QUICK GUIDE TO SEPSIS MANAGEMENT

Ministry of Health

1st Edition 2025

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FORWARD

I am pleased to present this first edition of *Quick Guide to Sepsis Management* 2025 which aims to provide a ready reference for early recognition and management of patients with sepsis and septic shock across the health facilities in the country.

Sepsis is a critical global health concern that affects millions of people each year, often with devastating consequences. Sepsis is responsible for 1 in 5 deaths worldwide. A 2020 report by the Institute for Health Metrics and Evaluation revealed that sepsis affects 49 million people globally each year, claiming 11 million lives particularly in low- and middle-income countries. In the United Kingdom alone, there are at least 200,000 cases of sepsis in adults each year, with estimates suggesting as many as 918,000 cases, leading to approximately 48,000 deaths. Sepsis claims more lives than breast, bowel, and prostate cancers combined.

In recognition of its global burden, the World Health Assembly in 2017 passed a pivotal resolution urging all countries to strengthen efforts in prevention, early recognition, and effective management of sepsis. All 194 United Nations member states were urged to develop national action plans to combat it. This call to action has inspired nations, including ours, to develop comprehensive strategies and clinical protocols to reduce sepsis-related deaths and improve outcomes for patients. and all 194 United Nations member states were urged to develop national action plans to combat it.

In Bhutan there has been no dedicated guidelines on sepsis management and patients often present late with multi-organ dysfunction resulting in poor outcomes. This new guideline represents an important milestone in our national commitment to improving patient care and strengthening our health system's

response to sepsis. It provides evidence-based recommendations for healthcare professionals across all levels—from primary health facilities to tertiary hospitals—enabling timely diagnosis, prompt treatment, and coordinated implement life-saving interventions.

I commend the dedicated clinicians, public health experts, and partners who contributed to the development of this guide. Their efforts reflect our shared vision of a healthier, safer future for our population. Let us all work together to implement this guide effectively and ensure that no life is lost unnecessarily to sepsis. Together, we can make a difference.

(Pemba Wangchuk)
Secretary

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ABBREVIATIONS

AMR	Antimicrobial Resistance
AKI	Acute Kidney Injury
BC	Blood Culture
BP	Blood Pressure
CI	Cardiac Index
CO	Cardiac output
CPRT	Capillary Refill Time
CRRT	Continuous Renal Replacement Therapy
CRP	C-reactive Protein
CBC	Complete Blood Count
CHF	Congestive Heart Failure
CVP	Central Venous Pressure
CT	Computerized Tomography
DIC	Disseminated Intravascular Coagulation
ESBL	Extended Spectrum Beta-lactamase
ESRD	End Stage Renal Disease
FiO2	Fraction of inspired Oxygen
GCS	Glasgow Coma Scale
GS	Gram Stain
IV	Intravenous
IPD	In- Patient Department
IVC	Inferior Vena Cava
IVF	Intravenous fluids
LMICs	Lower-Middle Income Countries
MAP	Mean Arterial Pressure
MCG	Microgram
MDRO	Multi Drug Resistant Organism
MRI	Magnetic Resonance Image
MRSA	Methicillin Resistant Staphylococcus Aureus
MU	Million unit

NEWS	National Early Warning Score
NS	Normal Saline
NICE	National Institute for Health and Care Excellence
NSTI	Necrotizing Soft Tissue infection
NSS	Normal Saline Solution
NIV	Non-invasive ventilation
OPD	Out-Patient Department
OR	Operation Room
PBW	Predicated Body Weight
PEEP	Positive End Expiratory Pressure
PLR	Passive Leg Raise
PLRT	Passive Leg Raise Test
PO	Per Oral
Pplat	Plateau Pressure
PP	Pulse Pressure
PPV	Pulse pressure variation
PCT	Pro-calcitonin
PBS	Peripheral Blood Smear
PHC	Primary Healthcare Centre
qSOFA	quick Sequential Organ Failure Assessment
RBC	Red Blood Cell
RL	Ringer Lactate
SIRS	Systemic Inflammatory Response Syndrome
SOFA	Sequential Organ Failure Assessment
SVV	Stroke Volume Variation
TAT	Turn Around Time
UFH	Unfractionated Heparin
UOP	Urine Output
VA	Veno Arterial
WHO	World Health Organization
WBC	White Blood Cell

CONTENTS

Forward i

Acknowledgement iii

Abbreviations iv

Chapter 1: Introduction 1

1.1 Definitions 3

1.2 Pathophysiology of sepsis 4

1.3 References 4

Chapter 2: Screening and identifications of sepsis 7

Chapter 3: Resuscitation strategies for sepsis 10

3.1 Measuring lactate 11

3.2 Obtaining cultures before administering antibiotics 11

3.3 Administer broad spectrum antibiotics 11

3.4 Fluid administration 12

3.5 Vasopressor administration 14

3.6 References 15

Chapter 4: Recommended initial empiric antibiotic therapy for patients with sepsis and septic shock 18

4.1 Indication for broad spectrum antibiotics in sepsis 18

4.2 Empirical antimicrobial choices for different infections 19

4.3 Antibiotic dosage 23

4.4 Dosing administration as per renal function (creatinine clearance) 24

4.5 References 25

Chapter 5: Fluid management in sepsis 26

5.1 Why fluids first in sepsis? 26

5.2 How much to give? 26

5.3 What fluid to give? 28

5.4 Fluid responsiveness 28

5.5.1 Heart lung interaction 30

5.5.2 Fluid redistribution 32

5.6 References 33

Chapter 6: Roles of nurses in sepsis management 36

6.1 Screening and early recognition 36

6.1.1 How to use the news assessment tool? 36

6.1.2 How to respond to news? 37

6.2 Rapid initial resuscitation and implementation of the 1-hour bundle 37

6.3 Hemodynamic support and monitoring 38

6.4 Nursing considerations for patient on antimicrobial therapy 40

6.5 Infection control and prevention 40

6.6 Multidisciplinary collaboration and communication 41

6.7 Post sepsis care and rehabilitation 41

6.8 References 41

Chapter 7: Laboratory role in early detection of sepsis 45

7.1 Introduction 45

7.2 Laboratory tests for early detection of sepsis: 45

7.3 Final laboratory action 48

7.4 Summary 48

7.5 References 49

Chapter 8: Source control in sepsis and septic shock **51**

8.1 What is source control? 51

8.2 What are the objectives of source control in sepsis and septic shock? 51

8.3 What are the methods for source control? 51

8.4 What is the optimal timing for source control? 53

8.5 What are the best practices on abdominal drains, sampling and antibiotics after source control? 55

8.6 References 56

Chapter 9: Refractory septic shock **59**

9.1 Definition 59

9.2 Adjunctive in management of refractory septic shock 59

9.3 References 63

Annexure **65**

Annexure 1: guide to infusion rate of noradrenaline as per body weight 65

Annexure 2: vasopressor extravasation management 67

Annexure 3: template for using sbar for communication 68

Annexure 4: flowchart for managing suspected sepsis patients at primary health centers 69

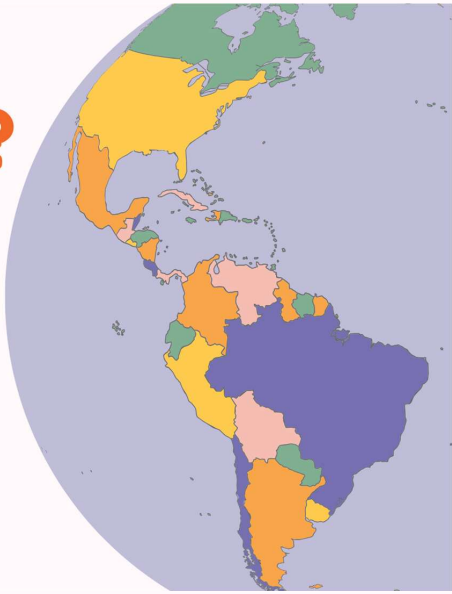
Annexure 5: flowchart for managing suspected sepsis patients at district hospitals 70

Annexure 6: flowchart for managing suspected sepsis patients at regional referral hospitals 71

Annexure 7: standard operating procedure (sop) on blood culture sample collection 72

Did You know?

While sepsis can affect any individual worldwide, significant regional disparities in incidence and mortality exist with the highest rates in lower-middle-income countries (LMICs)



CHAPTER 1
INTRODUCTION

The intent of the Quick guide to sepsis management is to provide a ready reference for early recognition and management of patients with sepsis and septic shock. This guide book is not to address all aspects and need of sepsis management but it is written to provide a quick reference in which to assist the healthcare professionals taking care of patients with sepsis during the early phase of resuscitation.

Sepsis and septic shock are medical emergencies with a morbidity and mortality rate high as 40% despite all advancements in medicine, especially in low and middle-income countries like ours [1-6]. In Bhutan, patients often present late with multi-organ dysfunction resulting in poor outcomes. Delay in sepsis recognition and initiation of treatment have been associated with worse outcomes, while early evidence-based treatment has been shown to improve survival.

The challenges that are associated with poor outcomes are sepsis being poorly recognized when compared to other medical conditions such as acute coronary syndromes and stroke. In addition, lack of screening tools for early detection and inadequate sepsis resuscitation knowledge in the acute phase are other identified challenges in our setting.

International guidelines, such as the Surviving Sepsis Campaign, and recent literature emphasizes the need for institutional protocols or guidelines tailored to local contexts for the management of sepsis [1-3,7]. In light of this, our team developed this quick guide to sepsis management, which is both feasible and practical within our healthcare setting. This document will complement the sepsis flowcharts already established for various levels of healthcare

facilities in Bhutan, offering a detailed reference for effective management. As the first national document on sepsis management, it will serve as a benchmark for future updates and guidelines in the country. Additionally, this initiative will bring together health care professionals of all backgrounds with a common goal to reduce sepsis-related morbidity and mortality through increased awareness and education.

The objectives of this Adult Sepsis Guideline are as follows;

1. **Local Protocol Development:** The creation of a Bhutan-specific adult sepsis guideline aims to address the gap in managing sepsis within the country's healthcare setting, taking into account the local constraints while aligning with international best practices.
2. **Public and Professional Awareness:** One of the critical goals is to improve both public and health professional understanding of sepsis, ensuring better recognition, early intervention, and overall outcomes for patients.
3. **To Support Healthcare Providers in Remote Areas:** Provide guidance to young doctors and nurses working in rural or district areas, where basic laboratory facilities for detecting infection may be unavailable. The guideline will help them identify sepsis early, make timely consultations, and refer patients to higher healthcare facilities for further management.
4. **To Reduce Sepsis Mortality:** Facilitate early recognition and resuscitation of sepsis patients, ultimately reducing the mortality rates associated with sepsis and septic shock.
5. **To Educate and Update Healthcare Professionals:** Ensure that all healthcare professionals are informed and updated on the latest evidence-based practices for the management of sepsis.

6. **To Advocate for Sepsis Management in Health Policy:** Highlight the importance of sepsis sensitization and management to administrators and policymakers, ensuring that sepsis and septic shock are incorporated into national health policies and programs, alongside other major medical conditions.
7. **Global Sepsis Alliance 2030 Targets:** The guideline will also contribute to achieving the ambitious targets set by the Global Sepsis Alliance, focusing on reducing global sepsis incidence, improving survival rates, and enhancing awareness.

