Journal of Current Medical Research and Opinion
Received 15-10-2022| Revised 02-11-2022| Accepted 05-11-2022| Published Online 07-11-2022

DOI: https://doi.org/10.52845/CMRO/2022/5-11-1 **ISSN (O) 2589-8779 | (P) 2589-8760**

CMRO 05 (11), 1462-1475 (2022)

Review Article

The Global Burden of Sepsis: A Health Economic Analysis

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Abstract:

Sepsis is a life threatening medical condition that formally called blood poisoning is usually triggered by a local infection such as pneumonia in lungs or infected wounds or infection of urinary tract should be bacterial(e.g. Staphylococcus aureus, Escherichia coli, Haemophilus influenza, etc.). Begin treatment and resuscitation immediately. Give at least 30 mL/kg of IV crystalloid fluid within the first 3 h in the resuscitation from sepsis-induced hypoperfusion (strong recommendation, low quality of evidence). Frequent reassessment of hemodynamic status following initial fluid resuscitation to guide additional fluids. Administer IV antimicrobials as soon as possible after recognition and within 1 h for both sepsis and septic shock. Apply fluid challenge technique where fluid administration is continued as long as hemodynamic factors continue to improve (BPS). Need based, response assessed fluid resuscitation with lookout for A/E (eg: pulmonary edema). Use crystalloids as the fluid of choice for initial resuscitation and subsequent intravascular volume replacement in patients with sepsis and septic shock. Sepsis is associated with newly acquired cognitive impairment and functional disability amongst survivors.

Key Words:

Septic Shock, Critical Care Treatment, Antimicrobial therapy, Sepsis, Infection control

Introduction:

Sepsis is a life threatening medical condition that formally called blood poisoning is usually triggered by a local infection such as pneumonia in lungs or infected wounds or infection of urinary tract should be bacterial(e.g. Staphylococcus aureus, Escherichia coli, Haemophilus influenza, etc.). From the local infection or the affected area infection spread or secrete toxic substances into the blood stream. Body

attempt to fight an infection results the immune system may sometimes go into overdrive casing inflammation through out the entire body.

Septic Shock should be define as a subset of sepsis, which is more serious condition that occurs when a body wide infection leads to dangerously low blood pressure. Septic Shocks are more often in new born, the elderly, pregnant women. Because of their immune system cannot deals more effectively as those of healthy adults. *The mortality rate from septic shock is approximately 25-50%.*[(1)]

At the cellular level, Sepsis is characterized by changes in the function of- endothelial tissue as well as in the coagulation process also in blood flow. Sepsis interferes with the blood flow which leads to a drop in blood pressure (*systolic BP < 100mgHg*). Making it difficult for the blood to carry the oxygen to the bodies major organs such as kidney,lungs or the. The pathophysiology of sepsis is more complex and outcomes from the effects of circulating bacterial substances, mediated by cytokine release, caused by sustained Bacteraemia. Cytokines are primarily responsible for the clinically observable effects of the bacteraemia in the host. In very small blood vessels the coagulation response, in combination with endothelial damage, may impede blood flow leading to blood vessels becoming leaky and clot formation. As fluid and microorganisms escape into the surrounding tissues, the tissues begin to swell in the lungs can lead to pulmonary oedema, manifesting as shortness of breath heart(*breathing rate ≥22mgHg*). In the worst cases the patient dies in a matter of hours, detecting sepsis early crucial. Must be attentive to physical condition such as breathing problem, fever & chills, Diarrhea & vomiting, confusion and slurred speech in the patient. Also low blood pressure, low urine production.[(2)]

Previously

Sepsis = Infection + two or more SIRS criteria

Severe Sepsis = Sepsis + Organ dysfunction or hypoperfusion

Septic Shock = Severe sepsis with persistent hypotension despite adequate fluids

SIRS Criteria

Temp >38o C or <36o C

HR > 90 bpm

RR > 20/min or PaCO2 <32 mmHg

WBC >12000/mm3 or <4000/mm3 or >10% immature neutrophils

Now

Life-threatening organ dysfunction caused by a dysregulated host response to infection. Organ dysfunction is measured by a 2 or more increase in the SOFA score.

