caused by Klebsiella pneumonia producing OXA-48. However, based on this local data, a significant proportion of CRE isolates (almost 25%) are still unlikely to be susceptible to ceftazidime-avibactam therapy (metallo-beta-lactamases) and thus culture and sensitivity must be used to guide its usage.

At present, CAZ-AVI is available at some tertiary facilities on a named-patient basis due to high cost and to prevent resistance. Standardised guidance on the appropriate use of CAZ-AVI should occur, to improve appropriate access; and in turn to limit resistance with improve health equity.

Our recommendations:

- The use of ceftazidime-avibactam in proven CRE bacteraemia should be restricted to infections with organisms that are proven to be sensitive to the drug and resistant to cheaper, equally effective alternatives.
- Access should be limited to, or after discussion with infectious disease sub-specialists or microbiologists, following strict antibiotic stewardship principles.
- A formal pharmacoeconomic analysis should be conducted to guide financial decision-making.
- Ongoing national surveillance for the development of CAZ-AVI resistance should be prioritized.

Limitations:

- This review cannot inform decision-making regarding empiric treatment of suspected CRE infections with CAZ-AVI therapy or monotherapy with CAZ-AVI compared with CAZ-AVI-containing combination therapy.
- The findings of this report, including the costing analyses, cannot be generalised to CRE infections other than bacteraemia.

Version	Date	Reviewer(s)	Recommendation and Rationale
1	21 September 2023	GT, JT, JN, MB	The PHC Adult Hospital Level ERC suggests using ceftazidime-avibactam in selected patients with bacteraemia due to carbapenem resistant organisms. In view of the cost and antibiotic stewardship concerns the decision to use this agent should not be based solely on sensitivity of the cultured organism to ceftazidime-avibactam. The decision should be made in consultation with a multidisciplinary antibiotic stewardship team and use should be avoided in patients with a very poor prognosis. **Rationale:** Systematic reviews and meta-analyses of observational data suggest a large reduction in mortality associated with treatment with ceftazidime-avibactam. At the current price, the incremental cost-effectiveness ratio suggests an additional cost of ZAR 109 786.21 to prevent one death (when compared to a regimen of tigecycline with amikacin), and an additional cost of ZAR 84 613.32 to prevent one

			death (when compared to a regimen of tigecycline and colistin). A formal pharmacoeconomic analysis is recommended to guide further decision-making.

EVIDENCE TO DECISION FRAMEWORK

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE OF BENEFIT	**What is the certainty/quality of evidence?** High: ☐ Moderate: ☐ Low: x Very low: ☐ *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	Observational data of low quality. No randomised controlled trial data available.
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** Large: x Moderate: ☐ Small: ☐ None: ☐	<u>Chen et al.</u> Reduced 30-day all-cause mortality: 11 studies; 1 205 participants: • RR 0.55 (95% confidence interval (CI) 0.45, 0.68) • p < 0.00001 • I^2= 0% • ARR 0.18 (95% CI 0.12; 0.24) • NNT 6 (NNT 5.52; 95% CI 4.21, 8.00) Improved clinical cure*: 6 studies; 567 participants: • RR 1.85 (95% CI 1.57, 2.18) • p < 0.00001 • I^2 = 0%, • ARR 0.34 (95% 0.26; 0.42) • NNT 3 (NNT 2.94; 95% CI 2.37, 3.88) Lower risk of nephrotoxicity:5 studies; 380 participants: • RR 0.41 (95% CI 0.20, 0.84) • p = 0.02 • I^2= 2% • ARR 0.08 (95% 0.02; 0.14) • NNT 13 (NNT 12.20 95% CI 7.17, 40.81 <u>Karampatakis et al.(3)</u> Reduced 30-day all-cause mortality: 7 studies; 774 patients; • OR 0.33 (95% CI 0.23, 0.48) • P = 0.00001 • I^2 = 0% • ARR 0.19 (95% CI 0.12, 0.25) • NNT 6 (NNT 5.32 95% CI 3.94, 8.18)