1.1 Definitions

Sepsis	Sepsis is characterized by a life-threatening organ dysfunction due to a dysregulated host response to infection [1]
Septic shock	Persistent hypotension requiring vasopressors to maintain MAP ≥65 mm Hg With Serum lactate level >2 mmol/L (18 mg/dL) despite adequate volume resuscitation [1]

Although elevated lactate is a criterion for septic shock, its presence in the definition of septic shock was debated. Some experts argued that combining hyperlactatemia with fluid resistant hypotension better identifies high-risk patients, others viewed lactate as a marker of cellular stress rather than shock [1]. Concerns were also raised about its limited availability in resource-poor settings, potentially hindering diagnosis [8]. As a result, the 2021 Surviving Sepsis Guidelines issued a weak recommendation for lactate as a test for determining the probability of sepsis. Alternative markers of tissue hypoperfusion such as delayed capillary refill time are being explored for settings without lactate measurement. Clinicians in

low-income regions emphasize the need to adapt guidelines to address these shortages [9-11]

1.2 Pathophysiology of sepsis

Sepsis is an inflammatory host response to infection. The sepsis pathophysiology involves an initial hyperinflammatory state with cytokine storm induced by proinflammatory mediators. The cytokine storm produces fever, shock, respiratory failure and multi organ dysfunction. The hyperinflammatory response is followed by an immune paralysis phase, where both the innate and adaptive immune cells undergo apoptosis. Apoptotic depletion of cells occurs in a greater magnitude among sepsis non-survivors than survivors. Due to the suppression of cell-based immunity, mortality associated with the late phase of sepsis is due to acquired secondary and opportunistic infections such as candida. Furthermore, sepsis is characterised by microvascular dysfunction with activation of the endothelium and changes to a proinflammatory phenotype for endothelial cells [3,12]

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CHAPTER 2
SCREENING and IDENTIFICATIONS of SEPSIS

Early identification of sepsis on presentation is important for early treatment initiation and mortality reduction [1]. A patient must be screened for sepsis when infection is suspected.

When to suspect infection?

- History of **one or more** of the following:
  - » Fever
  - » Cough, shortness of bearth
  - » loose stools, vomiting, abdominal pain
  - » Dysuria, reduced urine output
  - » Altered mental status
  - » Rashes, wounds
  - » poor appetite

- Ill looking patient

Some patients are at a heightened risk for sepsis. Who are they?

- **Older patients (over 75 years)**
- **People with impaired immune systems:**
  - » People on chemotherapy for cancer
  - » Diabetic patients
  - » People with splenectomy
  - » People on long term steroids, immunosuppressant drugs
  - » People with surgery or other invasive procedures in the past 6 weeks
  - » People with any breach of skin integrity (cuts, blisters, skin infections)
  - » People with indwelling lines/catheters

- Women who are pregnant, have given birth or had a termination of pregnancy miscarriage in the past 6 weeks

It is important to understand that the definition of sepsis requires the patient to have 'organ dysfunction'. Although a change in SOFA score is the most reliable indicator of organ dysfunction, calculating it in busy wards and low-resource settings like ours is challenging due to prolonged blood test turnaround times. Thus, we recommend using the NEWS. The NEWS has demonstrated the highest combined sensitivity and specificity for predicting sepsis, septic shock and related mortality, outperforming both SIRS and qSOFA [2,3].

The NEWS takes into consideration 7 parameters, all of which are vital signs and easily obtainable. Based on the score, patients are classified into low, medium or high risk of having sepsis. The NEWS assessment tool as in the following page.

Physiological Parameters	3	2	1	0	1	2	3
Respiration rate (bpm)	≤8		9-11	12-20		21-24	≥25
Oxygen Saturation	≤91	92-93	94-95	≥96			
Supplemental oxygen		Yes		No			
Temp (°C)	≤35		35.1-36.0	36.1-38.0	38.1-39.0	≥39.1	
Systolic BP (mmHg)	≤90	91-100	101-110	111-219			≥220
Heart Rate (bpm)	≤40		41-50	51-90	91-110	111-130	≥131
Level of Consciousness				A			V, P or U

NEWS	Clinical risk
1 – 4	Low
5 – 6	Medium
≥7	High

Patients with a NEWS >5 have a heightened clinical risk of sepsis and thus, will need immediate intervention / resuscitation.

CHAPTER 3
RESUSCITATION STRATEGIES for SEPSIS

Resuscitation and treatment must begin as soon as you suspect sepsis and septic shock [i.e. NEWS >5]. Sepsis need not be proven when you initiate resuscitation. Treatment modalities to be provided to suspected patients with sepsis and septic shock are delineated in the Sepsis Bundle of Care [4]. The latest Surviving Sepsis Guideline recommends activating the 'Hour – 1 Bundle' [Figure 1]. The elements in the hour – 1 bundle provides a greater benefit when applied together than individually.

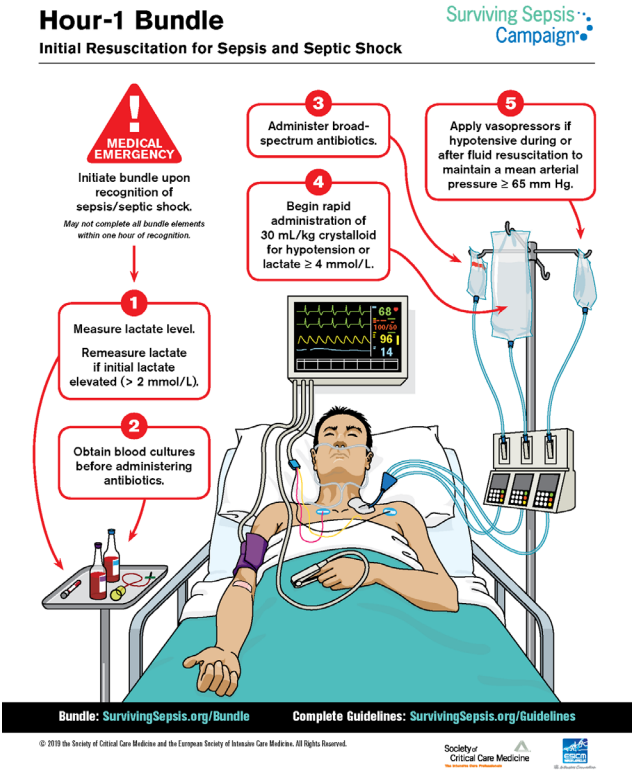


Fig. 1: Hour – 1 Bundle of sepsis and septic shock [4]

3.1 Measuring lactate

The first element in the Hour-1 Bundle is about measuring lactate and if high, to remeasure it. In our context, this might not always be feasible due to unavailability or non-sustained supply of blood gas cartridges. We thus recommend sending out a lactate, whenever possible.

3.2 Obtaining cultures before administering antibiotics

We recommend obtaining blood and other appropriate microbiological cultures (urine, sputum, pus) whenever available, before starting antimicrobial therapy in patients with suspected sepsis and septic shock. This is to be done if it results in no substantial delay in the start of antimicrobials [4].

3.3 Administer broad spectrum antibiotics

Early administration of appropriate antibiotics is proven to be the most effective measure to reduce mortality in septic patients and should be considered a time sensitive intervention [5,6]. For every hour of delay in antimicrobial administration, the mortality rises by 7.6% [7]. We recommend administering antimicrobials immediately and within 1 hour, for all patients with septic shock and those with confirmed sepsis. In cases of possible sepsis, up to 3 hours can be used for a rapid assessment of potential etiologies before administering antimicrobials.

Diagnosing sepsis is challenging because sepsis may be mimicked by non-infectious conditions and sepsis itself may present in subtle ways. Thus, there is a need to continuously evaluate the likelihood of infection and the necessity of antimicrobial use [8,9] This approach aligns with the 2021 Surviving Sepsis Guidelines [Figure 2] [4].

The choice of empiric antibiotic depends on the likely source of the infection and postulated organism [10].

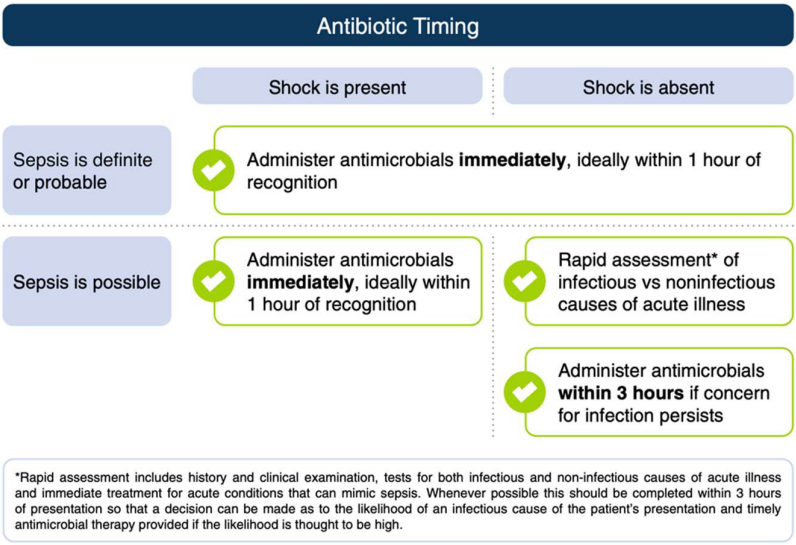
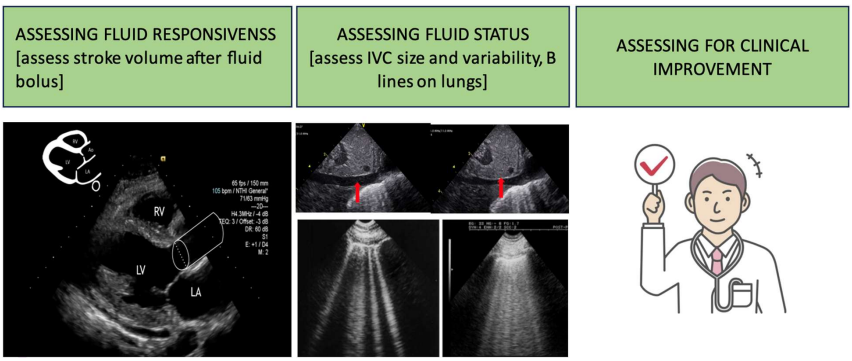


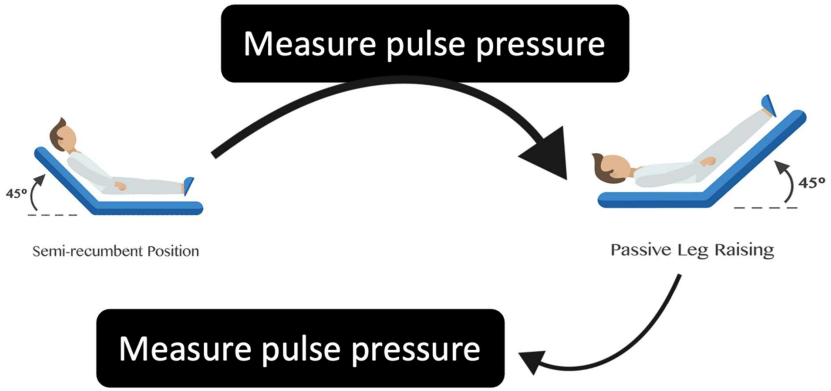
Fig 2: Recommendations on antibiotic administration [4]

3.4 Fluid administration

We recommend initiating appropriate fluid resuscitation immediately upon recognition of sepsis or septic shock. The aim is to administer 30ml/kg of IV crystalloids over 3 hours. Start by administering a bolus of 300-500ml over 15 to 30 minutes.