SOFA score	0	1	2	3	4
Respiration PaO_2/FiO_2 or SaO_2/FiO_2 mmHg	>400	<400 221-301	<300 142-220	<200 67-141	<100 <67
Coagulation	>150	<150	<100	<50	<20
Liver Birilubin(mg/dl)	<1.2	1.2-1.9	2.0-5.9	6.0-11.9	>12.0
Cardiovascular Hypotension	No hypotension	MAP <70	Dopamine ≤5 or any	Dopamine >5 or notepinephrine ≤0.1	Dopamine >15 or norepinephrine >0.1
CNS (GCS)	15	13-14	10-12	6-9	<6
Renal Creatinine (mg/dl) or urine output (ml/d)	<1.2	1.2-1.9	2.0-3.4	3.5-4.9 or <5.00	>5.0 or <200

Figure- 1 SOFA SCORE

Organ System	Manifestation
CNS	Encephalopathy (ischemic or septic), cortical necrosis
Heart	Tachycardia, bradycardia, supraventricular tachycardia, ventricular ect opy, myocardial ischemia, myocardial depression
Pulmonary	Acute respiratory failure caused by hypoperfusion of the diaphragm, A RDS
Kidney	Prerenal failure, acute tubular necrosis
GI	Ileus, erosive gastritis, pancreatitis, acalculous cholecystitis, colonic su bmucosal hemorrhage, transluminal translocation of bacteria and endot oxin
Liver	Ischemic hepatitis (“shock liver”)
Hematologic	DIC, dilutional thrombocytopenia
Metabolic	Hyperglycemia, glycogenolysis, gluconeogenesis, hypoglycemia (late), hypertriglyceridemia
Immune system	Gut barrier function depression, cellular immune depression, humoral i mmune depression

Figure-2 Organ wise manifestation or sign/symptoms

INTERNATIONAL GUIDELINES OF SEPSIS

Updated global adult sepsis guidelines, released in October 2021 by the Surviving Sepsis Campaign (SSC), place an increased emphasis on improving the care of sepsis patients after they are discharged from the Intensive care unit (ICU) and represent greater geographic and gender diversity than previous versions, Also adaptive with the external environment. The new guidelines specifically emphasize treating patients experiencing the long going effects of sepsis. Patients often experience lengthy ICU stays and fighting with arise infection and then face a long, complicated journey to recovery. In addition to physical rehabilitation challenges, patients and their families are often uncertain how to coordinate care that promotes recovery and matches their goals of care. To address these issues, the guidelines recommend involving patients and their families in goals-of-care discussions and hospital discharge plans, which should include early and ongoing follow-up with clinicians to support and manage long-term effects and assessment of physical, cognitive, and emotional issues after discharge.[(3)]

So the basic guidelines regarding sepsis-

We recommend against using qSOFA compared with SIRS, NEWS, or MEWS as a single screening tool for sepsis or septic shock. For adults suspected of having sepsis, we suggest measuring blood lactate(the serum lactate level > 18mg/dL). Both septic shock and sepsis are life threatening medical emergencies, the patient should be treated and resuscitation begin immediately. For patients with sepsis-induced hypoperfusion or septic shock, at least 30 mL/kg of IV crystalloid fluid be given within the first 3 hours of resuscitation. For adults with sepsis or septic shock at high risk of MRSA, is recommend using empiric antimicrobials with MRSA coverage over using antimicrobials without MRSA coverage. No recommendation concerning with the use of antiviral agents. Although using crystalloids as first-line fluid for resuscitation is a better choice regarding diagnosis, using norepinephrine as the first-line agent over other vasopressors. Quality of evidence –