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
		Reduced 30-day all-cause mortality (bloodstream infections only): 4 studies; 493 patients; • OR 0.39 (95% CI 0.25, 0.60) • p < 0.0001 • I^2 = 0% • ARR 0.15 (95% CI 0.07, 0.24) • NNT 7 (NNT 6.46 95% CI 4.16, 14.48) Improved clinical success*: 7 studies; 652 patients; • OR 3.55(95% CI 2.42, 5.19) • p < 0.00001 • I^2 = 6% • ARR 0.31 (95% CI 0.23, 0.38) • NNT 4 (NNT 3,26; 95% CI 2.62, 4.31) <u>Caston et al.(33)</u> In participants with INCREMENT-CPE > 7 (severe illness), CAZ-AVI therapy was associated with statistically significant improved survival at 30-days 78.1% vs. 53.1%; p-value = 0.004
QUALITY OF EVIDENCE OF HARM	**What is the certainty/quality of evidence?** High ☐ Moderate ☐ Low ☒ Very low ☐ *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	Observational data of low quality. Systematic reviews with meta-analyses only reported on mortality and nephrotoxicity.
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** Large ☐ Moderate ☐ Small ☒ None ☐	<u>Caston et al.(33)</u> Risk of any adverse events associated with CAZ-AVI compared with best available therapy: 5.8% vs. 20%; p < 0.001 Risk of diarrhoea associated with CAZ-AVI compared with best available therapy: 45.4% vs. 13.3%; p = 0.07
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable harms?** Favours intervention ☒ Favours control ☐ Intervention = Control *or* Uncertain ☐	
THERAPEUTIC INTERCHANGE	Therapeutic alternatives available: Yes ☐ No ☒ List the members of the group. List specific exclusion from the group:	Rationale for therapeutic alternatives included: Not applicable References: Not applicable Rationale for exclusion from the group:

<table>
<tr><th></th><th>JUDGEMENT</th><th>EVIDENCE & ADDITIONAL CONSIDERATIONS</th></tr>
<tr><td></td><td></td><td>Not applicable

References: Not applicable</td></tr>
<tr><td>FEASABILITY</td><td>Is implementation of this recommendation feasible?
Yes [ ] No [ ] Uncertain [x]</td><td>Evidence suggests a clear mortality benefit (NNT 5 – 7). The budgetary impact, however, is substantial. At the current price, the ICER suggests an additional cost of ZAR 109 786.21 to prevent one death (when compared to a regimen of tigecycline with amikacin), and an additional cost of ZAR 84 613.32 to prevent one death (when compared to a regimen of tigecycline and colistin).
The willingness to pay per death prevented is undefined.
The feasibility of implementation of the recommendation is thus uncertain.</td></tr>
<tr><td>RESOURCE USE</td><td>How large are the resource requirements?
More intensive [x] Less intensive [ ] Uncertain [ ]</td><td>Price of medicines/ treatment course
<table>
<tr><th>Medicine</th><th>Tender price (ZAR)</th><th>SEP (ZAR)</th></tr>
<tr><td>CAZ-AVI (2g/0.5g)</td><td>1 174.62</td><td>1 628.07</td></tr>
<tr><td>Colistin (1 MU)*</td><td>69.67</td><td>69.67</td></tr>
<tr><td>Tigecycline (50mg/ml)</td><td>308.26</td><td></td></tr>
</table>
*Section 21; current cost price

We strongly recommend a formal pharmacoeconomic analysis to guide decision making.

<u>DIRECT COSTS CAZ-AVI:</u>
7-day course:
(1174.62)*(3)*(7) = ZAR 24 667.02

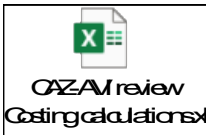
5 to 14-day course:
(1174.62)*(3)*(5) to (1174.62)*(3)*(14) =
ZAR 17 619.30 – 49 334.04

TOTAL BUDGETARY COSTs:
Based on NICD surveillance data:
2 144 x 76,8% = 1647 cases potentially susceptible to CAZ-AVI over 24 months
1647 x 0.5 = 824 cases potentially susceptible to CAZ-AVI per annum