This assessment will guide the need for continued fluid boluses and/or the need to initiate vasopressors. In settings where ultrasound isn't available, Passive Leg Raise Test (PLRT) is a simple bed side tool which can be used to assess fluid responsiveness. The figure below provides a glance to how the PLRT is performed.



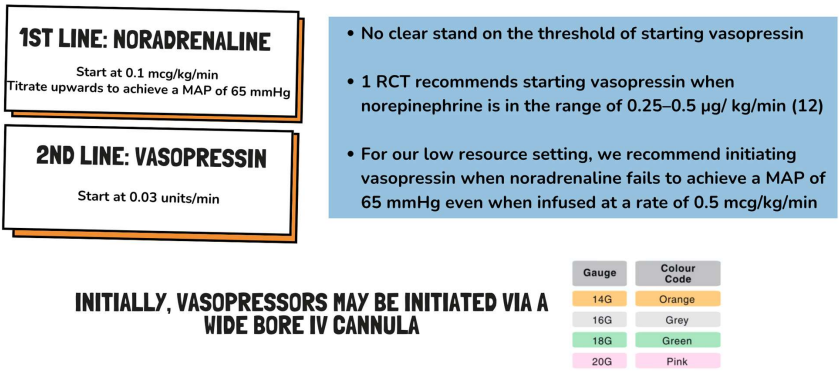
Passive leg raise test (PLRT) is one of the maneuvers to predict fluid responsiveness especially in patients having limitations for heart lung interaction maneuvers. Ideally, the response to PLRT is assessed by the changes in the stroke volume or cardiac output at the end of maneuver but if cardiac output monitoring tool is not available, we can measure the either pulse pressure (PP) or pulse pressure variation (PPV) if there is arterial line.

PLRT is performed by having the patient at a 45° semi recumbent position and measure the pulse pressure (systolic BP – diastolic BP). Then, raise the foot end of the bed and remeasure the pulse pressure. The PLR mimics a fluid challenge by delivering internal volume of around 300ml of venous blood from the lower limbs towards the heart. So, if the pulse pressure increases by 15%, it indicates fluid responsiveness.

While clinicians tend to hold back intravenous fluid boluses in patients with end stage renal disease and heart failure, there is evidence that shows that holding fluids do more harm [11]. It is also crucial to remember that a recommendation of 30ml/kg does not mean that vasopressors can be initiated only after this amount of fluid has been transfused.

3.5 Vasopressor Administration

When septic shock is refractory to treatment with intravenous fluids (30ml/kg), vasopressors need to be started to achieve a Mean Arterial Pressure (MAP) > 65mmHg.



When vasopressin is not available, epinephrine or dopamine may be used. If cardiac dysfunction with persistent hypoperfusion is present despite adequate volume status and blood pressure, consider adding dobutamine or switching to epinephrine. If a patient is in refractory shock, we recommend performing a blood gas analysis to assess the extent of acidosis.

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ATTENTION

For every 1000 hospitalized patients, an estimated 15 patients will develop sepsis as a complication of receiving health care.

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CHAPTER 4

RECOMMENDED INITIAL EMPIRIC ANTIBIOTIC THERAPY for PATIENTS with SEPSIS and SEPTIC SHOCK

4.1 Indication for broad spectrum antibiotics in sepsis

- Broad spectrum antibiotics are agents that cover a wide range of gram positive, gram negative and anaerobic organisms. Early administration of broad-spectrum antibiotics is crucial in management of sepsis and septic shock, with delays resulting in adverse clinical outcomes.
- The choice of antimicrobial agent primarily depends on the following factors:
  1. Suspected site of infection
  2. Disease severity
  3. Place of acquisition of the pathogen i.e. community and hospital acquired
  4. Antibiotic exposure in the past 3 months and previous organisms identified from the patient

- The antibiotics should be administered after the appropriate clinical samples are taken, ideally within 1 hour from the recognition of sepsis but taking samples should not delay the initiation of antibiotics. Antibiotic choice should be de-escalated and narrowed to the most appropriate agent based on the microbiological culture (48 to 72 hours). Antimicrobials should be switched to oral agents with an improvement in the clinical outcomes and starts tolerating oral feeds.
- Hospital acquired pathogens are more resistant to a wide range of antimicrobials and requires a broader spectrum of antibiotics. Patients in septic shock also requires a broad-spectrum antibiotic.

CLINICAL PEARLS

What are hospital acquired infections (HAI)?

HAIs are nosocomially acquired infections that are typically absent or might be incubating at admission. These infections are usually acquired after hospitalization and manifest 48 hours after admission to the hospital.

Risk factors for multi drug resistant organisms

1. Prior IV antibiotics within 90 days
2. 5 or more days of hospitalization prior to onset
3. Septic shock
4. Known colonization with MDROs
5. Known MRSA colonization / recent MRSA infection
6. If skin, skin structure and IV access sites have purulence or abscess
7. Severe, rapidly progressive necrotizing pneumonia

4.2 Empirical antimicrobial choices for different infections

The following table provides a guide to the empiric antimicrobials that can be used for patients with sepsis based on the site of infection and place of acquisition

Suspected source	Place of acquisition	Choice of antibiotic
Unknown source		Ceftriaxone 2 gm IV stat and 2gm IV q 24 hr OR Piperacillin -Tazobactam 4.5 gm IV stat and 4.5 gm IV q 8 hr OR Meropenem 2 gm IV stat and 1 gm IV q 8 hr If anaphylaxis to penicillin, then consider Ciprofloxacin 400 mg IV q 8 hr

Suspected source	Place of acquisition	Choice of antibiotic
Central nervous system	Community Acquired	Benzylpenicillin 4 MU IV q 4 hr OR Ceftriaxone 2 gm IV q 12 hr If anaphylaxis to penicillin, then consider Ciprofloxacin 400 mg IV q 8 hr If risk factor for listeria monocytogenes, then add Ampicillin 2 gm IV q 4 hr (with Ceftriaxone or Ciprofloxacin)
	Hospital Acquired	Meropenem 2 gm IV q 8 hr If anaphylaxis to penicillin, then consider Ciprofloxacin 400 mg IV q 8 hr If risk factor for listeria monocytogenes, then Ampicillin 2 gm IV q 4 hr
Pneumonia	Community Acquired	Ampicillin 1 gm IV q 6 hr OR Amoxicillin/clavulanate 1.2 gm IV q 8 hr OR Ceftriaxone 2 gm IV q 24 hr PLUS Azithromycin 500 mg IV q 24 hr OR Doxycycline 100 mg PO q 12 hr

Suspected source	Place of acquisition	Choice of antibiotic
	Hospital Acquired	Ceftriaxone 2 gm IV stat and 2 gm IV q 24 hr OR Piperacillin -Tazobactam 4.5 gm IV stat and 4.5 gm IV q 8 hr OR Meropenem 2 gm IV stat and 1gm IV q 8 hr ± Gentamicin 5-7 mg /kg IV q 24 hr OR Amikacin 15 mg/kg IV q 24 hr
Skin, soft tissue, bones and joints	Community Acquired	Cloxacillin 2 gm IV q 6 hr OR Cefazolin 2 gm IV q 8 hr OR Amoxicillin/clavulanate 1.2 gm IV q 8 hr OR If risk factor for MRSA, then consider: Vancomycin 25-30 mg/kg loading dose (over 2 hours) then 15 mg/kg q 12 hr
	Hospital Acquired	Piperacillin -Tazobactam 4.5 gm IV stat and 4.5 gm IV q 8 hr OR Meropenem 2 gm IV stat and 1 gm IV q 8 hr

Suspected source	Place of acquisition	Choice of antibiotic
	Necrotising fasciitis (NSTI), synergistic gangrene including Fournier's gangrene	Piperacillin - Tazobactam 4.5 gm IV stat and 4.5 gm IV q 8 hr OR Meropenem 2 gm IV stat and 1 gm IV q 8 hr PLUS Vancomycin 25-30 mg/kg loading dose(over 2 hours) and then 15mg/kg IV q 8 hr to q 6 hr PLUS Clindamycin 900 mg IV q 8 hr
Abdominal source	Community Acquired	Ampicillin 1 gm IV q 6 hr PLUS Gentamicin 5-7 mg/kg IV q 24 hr PLUS Metronidazole 500 mg IV q 8 hr OR Amoxicillin/clavulanate 1.2 gm IV q 8 hr OR Cefazolin 2 gm IV q 8 hr PLUS Metronidazole 500 mg IV q 8 hr OR Ceftriaxone 2 gm IV q 24 hr / Cefotaxime 2 gm IV q 8 hr/ Ciprofloxacin 400 mg IV q 8 hr PLUS Metronidazole 500 mg IV q 8 hr
	Hospital Acquired	Piperacillin -Tazobactam 4.5 gm IV stat and 4.5 gm IV q 8 hr OR Meropenem 2 gm IV stat and 1 gm IV q 8 hr
Urinary source	Community Acquired	Ampicillin 1 gm IV q 6 hr PLUS Gentamicin 5-7 mg/kg q 24 hr OR Ceftriaxone 2 gm IV q 24 hr

Suspected source	Place of acquisition	Choice of antibiotic
	Hospital Acquired	Ciprofloxacin 400 mg IV q 8 hr OR Piperacillin -Tazobactam 4.5 gm IV stat and 4.5 gm IV q 8 hr OR Meropenem 2 gm IV stat and 1 gm IV q 8 hr
Tropical infections		Azithromycin 500 mg IV q 24 hr OR Doxycycline 100 mg PO q 12 hr

4.3 Antibiotic Dosage

Dosing administration as infusion

1. Piperacillin -Tazobactam 4.5 gm stat dose over 30 mins 4.5 gm IV TID maintenance dose (Extended infusion) over 4 hours
2. Meropenem 2 gm stat dose over 30 mins, 1 gm IV TID maintenance dose (Extended infusion) over 3 hours
3. Ciprofloxacin 400 mg IV TID (Infusion) over 60 minutes
4. Metronidazole 5 ml/min eq. to the infusion of one bag (500 mg/100ml) over 20 to 60 min
5. Meropenem 2 gm stat dose over 30 mins, 2 gm IV TID for CNS
6. Vancomycin 25-30 mg/kg loading dose (infusion) over 2 hours, 15 mg/kg IV BD maintenance dose (infusion) 1gm over 1 hour

4.4 Dosing administration as per renal function (Creatinine clearance)

Sl. no	Antibiotics	Creatinine clearance	Renal Dosing
1	Piperacillin-Tazobactam	>20mL/min	4.5 gm IV q 8 hr
		< 20mL/min	2.25 gm IV q 8 hr
2	Meropenem (Double the dose in CNS infection)	≥50 mL/min	1 gm IV q 8 hr
		25 to 49 mL/min	1 gm IV q 12 hr
		10 to 24 mL/min	500 mg IV q 12 hr
		<10 mL/min	500 mg IV q 24 hr
3	Gentamicin (High dose extended interval)	>60 mL/min	5-7 kg/kg q 24 hr
		40 to 59 mL/min	5-7 kg/kg q 36 hr
		20 to 39 mL/min	5-7 kg/kg q 48 hr
		< 20 mL/min	Not recommended
4	Amikacin (High dose extended interval)	> 60 mL/min	15-20 mg/kg q 24 hr
		40 – 60 mL/min	15 mg/kg q 36 hr
		>30 mL/min	15 mg/kg q 48 hr
		<30 mL/min	Not recommended
5	Ciprofloxacin	> 50 mL/min	Not needed
		30-50 mL/min	400 mg IV q 12 hr to q 8 hr
		<30 mL/min	400 mg IV q 24 hr
6	Cefazolin	> 50mL/min	2 gm IV q 8 hr
		10-50 mL/min	2 gm IV q 12 hr
		<10 mL/min	2 gm IV q 24 hr

