SEPSIS GUIDELINES

Developing local guidelines for management of sepsis in adults: Sepsis Guidelines for Pakistan (SGP)

Endorsed by Global Sepsis Alliance

Madiha Hashmi[1]*, Fazal Hameed Khan[1], Ali bin Sarwar Zubairi[1], S. Tipu Sultan[2], Saeeda Haider[3] Sadqa Aftab[4], Javed Husain[5], Anwar ul Haq[1], Zahid Akhtar Rao[6], Amin Khuwaja[7], Syed Farjad Sultan[3], Zunairah Rais[8], Roohina Baloch[9], Naseem Salahuddin[3], Aslam Khan[10], Faisal Sultan[11], Kamran Chima[12], Amjad Ali[13], Gohar Ali[14]; Pakistan Society of Critical Care Medicine; Pakistan Society of Anaesthesiologists; Medical Microbiology & Infectious Diseases Society of Pakistan; Pakistan Chest Society.

[1]Aga Khan University, Karachi
[2]Sind Institute of Urology and Transplant, Karachi
[3]The Indus Hospital, Karachi
[4]Dow University of Health Sciences and Civil Hospital, Karachi
[5]South City Hospital, Karachi
[6]PNS Shifa Hospital, Karachi
[7]National Institute of Cardiovascular Diseases, Karachi
[8]Liaquat National Hospital, Karachi
[9]Jinnah Post Graduate Medical Center, Karachi
[10]Military Hospital, Rawalpindi
[11]Shaukat Khanum Memorial Hospital and Research Center, Lahore
[12] Services Institute of Medical Sciences, Lahore
[13]Bolan Medical College, Quetta
[14]Lady Readings Hospital, Peshawar

***Correspondence:** Madiha Hashmi, President PSCCM, Director SICU and Assistant Professor, Department of Anaesthesiology, Aga Khan University, Stadium Road, P.O. Box 3500, Karachi 74800, Email: hashmi_madiha@yahoo.ie

ABSTRACT

Background: The purpose of developing 'Sepsis Guidelines for Pakistan' (SGP) is to provide clinicians practicing in local hospitals with a framework to aid timely recognition and management of adult patients in sepsis by adopting evidence-based recommendations of Surviving Sepsis Campaign (SSC) tailored to available resources. These recommendations are not meant to replace the SSC Guidelines.

Methodology: SGP is an initiative of Pakistan Society of Critical Care Medicine (PSCCM). Four key decision points to be addressed in the guidelines were identified by a thirteen member multidisciplinary committee i.e., grading the hospitals in the country, recognition of sepsis and associated organ dysfunction, essential interventions to manage sepsis, and general measures for provision of a comprehensive care to patients in sepsis according to the level of education and training of healthcare providers and facilities and resources available in different levels of hospitals. The draft was presented at the 3rd Sepsis Symposium held on 13th September, 2014 in Karachi. The final document was approved by a panel of experts from across the country, representatives of relevant societies and Global Sepsis Alliance (GSA).

Recommendations: Hospitals are divided into basic, intermediate and tertiary depending on the availability of diagnostic facilities and training of the medical personnel. Modified definitions of sepsis, severe sepsis, and septic shock are used given the lack of facilities to diagnose sepsis according to international definitions and criteria in Pakistan. Essential interventions include fluid resuscitation, vasopressors to support the circulation, maintaining oxygen saturation ≥ 90% with oxygen, non-invasive ventilation or mechanical ventilation with lung protective strategies, prompt administration of antibiotics as recommended by the Medical Microbiology & Infectious Diseases Society of Pakistan (MMIDSP) and early source control. It is recommended to avoid starvation, keep an upper blood glucose ≤180 mg/dL, use daily pharmacoprophylaxis against venous thromboembolism (VTE), use stress ulcer prophylaxis, target haemoglobin of 7-9 g/dl in the absence of ischaemic heart disease, avoid sodium bicarbonate therapy as long as pH > 7.20, avoid fresh frozen plasma in the absence of bleeding, transfuse platelets

if indicated, not use intravenous immunoglobulins and avoid neuromuscular blocking agents (NMBAs) in the absence of ARDS, target specific titration endpoints when continuous or intermittent sedation is required in mechanically ventilated patients and use continuous renal replacement therapy (CRRT) to facilitate management of fluid balance in hemodynamically unstable septic patients in tertiary care centers. In addition a comprehensive, meticulous and multidisciplinary general care is required to improve outcome of sepsis by reinforcing hand hygiene and other infection control measures, adequate monitoring and documentation tailored to the available resources. Goals of care and prognosis should be discussed with patients and families early and either shifting the patient to a hospital with better facilities or limiting or withdrawing therapy in case of poor prognosis should be considered.