Dopamine:High Vasopressin:Moderate

Epinephrine:Low Selepressin:Low

Angiotensin 2: Very low

When using recruitment maneuvers, is recommend against using incremental PEEP titration. For hospitals and health systems, a performance improvement program for sepsis, including sepsis screening for acutely ill, high-risk patients and standard operating procedures for treatment is highly recommended.[4]

HISTORY AND SCOPE OF THE GUIDELINES

In middle of Late 2001- Early 2002 Separate from SSC activities, a sepsis definitions conference was held in December 2001 to determine whether new data existed to inform updates to criteria established in 1991. Later SSC was formed by SCCM, ESICM, and the International Sepsis Forum and was launched at the ESICM annual meeting in Barcelona in 2002. A plan to develop guidelines and A steering committee was formed with three representatives from each of the three societies. Further day by day step wise the SSC first published guidelines for the management of severe sepsis and septic shock in 2004.

And slowly updates were published in 2008, 2012, and 2017. In 2008 The second edition of the SSC guidelines was published in *Critical Care Medicine* and *Intensive Care Medicine*. Emphasize on data collection worldwide. In very 2012 The third edition of the SSC guidelines was published, along with revised bundles(a selected set of interventions or processes of care distilled from evidence-based practice guidelines). The bundle elements are likely Assess, Prevent, and Manage Pain, Both Spontaneous Awakening and Spontaneous Breathing Trials, Choice of Analgesia and Sedation, Delirium Monitoring and Management, Early Mobility and Exercise, Family Engagement and Empowerment.

The main motive is to ensure to facilitate quality improvement and implementation of guidelines recommendations. However, the bundles are developed through a separate process and published separately from the guidelines.

The guidelines are sponsored by the Society of Critical Care Medicine and the European Society of Intensive Care Medicine, with methodological support by the Guidelines in Intensive Care Development and Evaluation group, and endorsement by 24 additional societies. Following the recommendation of SCCM and ESICM, there are now individual guidelines for sepsis in children beside old aged. The SSC also published separate guidelines specific to the management of COVID.[5]

What is shock?

Inadequate oxygen delivery/utilisation.

Manifests clinically as circulatory disturbance and/or organ/cellular dysfunction.

What is Septic Shock?

Septic shock: A subset of sepsis with circulatory and cellular/metabolic dysfunction associated with higher risk of mortality. SEPSIS & Persistent hypotension requiring vasopressors to maintain MAP(despite adequate volume resuscitation) greater than or equal to 65 mm Hg, and Lactate greater than or equal to 2 mmol/L.

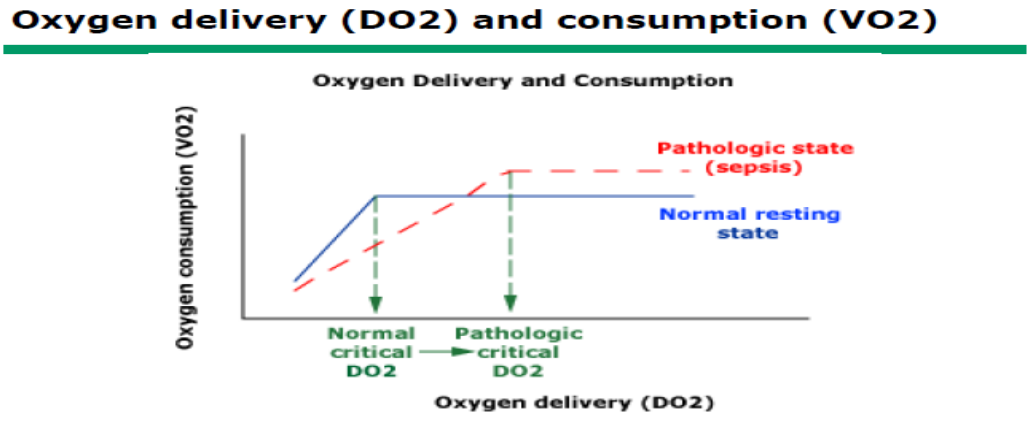

Figure- 3 Relationship between Oxygen delivery and consumption

How to Suspect Sepsis Outside ICU?