Sl. no	Antibiotics	Creatinine clearance	Renal Dosing
7	Ampicillin	> 50mL/min	1-2 gm IV q 6 hr
		(for meningitis)	2 gm IV q 4 hr
		10-50 mL/min	1 gm IV q 8 hr to q 6 hr
		(for meningitis)	2 gm IV q 12 hr to q 6 hr
		<10 mL/min	1 gm IV q 12 hr
		(for meningitis)	1 gm IV q 8 hr
8	Vancomycin		Initial dose of 15mg/kg Adjust next dose as per the trough serum vancomycin concentration

***For the first 24 hours give full dose of antibiotics irrespective of renal function in patients with sepsis and septic shock**

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5. Medscape, point of care medical reference app

CHAPTER 5
FLUID MANAGEMENT in SEPSIS

5.1 Why fluids first in sepsis?

IV fluids are the first and integral part of treatment of sepsis patients with hypotension and septic shock. The goal of initial fluid therapy is to increase depleted or functionally reduced intravascular volume, thereby cardiac output and blood pressure. This will help to maintain both macrovascular perfusion (e.g., stroke volume and cardiac output) and microvascular perfusion (e.g., capillary blood flow) [1].

5.2 How much to give?

Surviving Sepsis Guideline recommend, in the resuscitation for the sepsis-induced hypoperfusion, at least 30ml/kg of IV crystalloids fluid be given within the first 3 hours which is downgraded from strong to weak recommendation [2].

In the early phase of septic shock, where there is evidence of acute circulatory failure with obvious hypovolemia and hypoperfusion, volume expansion should be done with IV fluids as per SSG up to 30ml/kg in the first 3 hours. When the hypovolemia is not obvious but with persistent hypotension, try fluid challenge for fluid responsiveness. The Fluid challenge is not standardized and lacks of consistency among the published studies. The most common form of administration is 500 to 1000 mL of crystalloid over 30 minutes, and this is assessed by an increase in CI or CO ≥15% [1-5].

In trial by Aya, H. D.et al they found the minimal fluid volume that is able to increase the backward pressure of venous return is 4 mL/kg over 15 mins and it can reliably detect responders and non-responders [5].

Thus, we recommend the IV fluid resuscitation in septic shock as described in the figure 1.

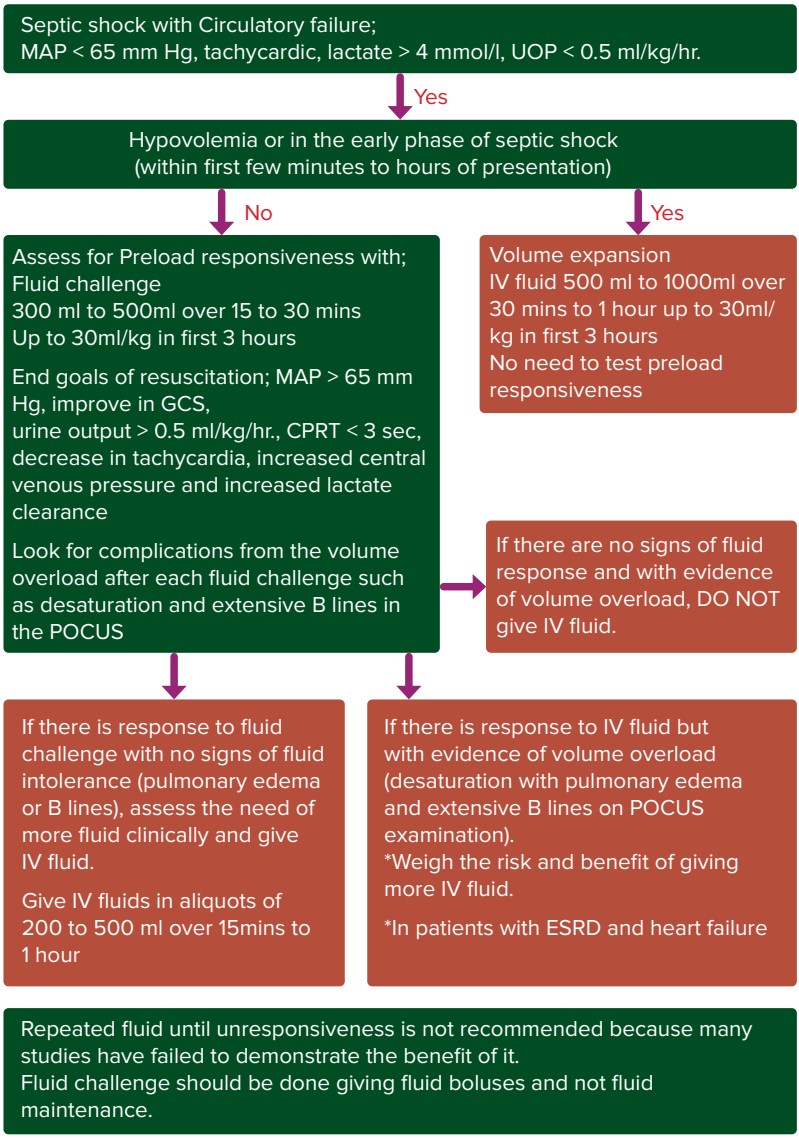

Figure 1; Fluid resuscitation and fluid challenge in septic shock

5.3 What fluid to give?

According to the surviving sepsis guideline,2021, the recommended first-line fluid for resuscitation in adults with sepsis and septic shock is crystalloids (Balanced crystalloids over normal saline)

Role of Colloids (20% albumin)

For adults with sepsis or septic shock, the surviving sepsis guidelines suggest using albumin in patients who received large volumes of crystalloids however exercise precaution when used in patients with traumatic brain injury, leaky lungs and cardiac issues.

5.4 Fluid responsiveness

This is a process that consists of predicting before fluid administration whether or not subsequent fluid administration will increase cardiac output. It avoids unnecessary fluid administration and contributes to reducing the cumulative fluid balance [6].

Prediction of fluid responsiveness is based on dynamic tests and indices, which observe the effect on cardiac output of changes in cardiac preload. The threshold to define fluid responsiveness depends on the change in cardiac preload induced by the test (e.g. 15% for fluid challenge, 10% for the PLR test, 5% for the end-expiratory occlusion test) [3,6].

Advanced monitoring tools such as cardiac echocardiography and arterial line are required to assess the fluid response.

Prediction of fluid responsiveness is based on dynamic tests and indices, which observe the effect on cardiac output of changes in cardiac preload.

Static Measures	Dynamic Measures
• Central venous pressure • Pulmonary artery occlusion pressure • Inferior vena cava size	• Pulse pressure variation • Stroke volume variation • Inferior vena cava variation or diameter size • Tidal volume challenge test • Fluid challenge • Mini fluid challenge test • Passive Leg Raise Test

Dynamic measures

Heart Lung Interaction	Fluid redistribution
• Pulse pressure variation (PPV). • Stroke volume variation (SVV). • Respiratory variation of IVC/ SVC. • Tidal volume challenge test	• Passive leg rising test • Mini-fluid challenge test • End-expiratory occlusion test

5.5.1 Heart lung interaction

Parameters	Pulse pressure variation (PPV) [7-9]	Stroke volume variation (SVV) [7-9]	Inferior vena cava (IVC) variability / IVC diameter [10,11]
Definition	Percentage change in pulse pressure (the difference between systolic and diastolic pressure) during a single respiratory cycle8-9	Represents the variation (as a percentage) of Stroke volume during the ventilation cycle	Reflects respiratory changes in venous return, IVC sizes changes with respiration and it is measured at each end of respiration IVC distensibility index is for the intubated patient IVC Collapsibility index is for the spontaneously breathing patient
How to calculate	PPV = [(PP max-PP min)/PP mean] *100	SVV (%) = (SVmax -SVmin)/ SVmean] *100	IVC distensibility index = IVC max-IVCmin *100 IVC min IVC collapsibility index = IVC max-IVCmin *100 IVC min IVC variability index = IVC max- IVCmin*100 IVC mean

Parameters	Pulse pressure variation (PPV) [7-9]	Stroke volume variation (SVV) [7-9]	Inferior vena cava (IVC) variability / IVC diameter [10,11]
Interpretation	PPV < 9%. not fluid responsive PPV > 13% fluid responsive PPV 9 - 13 grey zone	SVV > 12 % fluid responsive	IVC distensibility index >18% fluid responsiveness IVC collapsibility index > 40% fluid responsiveness IVC variability index >12% fluid responsiveness IVC size <1.0 cm fluid responsiveness IVC size >2.5 cm fluid unresponsiveness
Limitations	• Tidal volume (Vt)<8 ml/kg, • Right ventricular dysfunction • Arrythmias, • Heart rate/ respiratory rate ratio<3.6 • Impaired respiratory mechanic [9] • Need arterial line	• Tidal volume (Vt)<8 ml/kg, • Right ventricular dysfunction • Arrythmias, • Heart rate/ respiratory rate ratio<3.6 • Impaired respiratory mechanic [9] • Need arterial line	• Patients with right ventricular (RV) dysfunction • It is PEEP sensitive

5.5.2 Fluid redistribution

- **Tidal Volume Challenge test**
  - » Increase Tidal Volume transiently from 6ml/kg Predicted body weight (PBW) to 8ml/kg PBW for 1 minute [3,11]
  - » Observe change in PPV/SVV from baseline (Delta PPV/Delta SVV at PEEP 6-8)

    PPV 6-8 cut off 3.5% - fluid responsiveness.

    SVV 6-8 cut off 2.5% - fluid responsiveness.

    Tidal volume challenge test predicted by change in PPV

- **Passive leg raising test (PLRT)**

The response to PLRT is assessed by monitoring the changes in stroke volume (SV), cardiac output (CO), pulse pressure variation (PPV) or pulse pressure [12,13]
PLRT maneuver is performed as described in chapter 2 on screening and identification of sepsis
Positive PLRT test is indicated as in the following table;

Parameters	Positive test (Fluid responsive)
Cardiac output	Increases by 10 %
Stroke volume	Increases by 10 to 15%
Pulse pressure variation	Decreases by 30%
Pulse pressure	Increases by 10 to 15%

Limitations

Brain injury, Immobilization, Raised Intra-abdominal pressure
PLRT better predicted by change in cardiac output

- **Mini fluid challenge test**

Administer 50 to 100 ml crystalloid/colloid over 1 min
Assess Cardiac Output (CO) increased >10%

Limitations

Initial bolus may not predict fluid response
False negative response

- **Fluid challenge**

A fluid challenge is a dynamic test to assess fluid responsiveness by giving a fluid bolus and simultaneously monitoring the hemodynamic effect. The best response is predicted by increase in cardiac output (CO) > 10 to 15 % or mean arterial pressure (MAP) >10 % [1]

Fluid bolus

A fluid bolus is the rapid infusion of fluids over a short period of time.
In clinical practice, a fluid bolus is usually given to correct hypovolemia, hypotension, inadequate blood flow or impaired microcirculatory perfusion [6]

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CHAPTER 6
ROLES of NURSES in SEPSIS MANAGEMENT

Nurses are essential in identifying patients with sepsis, administering and assessing response to treatment, supporting the patient and family, and limiting complications from sepsis [1,2]

6.1 Screening and early recognition

Due to constant patient interaction; nurses are uniquely positioned to incorporate sepsis screening into their daily routine work [3] Nurses in all wards and units should use NEWS as a screening tool for sepsis in patients with signs of infection. Furthermore, first contact nurses at all health centers are pivotal in identifying sepsis early by using the NEWS tool.