Key words: Sepsis syndrome; Septic shock; Hypotension; Sepsis

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A. INTRODUCTION

The Surviving Sepsis Campaign (SSC)[1] Guidelines provide a framework for clinical decisions in the management of severe sepsis and septic shock. Despite their obvious benefits[2,3], the SSC guidelines have not been fully implemented in low and middle income countries (LMIC) due to lack of awareness, limited resources, financial constraints and a wide variation in the available healthcare facilities within most of the countries falling in the LMIC category[4,5,6,7]. Even in Pakistan the healthcare facilities range from well-equipped urban university hospitals to small hospitals lacking qualified medical personnel or basic life-saving equipment.

Most of the interventions in the resuscitation and treatment bundles recommended by SSC are independent therapies based on evidence and inability to comply with the full 'bundle' should not prevent the healthcare workers from implementing part of the 'bundle'. The purpose of developing 'Sepsis Guidelines for Pakistan' is to provide clinicians practicing in local hospitals with a framework to aid timely recognition and management of adult patients in sepsis by adopting evidence-based recommendations of SSC tailored to available resources. These recommendations are not meant to replace the SSC Guidelines.

The ultimate goal of developing Sepsis Guidelines for Pakistan is to reduce the unacceptable and undesirable variation in practice of healthcare professionals from different disciplines and different healthcare set ups and to improve sepsis outcomes.

B. METHODOLOGY

Sepsis Guidelines for Pakistan (SGP) is an initiative of Pakistan Society of Critical Care Medicine (PSCCM). The executive committee of PSCCM (Karachi Chapter) convened in 2014 and formed a multidisciplinary committee of physicians managing critically ill patients in teaching and non-teaching hospitals of Karachi in both government and private healthcare setup. The thirteen member committee consisted of eight anaesthesiologists, three pulmonary and critical care physicians, one full time intensivist, and one paediatric intensivist- all heading the intensive care units in their respective hospitals. No external funding was used and none of the authors had any financial conflict of interest in drugs or techniques discussed in the manuscript.

The task of the committee was to recommend interventions to recognize sepsis and associated organ dysfunction and to institute essential therapies according to available resources targeting all healthcare workers entrusted with the care of adult patients in sepsis.

Step 1: Key decision points:

Based on informal consensus discussions amongst the members of the committee, following key decision points to be addressed in the guidelines were identified;

- Grading the hospitals in the country
- Recognition of sepsis and associated organ dysfunction according to the level of education and training of healthcare providers and diagnostic facilities available in different levels of healthcare setup.
- Essential interventions to manage sepsis according to facilities and resources available in different levels of healthcare setup.
- General measures for provision of comprehensive care to patients in sepsis according to facilities and resources available in different levels of healthcare setup.

Step 2: Literature and evidence:

Expert opinion and clinical experience of the

authors working in hospitals with a wide variation in available resources was considered to grade the healthcare facilities in three categories. Interventions to address rest of the key decision points were based on 2012 Surviving Sepsis Campaign guidelines for the management of severe sepsis and septic shock[1] and relevant literature for implementing these guidelines in resource poor settings was reviewed. Five articles on sepsis management from resource-limited settings were selected by consensus[8,9,10,11,12] from a reference list prepared by conducting a structured literature review using the key words sepsis, management, resource-limited, resource poor and low-middle income countries. The coordinator of the committee circulated the key background material electronically to all members of the committee. A list of all possible interventions recommended in these articles was prepared. Feasibility of each intervention was debated in view of availability of resources and training of medical personnel in different healthcare facilities and accepted, rejected or modified based on the majority vote of the members of the committee. If an intervention was accepted as recommended by SSC, the original assessment of quality of evidence and strength of recommendations was quoted. None of the committee members were trained in application of Grading of Recommendations Assessment, Development and Evaluation (GRADE) system so in case an intervention was modified we did not use the GRADE system but mentioned that the recommendation was based on 'consensus opinion'.

Quality of evidence	
A	High
B	Moderate
C	Low
D	Very Low
UG	Ungraded
Strength of Recommendations	
Grade 1	Strong
Grade 2	Weak

Step 3: Drafting the Document:

The chairman of the SGP Committee prepared a draft of the proposed guidelines and circulated amongst the members of the committee. In-person discussions were held at the PSCCM monthly meetings to improve the draft. Disagreements amongst the members were resolved by adopting a consensus process. The draft was approved by all committee members and was presented in 3rd Sepsis Symposium held on 13th September, 2014 at Avari Hotel, in Karachi to commemorate the 3rd World Sepsis Day. Comments from audience and input from the founding member of MMIDSP were incorporated by the Chairman of the committee. The document was then reviewed by outside-committee experts from rest of the provinces of Pakistan, i.e. Punjab, Baluchistan, and Khyber Pakhtunkhwa. Guidelines were also presented in a tabulated format for easy retrieval and assimilation of information applicable to the various grades of the existing healthcare facilities.