The quickSOFA (qSOFA) score

Respiratory rate ≥22/minute

Altered mentation

Systolic blood pressure ≤100 mmHg

1. INITIAL RESUSCITATION

Begin treatment and resuscitation immediately. Give at least 30 mL/kg of IV crystalloid fluid within the first 3 h in the resuscitation from sepsis-induced hypoperfusion (strong recommendation, low quality of evidence). Frequent reassessment of hemodynamic status following initial fluid resuscitation to guide additional fluids.

Supplemental oxygen -pulse oximetry. Intubation and mechanical ventilation SOS to support the increased work of breathing that typically accompanies sepsis, or for airway protection since encephalopathy and a depressed level of consciousness frequently complicate sepsis. The insertion of a central line should not delay the administration of resuscitative fluids and antibiotics. Assess hemodynamics further (such as assessing cardiac function) to determine the type of shock if the clinical examination does not lead to a clear diagnosis. Use dynamic over static variables to predict fluid responsiveness, where available (weak recommendation, low quality of evidence). PLR or Fluid Challenge with SV assessment by echo. Target mean arterial pressure (MAP) of 65 mm Hg initially in patients with septic shock requiring vasopressors (strong recommendation, moderate quality of evidence). Resuscitation to be guided to normalize lactate in patients with elevated lactate levels as a marker of tissue hypoperfusion (weak recommendation, low quality of evidence).[6]

Check Lactate 6 hourly?

2. SCREENING FOR SEPSIS AND PERFORMANCE IMPROVEMENT

Hospitals and hospital systems have a performance improvement program for sepsis, including sepsis screening for acutely ill, high-risk patients (BPS).[7]

3. DIAGNOSIS

Obtain appropriate routine microbiologic cultures (including blood) before starting antimicrobial therapy in patients with suspected sepsis or septic shock if doing so results in no substantial delay in the start of antimicrobials.[7]

Suspected site	Symptoms/signs	Initial microbiologic evaluation
Upper respiratory tract	Pharyngeal inflammation plus exudate ± swelling and lymphadenopathy	Throat swab for aerobic culture
Lower respiratory tract	Productive cough, pleuritic chest pain, consolidative auscultatory findings	Sputum of good quality, Rapid influenza testing, urinary antigen testing (eg, pneumococcus, legionella; not recommended in children), Quantitative culture of protected brush or bronchoalveolar lavage.

Urinary tract	Urgency, dysuria, loin, or back pain	Urine culture and microscopy showing pyuria
Vascular catheters: arterial, central venous	Redness or drainage at insertion site	Culture of blood (from the catheter and a peripheral site), culture catheter tip (if removed)
Indwelling pleural catheter	Redness or drainage at insertion site	Culture of pleural fluid (through catheter), culture of catheter tip (if removed)
Wound or burn	Inflammation, edema, erythema, discharge of pus	Gram stain and culture of draining pus, wound culture not reliable

Suspected site	**Symptoms/signs**	**Initial microbiologic evaluation**
Skin/soft tissue	Erythema, edema, lymphangitis	Culture blister fluid or draining pus; role of tissue aspirates not proven
Central nervous system	Signs of meningeal irritation	CSF cell count, protein, glucose, Gram stain, and culture
Gastrointestinal	Abdominal pain, distension, diarrhea, and vomiting	Stool culture for Salmonella, Shigella, Campylobacter, and Clostridium difficile
Intra-abdominal	Specific abdominal symptoms/signs	Aerobic and anaerobic culture of percutaneously or surgically drained abdominal fluid collections
Peritoneal dialysis (PD) catheter	Cloudy PD fluid, abdominal pain	Cell count and culture of PD fluid

Genital tract	Women: Low abdominal pain, vaginal discharge Men: Dysuria, frequency, urgency, urge incontinence, cloudy urine, prostatic tenderness	Women: Endocervical and high vaginal swabs onto selective media Men: Urine Gram stain and culture
Bone	Pain, warmth, swelling, decreased use	Blood cultures, MRI, bone cultures at surgery or by interventional radiology
Joint	Pain, warmth, swelling, decreased range of motion	Arthrocentesis with cell counts, Gram stain, and culture

Figure -4 Initial evaluation of common sources of sepsis

Quickly obtain the following : is preferably within 45 minutes of presentation) but should not delay the administration of fluids and antibiotics: To support the diagnosis, indicate the severity of sepsis, and provide baseline to follow the therapeutic response. Serum lactate. Initial microbiologic evaluation.