6.1.1 How to use the NEWS assessment tool?

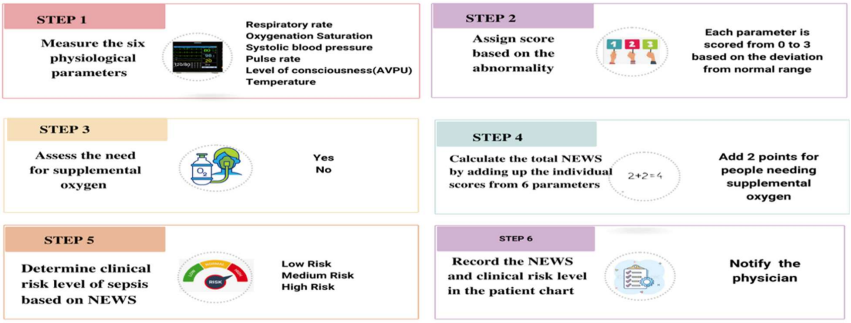

Fig 1: Steps to use the NEWS assessment tool [4]

6.1.2 How to respond to NEWS?

NEWS	Frequency of monitoring	Nurses action
0	Every 12 hour	Continue routine monitoring
0-4	Every 4-6 hours	Continue routine monitoring Inform the doctor on duty
5-6	Every 1 hour	Inform the doctor on duty Consider activating the sepsis pathway
>7	Every 15-30 minutes	Inform physician on duty Activate the sepsis pathway

6.2 Rapid initial Resuscitation and implementation of the 1-hour bundle

Nurse driven implementation of sepsis protocols have shown to be highly effective in early identification and treatment of septic patients within the crucial first hour. [5,6]

Nurses are responsible for the timely initiation of 1-hour bundle as shown in the figure 2:

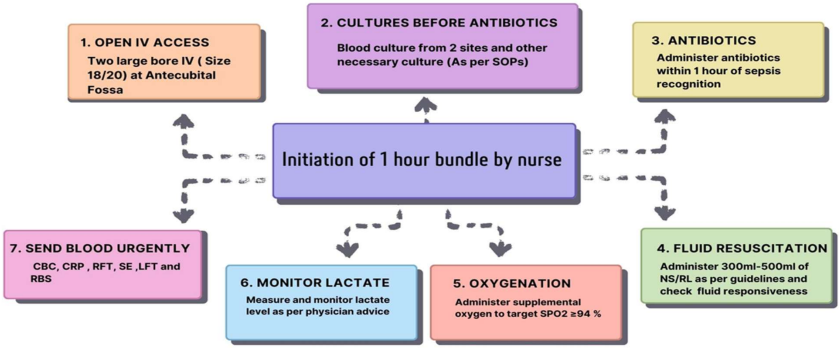

Fig 2: Responsibilities of nurse during the implementation of 1-hour bundle

6.3 Hemodynamic support and monitoring

- Monitor NEWS and communicate the findings with the doctor on duty for further management
- When required, start vasopressors, taking into consideration the following:
  1. Prepare noradrenaline infusion, the first line vasopressor, as follows:

Single Strength: Noradrenaline 4mg (4ml) + NS or D5% (46ml) = 50 ml solution
Concentration: 1 ml = 80mcg

Double Strength: Noradrenaline 8mg (8ml) + NS or D5% (42ml) = 50 ml solution
Concentration: 1 ml = 160mcg

Refer to Table in the annexure 1 for a simplified guide to the rate of noradrenaline infusion based on the patient's body weight [7]

2. When choosing the site for placement of the peripheral IV line, choose a site which can maximize the effect of the vasopressor while causing minimal physical harm to the patient. The recommended site is the peripheral vein proximal to antecubital fossa [8]. If a central line is in-situ, use the central line for administering the vasopressor.

   When using a peripheral access for infusing vasopressors, monitor for complications such as extravasation and thrombophlebitis. In case of extravasation

3. Immediate steps should be taken to prevent complications, following the flowchart in the annexure 2 on extravasation [9]

4. Use the single strength formulation (1 ml= 80mcg) of Noradrenaline for infusion via large bore peripheral access.

5. Inform the doctor on duty to insert a central line when one of the following conditions are met:

   5.1. Noradrenaline dose is > 0.5mcg/kg/min for more than 24 hours [8, 10, 11]

   5.2. Two or more vasopressors are required to achieve the target MAP [10]

6. Prepare Vasopressin infusion, the second line vasopressors as follows:

Vasopressin 20 units (1ml) + Normal Saline (39 Repeated fluid until unresponsiveness is not recommended because many studies have failed to demonstrate the benefit of it.

- Oxygenation and Perfusion support
  1. Continue to monitor SPO2 and administer supplemental oxygen to treat hypoxemia in patients with sepsis via different delivery devices
  2. Monitor urine output and inform the doctor if the urine output is <0.5ml/kg/hr [12]
  3. Monitor CRT and inform the doctor on duty if the CRT >3 seconds [1,10]

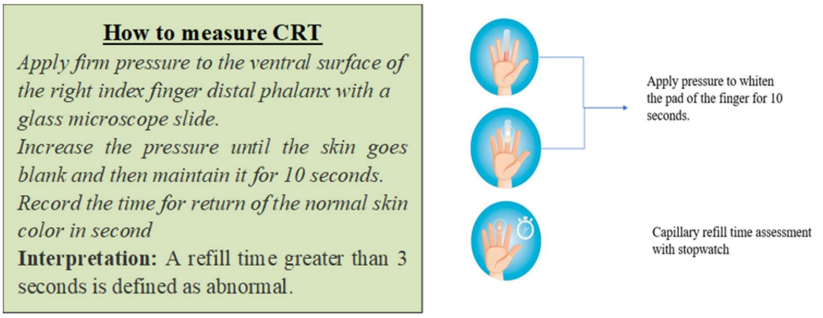

Fig 3: How to measure capillary refill time [10]

6.4 Nursing considerations for patient on antimicrobial therapy

Apart from the timely administration of antibiotics, nurses have the following additional roles:

- Inform the doctor on duty for the need for modification, de-escalation and discontinuation of antimicrobial therapy as indicated by findings of clinical assessment
- If the patient is on antibiotics that require prolonged infusion such as beta-lactams, consider the need for a dedicated IV access for antibiotic administration. This IV access must be different from the access used for the infusion of vasopressors [1]

6.5 Infection control and prevention

Nurses' roles in infection control and prevention spans across patient care, policy implementation and education. To achieve these, nurses must:

- Emphasize and educate on importance of hand hygiene
- Follow aseptic techniques for procedures such as IV cannulation or central line insertion
- Encourage early removal of invasive devices when no longer necessary

6.6 Multidisciplinary collaboration and communication

Timely interventions in sepsis are dependent on early recognition and effective communication among the health care team. A standard approach in communication is important to report acute events. Nurses have the following roles to ensure effective communication:

1. Maintain clear and timely communication with the doctors and other team members
2. Use the standard communication tool SBAR to communicate information to the team [13,14]. We recommend using the SBAR template in annexure 3 as a guide to communicate information to the doctor on duty and other team members.

6.7 Post sepsis care and rehabilitation

Nurses play a crucial role in the post sepsis care as sepsis survivors often face long term physical, cognitive and physiological challenges [15-17]. Nurses have the following roles:

1. Discuss goals of care (short and long term) and enforce shared decision making
2. Educate patient and family about post sepsis syndrome which includes fatigue, reduced muscle strength, anxiety and depression and provide appropriate intervention
3. Support and refer sepsis survivors to relevant rehabilitation therapies such as occupational therapy and physiotherapy.

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ATTENTION

For every 1000 hospitalized patients, an estimated 15 patients will develop sepsis as a complication of receiving health care.

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CHAPTER 7
LABORATORY ROLE in EARLY DETECTION of SEPSIS

7.1 Introduction

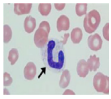
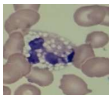
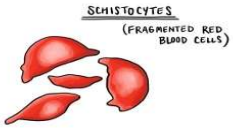
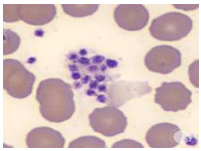
The clinical laboratory's ability to provide quick and precise diagnostic data is essential for the early diagnosis of sepsis. By means of blood cultures, biomarkers like procalcitonin (PCT) and C-reactive protein (CRP) aid in the identification of infections, evaluation of inflammation, and prompt treatment guidelines. Due to the rapid progression of sepsis and the need for prompt action, early detection is crucial to improve patient outcomes. Clinical laboratories facilitate evidence-based clinical decision-making, lower mortality rates, and improve sepsis therapy by combining automated testing and real-time monitoring.

7.2 Laboratory tests for early detection of sepsis:

Samples of suspected sepsis patient should be sent immediately after collection and laboratory personnel should be informed for urgent processing.

- **Complete Blood Count (CBC) with Differential –** Detects leukocytosis, leukopenia, indicating infection response. (10-20 minutes TAT)
- **C - reactive protein (CRP) –** Indicates systemic inflammation and infection severity. (20 – 30 minutes TAT).
- **Pro-calcitonin (PCT) –** Differentiates bacterial infections from other inflammatory conditions. While PCT levels can help confirm bacterial infection and guide the de-escalation of antibiotics, PCT IS NOT RECOMMENDED TO USE FOR INITIATION OF ANTIBIOTICS. (20 – 30 minutes TAT)
- **Peripheral Blood Smear (PBS) –** Morphological description of blood cells aid in detecting sepsis. (30 -60 minutes TAT). The following provides a guide to features seen in PBS of patient with

suspected sepsis.

WBC	RBC	PLATELETS
• WBC or • Toxic vacuolation of neutrophils • Left shift – Band Neutrophils  Band Neutrophils  Toxic vacuolation of Neutrophils	• Fragmentation (Schistocytes) – indicate (DIC). • Anisocytosis & Poikilocytosis – Irregularly shaped or sized RBCs, reflecting systemic stress and organ dysfunction. 	• Thrombocytopenia 

- **Gram Stain (GS) –** Differentiates gram positive and gram-negative bacteria causing sepsis. Once the machine flags positive for blood culture, the sample is processed for gram stain and sub-cultured simultaneously. Concerned health personnel are informed immediately if the bacteria is gram negative. Gram positive are mostly found to be contaminants, hence, treating physicians or nurses are not alarmed about it. Physicians can also request for urgent GS if needed. (24 hours TAT).
- **Blood Culture (BC) –** Identifies causative pathogens to guide antibiotic therapy. Test samples of the patient with suspected sepsis should be collected as soon as possible and send immediately for testing. As for blood cultures, drawing blood from multiple sites increases the chance of detecting the pathogen. If a suspected contaminant grows in only one set but not both, it is more likely to be a false positive and if the same organism grows in both sets, it suggests a true bloodstream infection. (5 to 7 days TAT)

- **Urine –** Urine microscopy and urine culture plays a crucial role in the early detection of sepsis, especially when the infection originates from the urinary tract or when sepsis affects kidney function. (1 day TAT)

Note: For blood culture sample collection, please refer the SOP attached for detailed information.