Step 4:Dissemination Plan:

Multifaceted interventions will be utilized to disseminate and implement the guidelines. Anaesthesiologists are the backbone of critical care in Pakistan, supported by pulmonary and critical care physicians. The guidelines will be propagated from the platform of Pakistan Society of Critical Care Medicine (PSCCM), Pakistan Society of Anaesthesiologists (PSA), Infectious Diseases Society of Pakistan (IDSP) and Pakistan Chest Society (PCS) in the form of presentations in the respective annual conferences. Posters based on a flow-chart format will be created for dissemination.

C. RECOMMENDATIONS

1. **Grading the Hospitals according to available resources:**

a. **BASIC:** Hospitals that have no intensive care unit backup and where only general physicians are available as medical personnel. These have access to outsourced laboratory facilities but there are no on-site radiological diagnostic facilities.

b. **INTERMEDIATE:** Hospitals with level-2 intensive care units that are managed by non-intensivist medical personnel. These have access to in-house basic laboratory and diagnostic radiological facilities.

c. **TERTIARY:** Hospitals with level-3 intensive care units, that are managed by physicians trained in intensive care medicine. These have access to advanced laboratory and diagnostic radiological facilities.

This grading is arbitrary and there will be hospitals that fall in-between the above mentioned categories. The aim of providing this framework is to allow the users to acknowledge the resources available in their hospitals. The available resources should be utilized to recognize sepsis, severity of organ dysfunction and the most likely source of infection

and to provide essential interventions to manage sepsis or consider transfer to another hospital with better facilities.

2. **Recognition of sepsis and associated organ dysfunction:**
   Recognizing a patient in sepsis is an essential step for effective treatment. A delay in diagnosis results in progression of sepsis and decreases chances of survival. Modified definitions of sepsis severe sepsis, and septic shock have to be applied given the lack of facilities to diagnose sepsis according to international definitions[13] and criteria in Pakistan.
   a. **SEPSIS**: Sepsis is defined as proven or highly suspected infection associated with some of the following conditions:
      - Altered mental state/confusion
      - Temperature ≥38°C or ≤ 36°C
      - Heart rate ≥90 bpm
      - Respiratory rate ≥ 20 bpm or $PaCO_2$ ≤ 32 mmHg
      - WBC ≤ 4000 /mm^{3}or ≥ 12000/mm^3 or ≥ 10% immature forms
      - Thrombocytopenia (platelet count, ≤ 100,000/mm^3)
      - Hyperglycemia (plasma glucose > 140 mg/dL in the absence of diabetes)
   b. **SEVERE SEPSIS:** When 'sepsis' leads to tissue hypoperfusion or organ dysfunction it becomes 'severe sepsis'.
      i. TISSUE HYPOPERFUSION
         a) Systolic blood pressure ≤ 90 mmHg or a systolic blood pressure decrease ≥40 mmHg from the baseline or mean arterial pressure (MAP) ≤ 65 mmHg.
         b) Decreased capillary refill or skin mottling
      ii. ORGAN DYSFUNCTION:
         a) Pulmonary dysfunction:
            - Signs of respiratory distress (i.e., dyspnea, added sounds on auscultation, cough, sputum)
            - Arterial Hypoxaemia (PaO_2/FiO_2 ≤ 300)

         b) Renal dysfunction
            - Acute oliguria (urine output ≤ 0.5 ml/kg/h for at least 2 h despite adequate fluid resuscitation)
            - Creatinine increase ≥ 0.5 mg/dL

         c) Hepatic dysfunction
            - Jaundice
            - Hyperbilirubinaemia (plasma total bilirubin ≥ 4 mg/dl)

         d) Coagulation dysfunction
            - Petechae or ecchymosis
            - Bleeding/oozing from puncture sites
            - Coagulation abnormalities (INR ≥1.5 or aPTT ≥ 60 s)

         e) Gastrointestinal dysfunction
            - Ileus (absent bowel sounds)

   c. **SEPTIC SHOCK**
      When sepsis-induced hypotension or signs of tissue hypoperfusion persist despite adequate fluid resuscitation, the condition is labeled as 'septic shock'.

3. **Essential interventions:**
   Essential interventions refer to treatments recommended to be administered without delay to maintain a near normal physiology. The compromised organ systems need support while identification of source of sepsis and its control is of paramount importance. Although these essential interventions are presented in a certain order, they may have to be performed simultaneously, depending on the condition of the patient.
   a. **Circulation**
      - Fluid resuscitation in patients with sepsis induced tissue hypoperfusion or organ dysfunction is the corner stone of sepsis management. Initial fluid challenge of a minimum of 20-30 ml/kg should be followed by continuous infusion for 24–48 h, though a more rapid administration and larger volume of fluid may be needed in some patients (grade 1C). Use of crystalloids is strongly recommended (LoE: 1B) because synthetic colloids have shown to precipitate acute kidney injury and should be avoided (LoE: 1B). Albumen can be used if excessive fluid requirement has a risk of aggravating tissue or pulmonary oedema or precipitating abdominal compartment syndrome (LoE: 2C).
      - In the basic setup, the clinicians should target an improvement in pulse volume, capillary re-fill, level of consciousness, urine output and a systolic arterial blood pressure > 90

mmHg, while frequently auscultating the chest for any sign of fluid overload (consensus opinion). If resources are available target for a mean arterial pressure (MAP) > 65 mmHg, CVP 8-12 mmHg, and urine output > 0.5 ml/kg/hr (LoE: 1C). In tertiary care hospitals target for $ScvO_2$ more than 70% and to normalize lactate in patients with elevated lactate levels as a marker of tissue hypoperfusion (LoE: 2C).