Complete blood counts with differential, chemistries,

Liver function tests, and coagulation studies including D-dimer level.

Arterial blood gas (ABG)

Imaging targeted at the suspected site of infection.

Procalcitonin : value in deescalating antibiotic therapy.

4. ANTIMICROBIAL THERAPY

Administer IV antimicrobials as soon as possible after recognition and within 1 h for both sepsis and septic shock (strong recommendation, moderate quality of evidence; grade applies to both conditions). Give empiric broad-spectrum therapy with one or more antimicrobials for patients presenting with sepsis or septic shock to cover all likely pathogens (including bacterial and potentially fungal or viral coverage) (strong recommendation, moderate quality of evidence). Narrow empiric antimicrobial therapy once pathogen identification and sensitivities are established and/or adequate clinical improvement is noted (BPS). Do not use sustained systemic antimicrobial prophylaxis in patients with severe inflammatory states of noninfectious origin (e.g., severe pancreatitis, burn injury) (BPS). Optimize dosing strategies of antimicrobials based on accepted PK/PD principles and specific drug properties in patients with sepsis or septic shock (BPS). Increased volume of distribution, GFR in sepsis need loading dose to rapidly achieve appropriate concentration at the site of infection. Use empiric combination therapy (at least two antibiotics of different antimicrobial classes) aimed at the most likely bacterial pathogen(s) for the initial management of septic shock (weak recommendation, low quality of evidence). Esp. if neutropenia or suspected pseudomonas infection.

Do not routinely use combination therapy for ongoing treatment of most other serious infections, including bacteremia and sepsis without shock (weak recommendation, low quality of evidence). Recommended: Do

not use combination therapy for the routine treatment of neutropenic sepsis/bacteremia (strong recommendation, moderate quality of evidence). De-escalation with discontinuation of combination therapy within the first few days in response to clinical improvement and/ or evidence of infection resolution. This applies to both targeted (for culture-positive infections) and empiric (for culture-negative infections) combination therapy (BPS). An antimicrobial treatment duration of 7–10 days is adequate for most serious infections associated with sepsis and septic shock (weak recommendation, low quality of evidence). Suggested: longer courses are appropriate in patients who have a slow clinical response, undrainable foci of infection, bacteremia with S. aureus, some fungal and viral infections, or immunologic deficiencies, including neutropenia (weak recommendation, low quality of evidence). Shorter courses in some patients, particularly those with rapid clinical resolution following effective source control of intra-abdominal or urinary sepsis and those with anatomically uncomplicated pyelonephritis (weak recommendation, low quality of evidence). Daily assessment for de-escalation of antimicrobial therapy in patients with sepsis and septic shock (BPS). Measure procalcitonin levels to support shortening the duration of antimicrobial therapy in sepsis patients (weak recommendation, low quality of evidence). Procalcitonin levels to support the discontinuation of empiric antibiotics in patients who initially appeared to have sepsis, but subsequently have limited clinical evidence of infection (weak recommendation, low quality of evidence).[8]

5. SOURCE CONTROL

Identify or exclude specific anatomic diagnosis of infection requiring emergent source control as rapidly as possible in patients with sepsis or septic shock, and implement any required source control intervention as soon as medically and logistically practical after the diagnosis is made (BPS). Remove intravascular access devices that are a possible source of sepsis or septic shock promptly after other vascular access has been established (BPS).[)]