Gross budgetary cost of CAZ-AVI to treat all cases in a year for 7-days:
(24 667.02*824)
ZAR 20 325 624.48

Gross budgetary cost of TIG+AMIK to treat all cases in a year for 7 days:
ZAR 3 924 530.72

Excess cost per annum of CAZ-AVI over TIG+AMIK:</td></tr>
</table>

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
		ZAR 16 401 093.76 Gross budgetary cost of TIG+COLISTIN to treat all cases in a year for 7 days: **ZAR 7 685 139** Excess cost per annum of CAZ-AVI over TIG+COLISTIN **ZAR 12 640 485.48** **ICER (TO PREVENT ONE DEATH):** **CAZ-AVI vs. TIG+AMIK:** Difference in cost: 19 904.24 per course Difference in mortality: -0.1813 ICER: ZAR 109 786.21 per death prevented **CAZ-AVI vs. TIG+COLISTIN:** Difference in cost: 15 340.40 per course Difference in mortality: -0.1813 ICER: ZAR 84 613.32 per death prevented **Other resources:**  CAZ-AVI review Costing calculations
VALUES, PREFERENCES, ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the options?** Minor ☐ Major ☐ Uncertain ☒ x **Is the option acceptable to key stakeholders?** Yes ☒ x No ☐ Uncertain ☐	Likely to be acceptable to stakeholder 2022: Total vials of Zavicefta® supplied to public sector by Pfizer: 590 Jan. 2023 to June 2023: Total vials of Zavicefta® supplied to public sector: 780
EQUITY	**Would there be an impact on health inequity?** Yes ☐ No ☐ Uncertain ☒ x	Favours health equity by improving access to all patients at all facilities, however, high budgetary costs may detract financial resources from other areas of care.

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APPENDICES

Appendix 1: AMSTAR

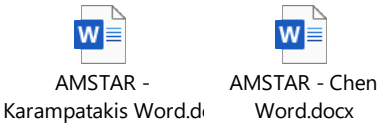

Figure A1: AMSTAR Assessment of Included Systematic reviews with meta-analyse

Appendix 2: ROBINS-I

	Almangour et al. 2022 (31)	Alradaddi et al. 2019 (32)	Caston et al. 2022 (33)
Bias due to confounding	Moderate	Critical	Moderate
Bias in selection of participants into study	Serious	Low	Low
Bias in classification of interventions	Moderate	Low	Low
Bias due to deviations from intended interventions	Low	Low	Low
Bias due to missing data	Low	Low	Low
Bias in measurement of outcomes	Moderate	Serious	Low
Bias in selection of reported result	Low	Low	Low
Overall	Serious	Critical	Moderate

Table A2 ROBINS-I Asssessment of Included Primary Research

Appendix 1**:** Table of primary study overla**p**

		Systematic Review	
Row	**Primary Study**	1. Chen, 2022	2. Karampatakis, 2023
1	Shields 2017	1	1
2	Tumbarello, 2019	1	1
3	Tsolaki, 2020	1	1
4	Karaiskos, 2021	1	1
5	Falcone, 2020	1	1
6	Falcone, 2021	1	1
7	Shen, 2021	1	0
8	Zhou, 2021	1	0
9	Chen, 2021	1	0
10	Hakeam, 2021	1	0
11	Caston, 2017	1	0
12	Fang, 2021	0	1
13	Gu, 2021	0	1
14	Shi, 2021	0	1
15	Zhang, 2021	0	1
16	Van Duin, 2018	0	1
	TOTAL	**11**	**11**

Table A3 of primary studies included in two systematic reviews used in this review of the evidence and the overlap thereof

Appendix 4: **Calculation of CCA**

$$CCA = \frac{N - r}{(r \times c) - r},$$

$$CCA = (22 - 16)/((16*2) - 16) = 0.375$$

$$= 37.5\%$$

N = total number of included publications (including double counting) = 22
r = number of rows (number of index publications) = 16
c = number of reviews = 2

Figure A4 Calculation of study overlap of primary studies included in two systematic reviews used in this review of the evidence using the corrected covered area (CCA) method by Hennessy & Johnson.