- Use of vasopressors is recommended in patients with persistent hypotension (MAP < 65) despite initiating fluid resuscitation (LoE: 1C). Norepinephrine is the vasopressor of choice (LoE: 1B) but dopamine can be used in selected patients in whom risk of tachyarrhythmias is low or they have absolute or relative bradycardia (LoE: 2C) or if norepinephrine is not available (consensus opinion). Epinephrine worsens metabolic acidosis and should be used in septic patients only when an additional agent is needed to maintain adequate blood pressure (grade 2B). Vasopressin at a rate of 0.03 units/minute can be added to norepinephrine (NE) to raise MAP or decrease NE dosage (UG), when available in a tertiary care setup. In patients requiring vasopressors, central access should be taken safely and invasive arterial blood pressure measured continuously (consensus opinion).
- Intravenous hydrocortisone (50 mg every six hours) should be administered if haemodynamic targets are not met with adequate fluid resuscitation and dose requirement of vasopressors rapidly escalates (LoE: 2C).

b. Ventilation:

- Oxygen saturation should be kept ≥ 90%. If pulse oximeter is not available patients with severe sepsis or septic shock should be given oxygen empirically (consensus opinion). If hypoxaemia persists despite oxygen therapy, use of non-invasive ventilation (NIV) is recommended, provided medical staff is adequately trained in its use (LoE: 2B) and patient is awake and able to clear and protect the airway. However a low threshold for endotracheal intubation should be maintained.
- For mechanical ventilation of patients with sepsis induced ARDS, lung protective strategies should be used i.e. a tidal volume of 6-8 ml/kg of predicted body weight (LoE: 1A), adequate PEEP to avoid alveolar collapse (LoE: 1B) and measuring and keeping plateau pressure < 30 mmHg (LoE: 1B). Mechanically ventilated patients should be placed in a semi-recumbent position (head of the bed raised to 30–45°) to reduce the risk of aspiration and ventilator-induced pneumonia, unless contraindicated (LoE: 1B).
- Lung recruitment maneuvers and prone positioning is recommended to manage severe hypoxaemia (PaO_2 /FiO_2 <100), in tertiary care setup, according to the hospital protocols (LoE: 2C).

c. Antimicrobial therapy

Prompt administration of appropriate intravenous antimicrobials to cover the most likely infection should be the goal of therapy.

i. *MMIDSP Recommendations before selecting empirical antibiotic therapy (Table 1):*

- Selection of antibiotic must be based on clinical assessment of site of infection
- Viraemia, severe malaria or fungaemia must be considered as possible causes of sepsis
- Antibiotics must be administered as soon as possible, within 2 hours of admission to ER or ICU
- Two sets of blood cultures, urine analysis and urine culture must be drawn *prior to* institution of antibiotic
- Obtain history of previous use of antibiotics in past 3 months. Avoid same antibiotic if possible
- Dose must be prescribed on weight basis
- Dose must be adjusted for renal or hepatic insufficiency
- Hematologic malignancy or febrile

neutropenia must be considered
- Combination therapy may be prescribed for suspected highly resistant pathogens
- Only intravenous antibiotic should be used until there is clinical improvement

ii. *MMIDSP Recommendations during antibiotic therapy (Table 2):*
- Once culture and sensitivity reports are available, de-escalate to a narrower spectrum antibiotic
- Once patient shows clinical improvement and is stable, de-escalate to oral preparation, if an equally effective oral preparation is available
- Antibiotic should be given for no longer than 7-10 days
- Source control is essential, i.e. drainage of abscess, repair or resection of perforated viscus, removal of cannula, catheter or devices and debridement of infected tissue.

d. Source control
- A detailed history of illness from the patients or the relatives along with a thorough clinical examination is essential to identify the likely source of infection.
- Appropriate imaging techniques should be utilized for specific anatomical diagnosis of infection and surgical and interventional radiology expertise sought as early as feasible for source control.
- Implants, devices, or central lines should be removed if suspected to be the source of infection.
- Use of oral chlorhexidine gluconate should be promoted in mechanically ventilated patients in intermediate and tertiary care set up as a form of oropharyngeal decontamination to reduce the risk of ventilator-associated pneumonia (LoE: 2B).