- **Collection and labeling of samples:** Pre-analytical errors are one of the major causes in the delay of laboratory reports. Labeling, proper mixing of blood in tubes with anticoagulants and adequate volume should be considered before sending the sample to the lab in order to prevent delay of reports.

The minimum information required on the sample container are:

	Patient name, age, gender, CID, contact number
	Location (IPD, OPD, etc.).
	Date and time of sampling.
	Label two bottles with its site of venipuncture respectively (for the blood culture bottles)

The request form must also contain the same information as well as:

	Relevant clinical findings.
	Travel history over past 12 months.
	Recent and current anti-microbial therapy.
	Requesting physician or nurse's name and signature.

7.3 Final Laboratory action

After reception of samples, laboratory personnel should start processing immediately and release the reports as soon as possible. For panic values, the treating physician or other concerned health personnel should be alarmed immediately.

7.4 Summary

Early detection of sepsis is found to be very critical for saving lives, and the clinical laboratory serves as a cornerstone in this process. Labs enable prompt diagnosis and therapy by offering crucial insights into infection, inflammation, and organ function through accurate and quick testing. Clinicians can identify sepsis early on with the use of advanced biomarkers, blood cultures, and urine analysis, which improves patient outcomes and lowers complications. The clinical laboratory continues to be a vital ally in the battle against sepsis, guaranteeing prompt and efficient medical intervention due to ongoing developments in diagnostic technologies.

7.5 References

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DID YOU KNOW?

Sepsis is costly; the average hospital-wide cost of sepsis was estimated to be more than US$ 32,000 per patient in high-income countries.

www.who.com

CHAPTER 8
SOURCE CONTROL in SEPSIS and SEPTIC SHOCK

Source control is a crucial aspect of managing sepsis and septic shock.

8.1 What is source control?

Source control is physical measures to eradicate a focus of infection and eliminate or treat microbial proliferation. It should be undertaken in timely manner wherever feasible since undrained foci of infection may not respond to antibiotics alone.

8.2 What are the objectives of source control in sepsis and septic shock?

Objectives of source control are:

1. To eliminate the source of infection, control ongoing contamination, and restore premorbid anatomy and function.
2. Reduce systemic inflammatory response and bacterial load.
3. Source control is required for effective antimicrobial therapy.

8.3 What are the methods for source control?

- Source control strategies vary depending on the infection type and may include drainage, debridement, or removal of obstructions.
- A multidisciplinary approach is essential when determining the best source control strategy, as different infections require tailored interventions.
- Factors such as patient stability, infection location, and available expertise must be considered.
- In bloodstream infections, source control can be challenging, especially in catheter-related infections, where catheter removal

is often necessary.

- In some cases, less invasive temporizing measures like percutaneous drainage can be used initially, but definitive intervention should not be delayed once the patient stabilizes.
- Poorly controlled infections can lead to persistent sepsis, necessitating a more aggressive approach.

Failed source control can result from incomplete removal of the infection source, ongoing contamination, or inadequate antimicrobial therapy. Diagnosing failure is difficult due to a lack of definitive diagnostic tools, making clinical monitoring and imaging essential. The success of source control depends on balancing intervention risks with potential benefits, ensuring minimal harm while maximizing effectiveness. While source control is commonly associated with abdominal infections, its principles apply broadly, reinforcing the need for individualized, multidisciplinary decision-making.

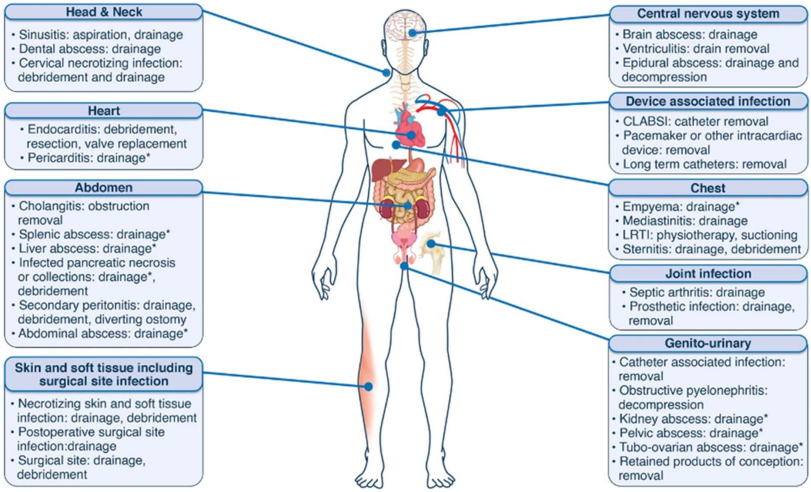

Fig 1: Methods for source control [1]

8.4 What is the optimal timing for source control?

A growing body of evidence supports the importance of early source control. The optimal timing of source control is unknown however the surviving sepsis guidelines, 2021, suggest no more than 6 to 12 hours after diagnosis since survival is negatively impacted by inadequate source control.

From a practical point of view, the urgency of source control is determined by three factors:

1. The presence and magnitude of ongoing contamination,
2. The degree of organ dysfunction, and
3. Patient physiology at presentation.

Based on these characteristics, patients can be classified into three categories according to the degree of urgency for source control.

Levels of Urgency	Patients in category 1	Patients in category 2	Patients in category 3
	Source control is required as soon as possible (i.e., suspicion of sepsis or confirmation of diagnosis). Any delay in source control in these patients is associated with an increased risk of mortality.	**Source control is required as soon as their physiology permits intervention.** Although these patients may appear stable, there is some time for correction of metabolic disorders; it is important to implement source control interventions as soon as possible.	**Source control is required once the process of infection has been demarcated.**
Examples	Examples include necrotizing skin and soft tissue infections, intra-abdominal infections (particularly in cases characterized by rapid deterioration of organ dysfunction), or abdominal compartment syndrome. In these patients, fluid resuscitation should be promptly performed and continued during the source control procedure.	Examples include patients with secondary peritonitis, pleural empyema, and acute cholecystitis. Most patients are classified into this category.	A typical example is infected pancreatic necrosis in clinically stable patients. Delaying a percutaneous intervention or surgical procedure makes the procedure easier and causes less collateral damage.

For instance, performing surgery on a hemodynamically unstable patient may further worsen their condition, resulting in adverse outcomes despite timely source control. In such scenarios, initial resuscitation to stabilize the condition may be required before proceeding with invasive source control measures, although resuscitation and source control can be simultaneously performed in many instances.

8.5 What are the best practices on abdominal drains, sampling and antibiotics after source control?

1. Use of abdominal drains
   - » Avoid the use of drains in non-pancreatic abdominal surgery
   - » Limit the duration of abdominal drains in the treatment of abdominal sepsis
   - » Remove abdominal drains as soon as patient physiology allows

2. Sampling abdominal drains
   - » Sample intra-operatively – not postoperatively – for reliable microbiology results
   - » Do not sample fluid from a drain that has been in situ for 24 h or longer
   - » Avoid culturing drains/parts of drains upon removal

3. Antimicrobial use
   - » Ignore skin flora cultured from abdominal drains
   - » When infection is suspected clinically, do not solely target pathogens obtained from drain cultures

4. In adult patients with complicated intra-abdominal infections who have undergone definitive source control, we recommend a short (4 days) versus long (8 days) duration of antimicrobial treatment.

At a Glance

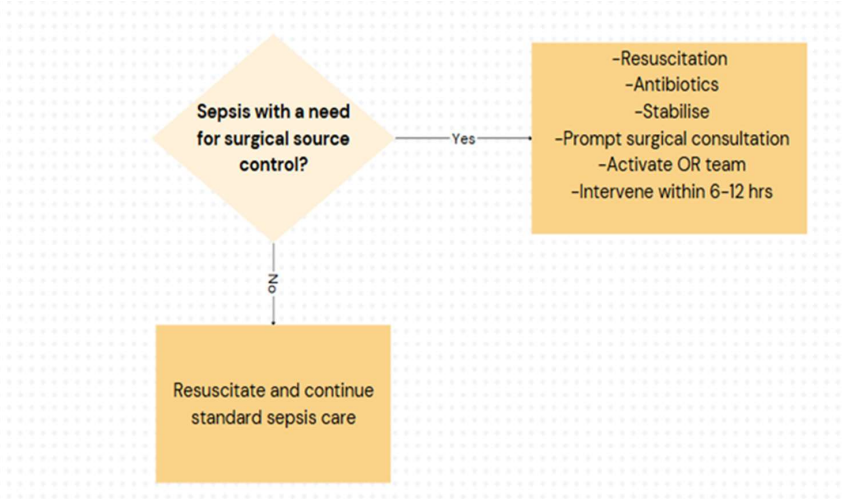

Fig 2: At a glance.

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DID YOU KNOW?

NSTI is a surgical emergency - delays increase mortality. When in doubt, cut, don't wait!

CHAPTER 9
REFRACTORY SEPTIC SHOCK

9.1 Definition

Refractory septic shock is defined variably as persistent hypotension, with end-organ dysfunction and requiring high-dose vasopressor greater than 0.5 mcg/kg/min norepinephrine or equivalent [1]. There is an associated mortality of up to 60%. [1-3]

Consider the following causes in refractory septic shock;

- Severe metabolic acidosis (pH 7.15)
- Organ failure
- Critical illness related corticosteroid insufficiency
- Side effects of high dose catecholamine
- Microcirculatory dysfunction
- Unable to control source [4].