e. Nutrition

Complete fasting should be avoided in septic patients and oral or tube-feeding should be started within the first 48 hours after a diagnosis of sepsis (LoE: 2C). Feed should be started with 500 calories per day and gradually advanced as tolerated (LoE:2B). Total parenteral nutrition (TPN) alone or to supplement enteral feeding is not recommended in the first 7 days of a severe infection (LoE: 2B).

f. Other measures
- Two consecutive blood glucose levels >200 mg/dL should prompt initiation of intravenous insulin infusion with an aim to keep an upper blood glucose ≤180 mg/dL Blood glucose values should be monitored frequently until glucose values and insulin infusion rate stabilizes. Intermediate and tertiary care hospitals should exercise a protocolised approach to blood glucose management in patients with severe sepsis (consensus opinion).
- Daily pharmacoprophylaxis against venous thromboembolism (VTE) is recommended according to the hospital policy (consensus opinion).
- When stress ulcer prophylaxis is indicated in patients with severe sepsis/septic shock due to the presence of bleeding risk factors, proton pump inhibitors should be preferred over H2 -receptor blockers (LoE: 2D).
- Sodium bicarbonate therapy should be used to improve hemodynamics or reduce vasopressor requirements only if there is life threatening lactic acidosis i.e. pH < 7.20 (consensus opinion).
- In the absence of bleeding and myocardial ischaemia target haemoglobin of 7-9 g/dl or 10 g/dl if there is a history of ischaemic heart disease (consensus opinion). Fresh Frozen Plasma should not be transfused in the absence of bleeding only to correct lab abnormalities. Transfuse platelets if <10,000/mm^3 and no risk of bleeding, <20,000/mm^3 if there is significant risk of bleeding and < 50,000/mm^3 if bleeding continues, or patient going for surgery or invasive procedure.
- Intravenous immunoglobulins are not indicated in adult patients with severe sepsis or septic shock (LoE: 2B).
- Neuromuscular blocking agents (NMBAs) should be avoided if possible in the septic patient without ARDS. Target specific titration endpoints

when continuous or intermittent sedation is required in mechanically ventilated patients (LoE: 1B)

- Renal replacement therapy may be required in patients with severe sepsis and acute renal failure in tertiary care hospitals. Use of continuous therapies (CRRT) facilitates management of fluid balance in hemodynamically unstable septic patients (LoE: 2D).

4. General considerations:
   A comprehensive, meticulous and multidisciplinary general care is required in addition to therapies targeted at optimizing organ function and eradicating the source of infection in order to improve outcome of sepsis. The level of monitoring, documentation and investigations will depend upon the level of training of medical personnel and available resources. Hand hygiene and other infection control measures should be adopted enthusiastically. It is also important to discuss goals of care and prognosis with patients and families early and consider either shifting the patient to a hospital with better facilities or limit or withdraw therapy in case of poor prognosis.

D. CONCLUSION

A multidisciplinary national panel of experts developed consensus sepsis guidelines to streamline provision of uniform sepsis care and improve sepsis outcome. The guidelines provide a framework to identify sepsis and associated organ dysfunction in a timely manner and recommend essential interventions, taking into account the knowledge and training of medical personnel and resources available in various grades of hospitals in Pakistan.

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   BC Children's Hospital and Sunny Hill Health Centre for Children
   UBC & BC Children's Hospital Professor in Critical Care – Global Child Health
   Department of Pediatrics and Emergency Medicine, UBC
   Vancouver, Canada
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   Chair of Anesthesiology, Pain and Intensive Care Department
   Federal University of Sao Paulo
4. Ron Daniels
   Chief Executive- Global Sepsis Alliance
   CEO- UK Sepsis Trust
   Clinical Adviser (Sepsis) to NHS England
   UK
5. Professor Simon Finfer
   Senior Staff Specialist in Intensive Care
   Royal North Shore Hospital of Sydney and Sydney Adventist Hospital
   Australia

TABLE 1: SEPSIS RECOGNITION

	Basic setup	Intermediate setup	Tertiary care setup
• Recognize sepsis	• Temperature ≥ 38°C or ≤ 36°C • Heart rate ≥ 90 bpm • Respiratory rate ≥ 20 bpm • Altered mental state/confusion	In addition • WBC ≤4000 or ≥ 12000 /mm^3 or ≥ 10% immature forms • Hyperglycemia (plasma glucose > 140 mg/dL in the absence of diabetes)	In addition • Significant edema or positive fluid balance (> 20 mL/kg over 24 hr)
• Recognize organ dysfunction	• Systolic blood pressure < 90 mmHg • Decreased capillary refill or mottling • Laboured/difficult breathing • Decreased urine output reported by patient or family • Ileus (absent bowel sounds)	In addition • Urine output <0.5ml/kg/hr for > 2 hrs • Platelet <100,000/mm^3 • Creatinine > 2 mg/dl • INR >1.5 • Bilirubin > 2 mg/dl • Acute Lung Injury with PaO_2/FiO_2 <300 • Plasma C-reactive protein>2SD above normal	In addition; • Serum Lactate > 1 mmol/L (or above the reported normal range of the laboratory)

WBC = white blood cells, INR = international normalized ratio, PaO_2 = partial pressure of arterial oxygen
FiO_2 = fractional inspired oxygen

TABLE 2: ESSENTIAL INTERVENTIONS

	Basic setup	Intermediate setup	Tertiary care setup
Circulation	• Oral rehydration salts • Iv fluid bolus of a crystalloid (20-30ml/kg), guided by clinical assessment of pulse, BP, capillary re-fill, chest auscultation and level of consciousness • Consider shifting to a hospital with ICU facility if no response to fluid replacement or deterioration in general condition **WARNING:** • **Avoid synthetic colloids during resuscitation**	• Fluid management using crystalloids and targeting; • MAP > 65mmHg • Urine output > 0.5ml/kg/hr • CVP 8-12 mmHg • Use vasopressor (norepinephrine is first choice vasopressor but use dopamine if NE is not available) infusion through a central line if targets not met after 2000ml fluid replacement. • Consider iv low dose corticosteroids (50mg 6 hourly) if vasopressor support is rapidly escalating **WARNING:** • **Give vasopressors through a central line** • **Use single lumen femoral vein access if inexperienced or coagulopathy identified**	In addition • Target mixed venous oxygen saturation >70% • Normalize lactate levels • Use albumin if fluid requirement > 30ml/kg. • Add vasopressin (0.03 units/minute) to raise the BP or reduce the dose of norepinephrine **WARNING:** • **Preferably use triple lumen internal jugular central venous access**
Ventilation	• Supplement oxygen via face mask at 6-10 L/min	• NIV (CPAP or BIPAP) guided by ABG analysis • Endotracheal intubation & ventilatory support if hypoxaemia or metabolic acidosis worsens or level of consciousness deteriorates. • Keep the head-end of the bed at 30-45° in mechanically ventilated patients. **WARNING:** **Use NIV only if patient is awake and able to clear secretions and protect airway**	In addition • If mechanical ventilation indicated, use lung protective strategies, i.e. • Tidal volume of 6-8 ml/kg of PBW • Plateau pressure <30mmHg • Use adequate PEEP • Use lung recruitment maneuvers and prone positioning in severe hypoxaemia ($PaO_2/FiO_2 \leq 100$)
***Antimicrobial therapy**	• Prompt oral or iv antibiotics to cover the most likely infection	• Empiric broad spectrum antibiotic cover later guided by gram stain and culture and sensitivity reports.	• Same • Procalcitonin levels to guide the duration of antibiotic therapy • Consider antifungal therapy if indicated in selective cases

	Basic setup	Intermediate setup	Tertiary care setup
Source control	• Sought an anatomical diagnosis of infection • Incision & drainage of abscess within 12 hours	In addition • Consider surgical intervention for deep foci of infection **WARNING:** **Consider removing implants, devices, or central lines if suspected to be the source of infection**	In addition • Consider CT guided diagnosis and drainage along with surgical intervention **WARNING:** **Promote use of oral chlorhexidine gluconate in ventilated patients as a form of oropharyngeal decontamination**
Nutrition	• Oral feeding as tolerated within 48 hours instead of only iv glucose	• Consider enteral feeding within 48 hours of sepsis/severe sepsis as tolerated starting with 500Kcal/day **WARNING:** **Avoid full caloric feed in the first week**	**WARNING:** **Avoid TPN for first 7 days of onset of sepsis/severe sepsis**
Others	• Monitor and keep blood glucose level < 200 mg/dl	• Protocolized approach to blood glucose management to target levels < 180 mg/dl with repeated point-of-care testing. • Stress ulcer prophylaxis with H_2 Blockers or PPI • DVT Prophylaxis with twice daily UFH or compression stockings in case of coagulopathy or low platelets • Target Hb 7-9 g/dl in the absence of bleeding and myocardial ischaemia or 10 g/dl if history of IHD **WARNING:** • **Do not use sodium bicarbonate as long as pH ≥7.20** • **Avoid FFP transfusion in the absence of bleeding to correct laboratory abnormalities**	• Protocolized approach to blood glucose management to target levels < 180 mg/dl • Stress ulcer prophylaxis with PPI is preferred • DVT Prophylaxis with daily LMWH & consider intermittent pneumatic compression device in case of coagulopathy or low platelets • Administer platelets if <10,000 and no risk of bleeding, <20,000/mm^3 if there is significant risk of bleeding and < 50,000/mm^3 if bleeding continues, or patient going for surgery or invasive procedure • Consider Renal Replacement Therapy (CRRT or HD) **WARNING:** • **Avoid use of neuromuscular blocking agents (NMBAs) in septic patient *without ARDS.*** • **Target specific titration endpoints for sedation in mechanically ventilated sepsis patients.**

MAP = mean arterial pressure, CVP = central venous pressure, NIV = non-invasive ventilation, CPAP = continuous positive airway pressure, BIPAP = Bilevel positive airway pressure, ABG = arterial blood gas, PBW = predicted body weight, PEEP = positive end-expiratory pressure, CT= computerized tomography, TPN = total parenteral nutrition, PPI = proton pump inhibitors, DVT = deep vein thrombosis, UFH = unfractionated heparin, LMWH = low molecular weight heparin, IHD = ischaemic heart disease, FFP = fresh frozen plasma, CRRT = continuous renal replacement therapy, HD = haemodialysis, ARDS = acute respiratory distress syndrome.