9.2 Adjunctive in management of refractory septic shock

Consider the following adjunctive while managing patients with refractory septic shock;

Adjunctive	
Albumin	To consider using human albumin (5% or 20%) solution if ongoing fluid resuscitation is required. Albumin helps maintains plasma oncotic pressure and acts as an antioxidant and as a buffer for acid-base equilibrium. During the early phase of severe shock, target a serum albumin level of > 30 g/l [2]. Reduce mortality in patients with septic shock **Weak recommendation, low quality of evidence**

Adjunctive	
Hydrocortisone	It is a glucocorticoid which helps to downregulates the proinflammatory response and limits the anti-inflammatory response while preserving innate immunity [2,4,5]. Indicated when there is ongoing requirement of norepinephrine or epinephrine ≥ 0.25 mcg/kg/min for at least 4 hours after initiation of vasopressors to maintain the target MAP. Dose; IV hydrocortisone 50 mg QID or as an infusion 200mg/24 hour Increase the number of vasopressor free days **Weak, moderate-quality evidence**
Thiamine	Absolute or relative thiamine deficiency is common in patients with septic shock. Such a deficiency may present as an unexplained lactic acidosis. Intravenous thiamine replacement has been shown to reduce lactate levels and mortality in patients with proven thiamine deficiency. Furthermore, intravenous thiamine replacement is associated with a reduced need for renal replacement therapy and improved renal function in patients with septic shock [6,7]. Dose; IV Thiamine 200mg stat and IV 200 mg BD **Weak, low quality of evidence**

Adjunctive	
Ascorbic acid (Vitamin C)	Strong antioxidant and Cofactor for catecholamine and vasopressin synthesis. Septic patients have absolute or relative vitamin C deficiency [4,6,7] Dose; 25 mg/kg or 1.5 gm 6 hourly Thiamine in combination with Vit C and hydrocortisone was associated with a reduction in organ failures and early recovery **Weak, low quality of evidence**
Sedation and analgesia	Sedative medications exacerbate hypotension through myocardial depression and systemic vasodilation. Current guidelines suggest minimizing sedation in mechanically ventilated patients with sepsis. Suggest to combine sedatives agents (Opioid and non-opioid)
Bicarbonate therapy	Refractory septic shock is associated with severe acidosis which is further associated with vasopressor hypo responsiveness due to impaired catecholamine signaling. Suggest to give bicarbonate as bolus followed by infusion when PH < 7.2 or HCO3 < 15 Dose; Bolus 200mmol/l or 200 meq/l over 1 to 2 hours Maintenance dose 50mml/l or 50meq/l per hour over 4 to 6 hours Monitor with Arterial blood gas every 2 hourly for 6 hours then every 4 hourly further continuation or to stop [4,8] **Weak, low quality of evidence**

Adjunctive	
Calcium chloride/ calcium gluconate	Calcium is essential for cardiac and smooth muscle contractility. Calcium deficiency is common in refractory septic shock due to various reasons such as calcification of necrotic foci, chelation by blood products, renal dysfunction and parathyroid deficiency [4,9,10]. Dose – can be given as bolus (2 Ampules) or as an infusion when ionized serum calcium level are very low **However, no strong evidence that calcium correction improves outcome**
Adjunctive antimicrobial therapy	In addition to beta lactams, we suggest adding another gram-negative coverage antibiotics such as aminoglycosides like amikacin (2 antibiotics from different groups) [5]
Respiratory support	For adults with refractory septic shock, we suggest the use of non- invasive ventilation (NIV) or positive pressure ventilation for the respiratory support. For the positive pressure ventilation use lung protective ventilatory strategy with tidal volume 6 to 8ml/kg of predicted body weight (PBW) and target P plateau pressure (Ppla) less than 30 cm H2O
Renal replacement therapy	In case of refractory shock and acute renal insufficiency, the expert suggests initiation of renal replacement therapy (RRT) if pH<= 7.15 in the absence of severe respiratory acidosis and despite appropriate treatment [4] No difference in mortality between early and late RRT. Continuous renal replacement therapy (CRRT) is preferred over the intermittent hemodialysis.

Adjunctive	
Blood purifications	There is insufficient evidence to make a recommendation on the use of other blood purification techniques. **No recommendation**
Hemodynamic monitoring	Invasive BP monitoring with arterial line via radial or femoral access
Others [4]	There is insufficient evidence to make a recommendation on the use of the followings; • Intravenous Immunoglobulin • Levosimendan • Intravenous prostacyclin • Methylene blue • Angiotensin II • VA ECMO

9.3 References

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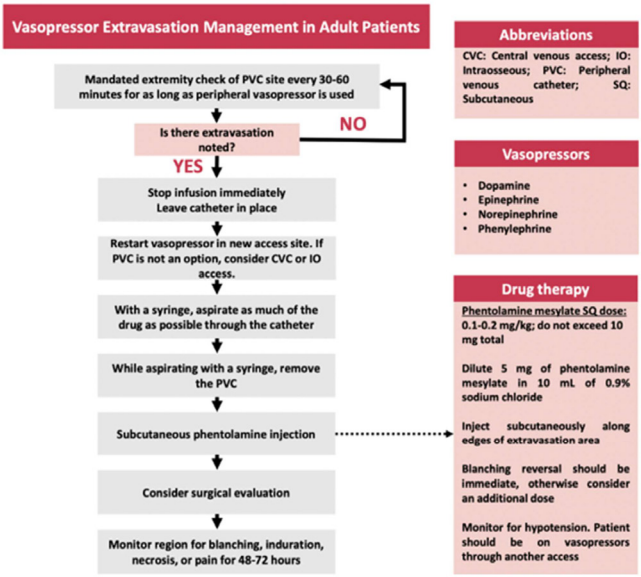
ANNEXURE

Annexure 1: Guide to infusion rate of noradrenaline as per body weight

Single strength Noradrenaline Noradrenaline 4mg (4ml) + NS or D5% (46ml) = 50 ml solution (1 ml = 80mcg)									
Weight (kg) and dose in microgram/kg/minute									
Rate(ml/hr)	40	50	60	70	80	90	100	110	120
1	0.03	0.03	0.02	0.02	0.02	0.01	0.01	0.01	0.01
2	0.07	0.05	0.04	0.04	0.03	0.03	0.03	0.02	0.02
3	0.10	0.08	0.07	0.06	0.05	0.04	0.04	0.04	0.03
4	0.13	0.11	0.09	0.08	0.07	0.06	0.05	0.05	0.04
5	0.17	0.13	0.11	0.10	0.08	0.07	0.07	0.06	0.06
6	0.20	0.16	0.13	0.11	0.10	0.09	0.08	0.07	0.07
7	0.23	0.19	0.16	0.13	0.12	0.10	0.09	0.08	0.08
8	0.27	0.21	0.18	0.15	0.13	0.12	0.11	0.10	0.09
9	0.30	0.24	0.20	0.17	0.15	0.13	0.12	0.11	0.10
10	0.33	0.27	0.22	0.19	0.17	0.15	0.13	0.12	0.11
11	0.37	0.29	0.24	0.21	0.18	0.16	0.15	0.13	0.12
12	0.40	0.32	0.27	0.23	0.20	0.18	0.16	0.15	0.13
13	0.43	0.35	0.29	0.25	0.22	0.19	0.17	0.16	0.14
14	0.47	0.37	0.31	0.27	0.23	0.21	0.19	0.17	0.16
15	0.50	0.40	0.33	0.29	0.25	0.22	0.21	0.18	0.17
16	0.53	0.43	0.36	0.30	0.27	0.24	0.22	0.19	0.18
17	0.57	0.45	0.38	0.32	0.28	0.25	0.23	0.21	0.19
18	0.60	0.48	0.40	0.34	0.30	0.27	0.24	0.22	0.20
19	0.63	0.51	0.42	0.36	0.32	0.28	0.25	0.23	0.21
20	0.67	0.53	0.44	0.38	0.33	0.30	0.27	0.24	0.22

Double strength Noradrenaline Noradrenaline 8mg (8ml) + NS or D5% (42ml) = 50 ml solution (1 ml = 160mcg)									
Weight (kg) and dose in microgram/kg/min.									
Rate(ml/hr)	40	50	60	70	80	90	100	110	120
1	0.07	0.05	0.04	0.04	0.03	0.03	0.03	0.02	0.02
2	0.13	0.11	0.09	0.08	0.07	0.06	0.05	0.05	0.04
3	0.20	0.16	0.13	0.11	0.10	0.09	0.08	0.07	0.07
4	0.27	0.21	0.18	0.15	0.13	0.12	0.11	0.10	0.09
5	0.33	0.27	0.22	0.19	0.17	0.15	0.13	0.12	0.11
6	0.40	0.32	0.27	0.23	0.20	0.18	0.16	0.15	0.13
7	0.47	0.37	0.31	0.27	0.23	0.21	0.19	0.17	0.16
8	0.53	0.43	0.36	0.30	0.27	0.24	0.21	0.19	0.18
9	0.60	0.48	0.40	0.34	0.30	0.27	0.24	0.22	0.20
10	0.67	0.53	0.44	0.38	0.33	0.30	0.27	0.24	0.22
11	0.73	0.59	0.49	0.42	0.37	0.33	0.29	0.27	0.24
12	0.80	0.64	0.53	0.46	0.40	0.36	0.32	0.29	0.27
13	0.87	0.69	0.58	0.50	0.43	0.39	0.35	0.32	0.29
14	0.93	0.75	0.62	0.53	0.47	0.41	0.37	0.34	0.31
15	1.00	0.80	0.67	0.57	0.50	0.44	0.40	0.36	0.33
16	1.07	0.85	0.71	0.61	0.53	0.47	0.43	0.39	0.36
17	1.13	0.91	0.76	0.65	0.57	0.50	0.45	0.41	0.38
18	1.20	0.96	0.80	0.69	0.60	0.53	0.48	0.44	0.40
19	1.27	1.01	0.84	0.72	0.63	0.56	0.51	0.46	0.42
20	1.33	1.07	0.89	0.76	0.67	0.59	0.53	0.48	0.44

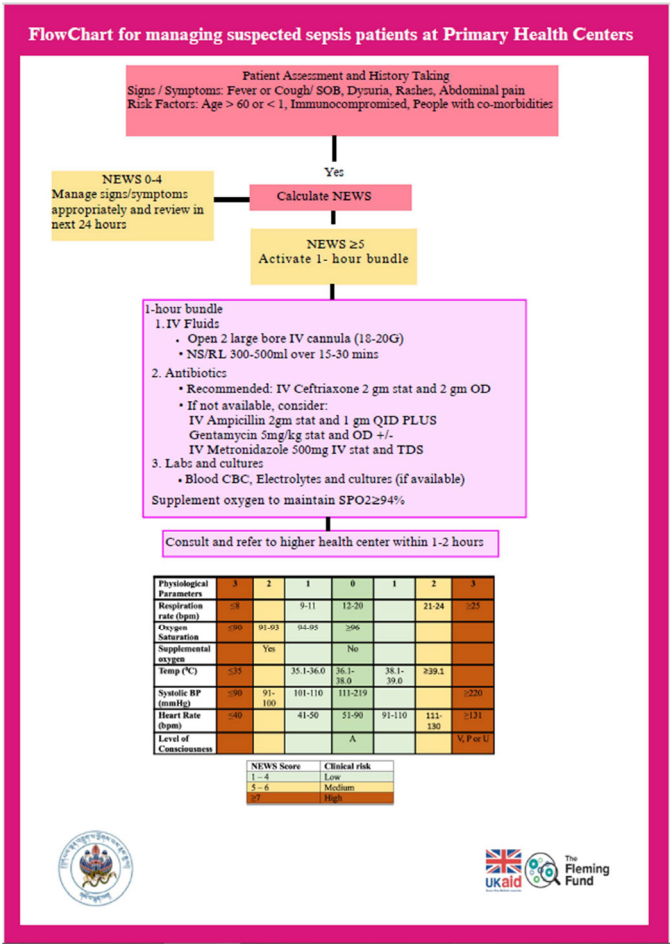
Annexure 2: Vasopressor extravasation management