TABLE 3: GENERAL CONSIDERATIONS

	Basic setup	Intermediate setup	Tertiary care setup
Hygiene	• Observe Hand hygiene by soap & water	• Observe Hand hygiene by alcohol hand rub. • Use disposable gloves while handling blood • Use sterile gloves , gown & face masks while doing sterile procedures • Use face mask if droplet infection suspected	• In addition provide isolation for patients who are highly contagious
Monitoring	Clinically monitor pulse, blood pressure, temperature & mental state	In addition • Use continuous non-invasive monitor for BP, SaO2, ECG, • Monitor GCS & hourly urine out put	In addition monitor invasive arterial blood pressure & CVP
Documentation	• TPR • BP • Urine output • Level of consciousness (AVPU)	In addition document • HR, MAP, SaO2 • GCS • Hourly intake and output	In addition document • Invasive pressures • CVP • Intra-abdominal pressure
Investigations	• Hb/Hct • WBC • Platelet count • Urinalysis • RBS	In addition • UCE • Coagulation profile • ABG • LFT & albumen • Bilirubin • Gram staining • Malaria thick and thin smear • CRP • Cultures (blood, urine, tracheal, other body fluid)	In addition • Lactate • Procalcitonin, • Dengue serology • Malarial parasite
Multidisciplinary care	• Take opinion from medicine and surgery	Involve Anaesthesia Team	In addition involve critical care team • Radiology • Sub-specialty
Estimate prognosis and limit therapy	• Discuss goals of care and prognosis with family earlier. • Consider shifting the patient to a hospital with ICU facilities	• Estimate prognosis by assessing degree of organ failure or SOFA-score • Discuss goals of care no later than 72 hours after admission	• Estimate prognosis by assessing degree of organ dysfunction or APACHE II score • Limit or withdraw therapy in case of poor prognosis • Ethical consult

TPR = temperature, pulse rate, respiratory rate, BP = blood pressure, AVPU = awake, responds to verbal command, responds to painful stimulus, unresponsive, Hb = haemoglobin, Hct = haematocrit, RBS = random blood sugar, SaO_2 = arterial oxygen saturation, ECG = electrocardiogram, GCS = Glasgow coma scale, UCE = urea-creatinine-electrolytes, LFT = liver function tests, CRP = C-reactive protein, SOFA-score = sequential organ failure assessment score, APACHE-score = acute physiology and chronic health evaluation score

APPENDIX I

MEMBERS OF SEPSIS GUIDELINES FOR PAKISTAN (SGP) COMMITTEE

Chair:

Professor Fazal Hameed Khan FCPS, EDIC
Professor of Anaesthesiology
Interim Chair Emergency Department
Aga Khan University, Karachi

Members:

- Professor S. Tipu Sultan
  Patron PSCCM
  Professor of Anaesthesiology
  Sind Institute of Urology and Transplant
  Karachi

- Professor Saeeda Haider
  Professor of Anaesthesiology
  The Indus Hospital
  Karachi

- Professor Sadqa Aftab
  Professor of Anaesthesiology
  DUHS & Civil Hospital
  Karachi

- Professor Roohina Baloch
  Chair Department of Anaesthesia
  Jinnah Post Graduate Medical Centre (JPMC)
  Karachi

- Dr Ali bin Sarwar Zubairi
  Associate Professor & Section Head, Pulmonary & Critical Care Medicine
  Aga Khan University
  Karachi

- Dr Javed Hussain
  Consultant Pulmonary & Critical Care Medicine
  South City Hospital
  NFT, Aga Khan University
  Karachi

- Dr Anwar ul Haq
  Associate Professor & Director PICU
  Aga Khan University
  Karachi

- Dr Madiha Hashmi
  President PSCCM
  Director SICU & Assistant Professor, Department of Anaesthesiology
  Aga Khan University
  Karachi

- Dr Zahid Akhtar Rao
  Director SICU
  PNS Shifa Hospital
  Karachi

- Dr Amin Khawaja
  National Institute of Cardiovascular Diseases (NICVD)
  Karachi

- Dr Zunairah Rais
  Consultant Pulmonary & Critical Care Medicine
  Liaquat National Hospital (LNH)
  Karachi

- Dr Syed Farjad Sultan
  Director ICU
  The Indus Hospital
  Karachi

Outside-Committee-Panel of Experts:

PUNJAB:

- Brig Aslam Khan
  Professor of Medicine & Consultant Pulmonologist and Intensivist
  Military Hospital
  Rawalpindi.

BALUCHISTAN:

- Prof. Amjad Ali
  Head of the Department
  Bolan Medical College
  Quetta

KPK:

- Prof. Gohar Ali
  Head of the Department
  Lady Reading Hospital
  Peshawar

MMIDSP:

- Prof Naseem Salahuddin
  Founder MMIDSP
  Infectious Diseases Consultant
  The Indus Hospital
  Karachi

- Dr Faisal Sultan
  Consultant Physician, Internal Medicine & Infectious Disease
  Shaukat Khanum Memorial Cancer Hospital & Research Centre, Lahore

PCS:

- Prof Kamran Cheema
  President PCS
  Professor of Pulmonary Medicine
  Services Institute of Medical Sciences, Lahore

APPENDIX II
MMIDSP RECOMMENDATIONS FOR EMPIRIC ANTIBIOTIC THERAPY

Source of infection	Likely pathogen	Best empirical antibiotic
Urinary tract	E. coli	Carbapenem or Piperacillin –tazobactam or Cefaperazone-sulbactam
Genital tract	E. coli, Enterococcus, S hemolyticus, Anaerobes	Carbapenem or Piperacillin –tazobactam or Cefaperazone-sulbactam + vancomycin
Respiratory tract (CAP)	S. pneumoniae, atypical pathogens	Ceftriaxone +levofloxacin or clarithromycin
Respiratory tract (HAP)	GPC, GNR, atypical	Carbapenem or Piperacillin –tazobactam or Cefaperazone-sulbactam + levofloxacin or clarithromycin
Respiratory tract (VAP)	GNR, MRSA	Carbapenem or Piperacillin –tazobactam or Cefaperazone-sulbactam + vancomycin
Intra-abdominal	Gram negatives, anerobes	Carbapenem or Piperacillin –tazobactam or Cefaperazone-sulbactam + vancomycin
SSTI (necrotizing fasciitis)	S. aureus, Streptococci anerobes	Amoxicilin/clavulanate or clindamycin +vancomycin
Burn sepsis	S. aureus, Streptococci, Pseudomonas, Candida	Carbapenem or Piperacillin –tazobactam or Cefaperazone-sulbactam + vancomycin
Line sepsis	S. aureus, (MSSA, MRSA), Pseudomonas	Ceftazidime or amikacin+ vancomycin
Infected device	S. aureus, (MSSA, MRSA), Pseudomonas	Ceftazidime or amikacin+ vancomycin
Bacterial meningitis	S pneumonia, Meningococcus	Ceftriaxone + vancomycin + steroid

APPENDIX III
ANTIBIOTIC GROUPS, THEIR CHARACTERISTICS AND USES

Class	Spectrum	Available preparations	Route of administration	Effective against	Not effective against
Carbapenem	Broad	Meroponem/imepenem / ertapenem	Intravenous	GPC, GNB, anaerobes	MRSA, VRE. Ertapenem ineffective against pseudomonas
B lactamase inhibitor	Broad	Piperacillin –tazobactam	Intravenous	GPC, GNB, anaerobes.	MRSA, VRE
3rd gen Cephalosporin	Broad	Cefaperazone-sulbactam	Intravenous	GPC, GNB, anaerobes.	MRSA, VRE
1st gen cephalosporin	Narrow	Cefazolin, Cephradine	Intravenous	Strept	MRSA, VRE, anaerobes
3rd gen Cephalosporin	Broad	Ceftriaxone	Intravenous	Strept, GNR	MRSA, VRE, anaerobes
3rd gen Cephalosporin	Broad	Ceftazidime	Intravenous	GNR, esp pseudom	MRSA, VRE, anaerobes
Glycopeptide	Narrow	Vancomycin	Intravenous	MRSA, enterococcus	GNR, anaerobes
Aminoglycoside	Narrow	Amikacin, Tobramycin, Gentamicin	Intravenous	GNR	Strept and Entero,, anaerobes
B lactamase inhibitor	Broad	Amoxicillin-clavulanate	Intravenous and oral	GPC, some GNR, anaerobes	E coli, enterobacteriacae
Fluoroquinolones	Broad	Levofloxacin	Intravenous and oral	GPC, atypical resp pathogens	Anaerobes
Macrolides	Narrow	Azithromycin, clarithromycin	Oral	Atypical resp pathogens	GNR, anaerobes
Lincosamide	Narrow	Clindamycin	Intravenous and oral	Strep, Staph (MSSA)	GNR

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The ultimate measure of a man is not where he stands in moments of comfort and convenience, but where he stands at times of challenge and controversy

MARTIN LUTHER KING