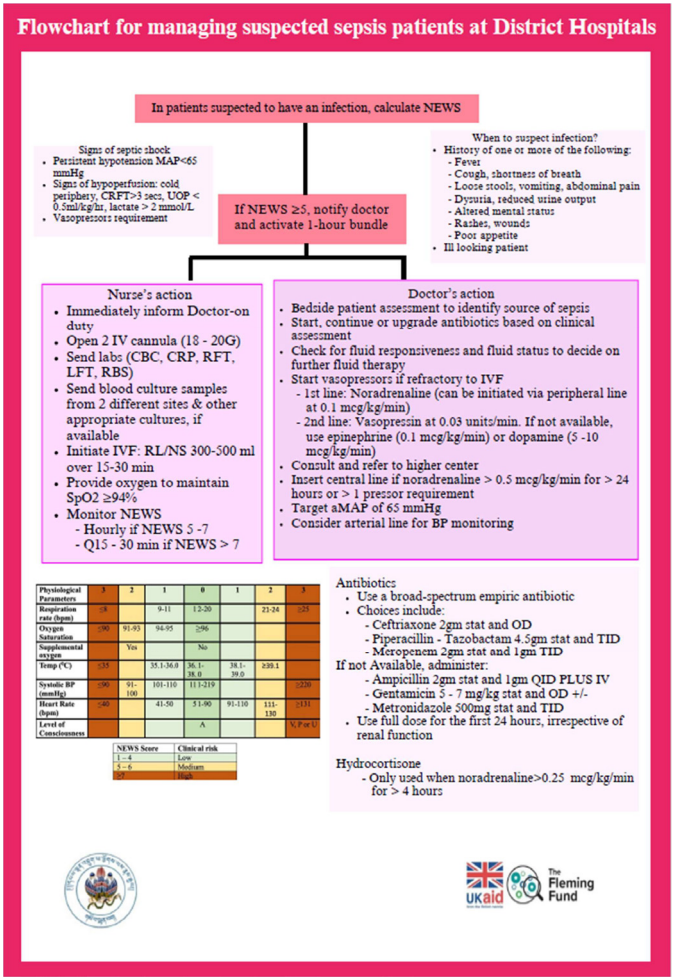
Annexure 3: Template for using SBAR for communication

S Situation	**What is going on with the patient?** Example: I am calling about: (patient's name and location) I am calling because this patient has met the screening criteria for possible sepsis
B Background	**What is the clinical background or context?** Example: The patient is in the hospital because _____ and has suspected/conformed infection
A Assessment	**What do you think the problem is?** Example: I am concerned that the patient possibly has Sepsis Current status Heart Rate: _____ RR: ____ T: _____ BP: _____ O2 Sat: _____ WBC: _____ Last C&S done: _____ NEWS score is _____
R Recommendation	**What would I do to correct it?** Example: I would like administer IV fluid and send blood for culture. Do you want me to do anything else? I need you to come within 30 minutes, assess the patient and complete the sepsis order

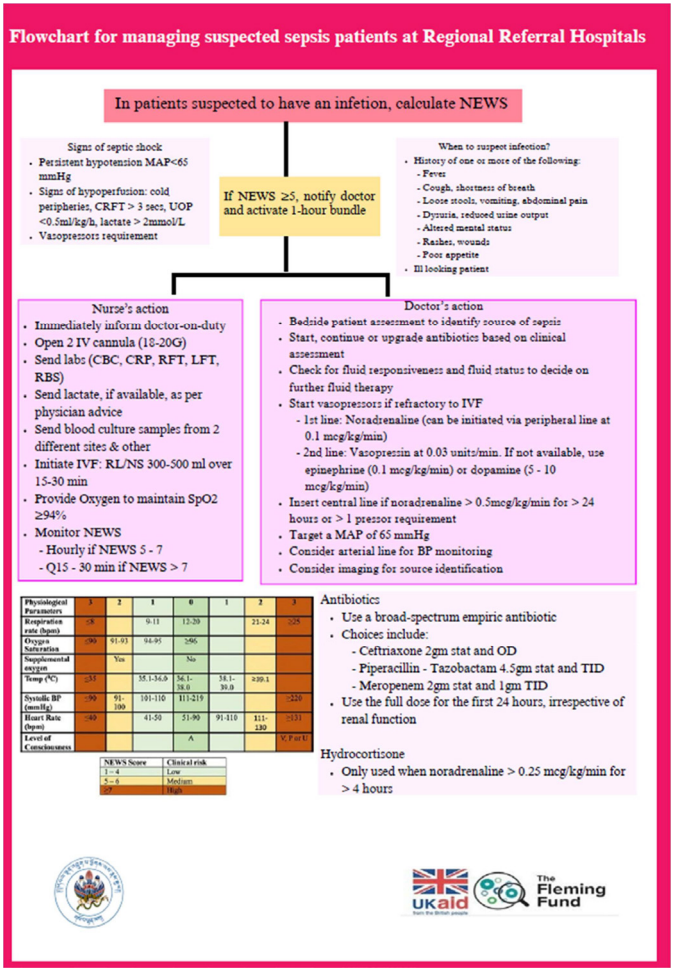
Annexure 4: Flowchart for managing suspected sepsis patients at Primary Health Centers



Annexure 5: Flowchart for managing suspected sepsis patients at District Hospitals



Annexure 6: Flowchart for managing suspected sepsis patients at Regional Referral Hospitals



Annexure 7: Standard Operating Procedure (SOP) on blood culture sample collection

Copy No.

SOP No.	Title	Version No.	Total Pages
JDW/MICRO/BACT/	SOP on Blood culture Sample collection	01	9

Issue Date	Effective Date	Review Period
		3 yearly

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REVISION SUMMARY

Version No	Effective Date	Reason for Change	Details of the change

Table of Contents

1. Scope
2. Objective
3. Responsibilities
4. Definitions
5. Principle
6. Pre-requisite
7. Process Map in Flow Chart
8. Procedures
9. Annexure (Related Forms or Work Instructions)
10. References

1. Scope

This SOP applies to all healthcare professionals involved in the collection of blood cultures in a clinical setting, including but not limited to nurses, phlebotomists, and medical practitioners.

2. Objective

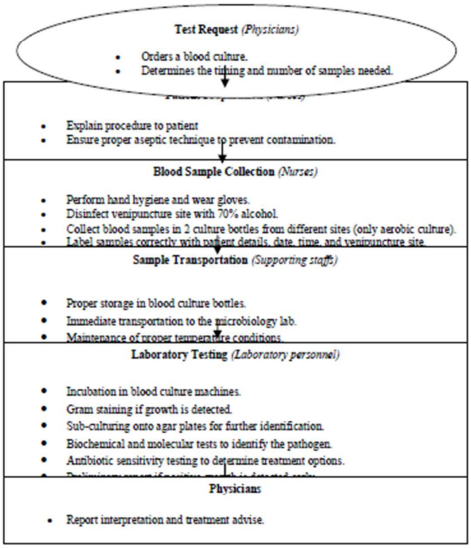
This Standard Operating Procedure (SOP) provides detailed instructions for the collection of blood samples for blood culture to facilitate the early detection of sepsis. The goal is to ensure accurate and reliable results, contributing to timely diagnosis and treatment.

3. Responsibilities

Sl. No.	Official Designation	Responsibilities
1.	Requesting physicians	Order the Blood Culture, determine timing and Site, interpret Results, initiate Treatment, and follow up on Patient Response.
2.	Nurses	Prepare the Patient, collect blood samples using proper techniques to avoid contamination, ensure proper labeling and handling, ensure timely transport to lab, monitor the patient, administer treatment, and educate the patient.
3.	Supporting Staffs	Ensure timely and proper sample transport to the laboratory for testing in order to prevents bacterial contamination which could affect results.
4.	Laboratory personnel	Process and analyze blood cultures following standard protocols.

4. **Definitions**
   - 4.1. **Blood Culture**: A test to detect the presence of microorganisms in blood.
5. **Principle**
   - 5.1. To have a uniform standard for obtaining blood culture sample.
6. **Pre-requisites**
   - 6.1. 1 set (2 blood culture bottles).
   - 6.2. Sterile blood collection set (needle and syringes)
   - 6.3. Antiseptic solution (70% alcohol)
   - 6.4. Adhesive bandage
   - 6.5. Personal protective equipment (PPE): sterile gloves and masks.
   - 6.6. Sharps disposal container
   - 6.7. Dry cotton

7. Process Map in Flow Chart



7. **Procedure**

7.1. Preparation

7.1.1 Verify Patient Identification

7.1.1.1. Confirm the patient's identity using three identifiers (Name, Date of birth, and CID number).

7.1.1.2. Ensure the patient understands the procedure and obtains informed consent.

7.1.2. Prepare Equipment

7.1.2.1. Gather all necessary equipment and ensure that all items are sterile and within their expiration dates.

7.2. Prepare the Work Area

7.2.1 Clean the work area with an appropriate disinfectant.

7.3 Hand Hygiene and Personal Protective Equipment

7.3.1 Perform hand hygiene thoroughly using soap and water or an alcohol-based hand sanitizer.

7.3.2 Don appropriate PPE, including sterile gloves and, a mask.

7.4 Blood Collection

7.4.1 Site Preparation

7.4.1.1 Select an appropriate vein on two sites. In the presence of a central line, ensure one sample is from the central line and the other from the peripheral vein.

7.4.1.2 Cleanse the venipuncture site with an antiseptic solution (70% alcohol wipes) using a circular motion starting from the center and moving outward. Allow the site to air dry completely to ensure the efficacy of the antiseptic.

7.4.2 Blood Collection

7.4.2.1 Prepare the blood culture bottles according to the manufacturer's instructions (one of the culture bottles is filled, followed by the next bottle from another venipuncture site).

7.4.2.2 Using a sterile needle and syringe or a vacuum collection system, insert the needle into the selected vein. If using a syringe, gently aspirate the blood into the syringe.

7.4.2.3 Disinfect the rubber septum on the blood culture bottles or evacuated tube(s) with 70% alcohol wipes.

7.4.2.4 Transfer the blood into the culture bottles. Fill the bottles according to the recommended volume (10 ml per bottle for adults; 1-5 ml for pediatric patients).

7.4.2.5 Avoid overfilling or under filling the bottles as this can affect culture results. Time of collection is not important but volume is critical.

7.4.3 Post-Collection Care

7.4.3.1 Once the blood is collected, remove the needle and apply pressure to the puncture site with sterile dry cotton to prevent bleeding.

7.4.3.2 Apply an adhesive bandage after the bleeding has stopped.

7.4.3.3 Dispose of the needle and other sharps immediately into a sharp disposal container.

7.4.4 Documentation

7.4.4.1 Record the following details in the patient's medical record

7.4.4.1.1 Patient's name and identification number
7.4.4.1.2 Date and time of collection
7.4.4.1.3 Site of collection
7.4.4.1.4 Name of the person who collected the sample
7.4.4.1.5 Any special instructions or comments

7.4.4.2 Ensure that all documentation is accurate and legible.

7.4.5 Sample Transport

7.4.5.1 Transport the blood culture bottles to the laboratory promptly to avoid any potential degradation of the sample.
7.4.5.2 Ensure that the bottles are transported at room temperature
7.4.5.3 If the sample cannot be transported immediately to the laboratory, store the sample in a clean area at optimal room temperature. Do not refrigerate the sample.

7.5 Quality Control and Safety

7.5.1 Follow infection control procedures to minimize the risk of cross-contamination.
7.5.2 Regularly check the expiration dates and sterility of all collection equipment.
7.5.3 Review and adhere to institutional policies regarding blood culture collection and handling.

7.6 Troubleshooting

7.6.1 **Under filled/overfilled sample Volume**: If the sample volume is insufficient or overfilled, send a new sample in a new bottle

7.6.2 **Contamination**:

7.6.2.1 If contamination is suspected (e.g. if the same organism is isolated in multiple cultures from different patients), review the collection technique and address any procedural issue.

8 References

8.1 Centre of Diseases Control (CDC), **Atlanta, Georgia. United States.**