6. FLUID THERAPY

Apply fluid challenge technique where fluid administration is continued as long as hemodynamic factors continue to improve (BPS). Need based, response assessed fluid resuscitation with lookout for A/E (eg: pulmonary edema). Use crystalloids as the fluid of choice for initial resuscitation and subsequent intravascular volume replacement in patients with sepsis and septic shock (strong recommendation, moderate quality of evidence). Use either balanced crystalloids or saline for fluid resuscitation of patients with sepsis or septic shock (weak recommendation, low quality of evidence). Use albumin in addition to crystalloids for initial resuscitation and subsequent intravascular volume replacement in patients with sepsis and septic shock when patients require substantial amounts of crystalloids (weak recommendation, low quality of evidence).

Do not use hydroxyethyl starches (HESs) for intravascular volume replacement in patients with sepsis or septic shock (strong recommendation, high quality of evidence). Use crystalloids over gelatins when resuscitating patients with sepsis or septic shock (weak recommendation, low quality of evidence).[9]

What type of fluid?

Avoid pentastarch or hydroxyethyl starch: raised mortality and AKI.

Crystalloids: Balanced salt solution or 0.9% saline.

Albumin (weak evidence): avoids hyperchloremia of large volume saline.

7. VASOACTIVE MEDICATIONS

Use norepinephrine as the firstchoice vasopressor (strong recommendation, moderate quality of evidence). Add either vasopressin (up to 0.03 U/min) (weak recommendation, moderate quality of evidence) or epinephrine (weak recommendation, low quality of evidence) to norepinephrine with the intent of raising MAP to target, or adding vasopressin (up to 0.03 U/min) (weak recommendation, moderate quality of evidence) to decrease norepinephrine dosage. Use dopamine as an alternative vasopressor agent to norepinephrine only in highly selected patients (e.g., patients with low risk of tachyarrhythmias and absolute or relative bradycardia) (weak recommendation, low quality of evidence). Do not use low-dose dopamine for renal protection (strong recommendation, high quality of evidence). Use dobutamine in patients who show evidence of persistent hypoperfusion despite adequate fluid loading and the use of vasopressor agents (weak recommendation, low quality of evidence). All patients requiring vasopressors have an arterial

catheter placed as soon as practical if resources are available (weak recommendation, very low quality of evidence).[10]

8. CORTICOSTEROIDS

Do not use IV hydrocortisone to treat septic shock patients if adequate fluid resuscitation and vasopressor therapy are able to restore hemodynamic stability.

If this is not achievable, suggested to use IV hydrocortisone at a dose of 200 mg per day (weak recommendation, low quality of evidence).[11]

9. BLOOD PRODUCTS

RBC transfusion only when hemoglobin concentration decreases to <7.0 g/dL in adults in the absence of extenuating circumstances, such as myocardial ischemia, severe hypoxemia, or acute hemorrhage (strong recommendation, high quality of evidence).

Do not use of erythropoietin for treatment of anemia associated with sepsis (strong recommendation, moderate quality of evidence). Do not use of fresh frozen plasma to correct clotting abnormalities in the absence of bleeding or planned invasive procedures (weak recommendation, very low quality of evidence). Transfuse platelet prophylactically when counts are <10,000/mm3 (10 × 109/L) in the absence of apparent bleeding and when counts are <20,000/mm3 (20 × 109/L) if the patient has a significant risk of bleeding. Higher platelet counts [≥50,000/mm3 (50 × 109/L)] are advised for active bleeding, surgery, or invasive procedures (weak recommendation, very low quality of evidence).[12]

10. IMMUNOGLOBULINS

Do not use of IV immunoglobulinsin patients with sepsis or septic shock (weak recommendation, low quality of evidence).[13,14]

11. BLOOD PURIFICATION

No recommendation regarding the use of blood purification techniques.

12. ANTICOAGULANTS

Do not use antithrombin for the treatment of sepsis and septic shock (strong recommendation, moderate quality of evidence). No recommendation regarding the use of thrombomodulin or heparin for the treatment of sepsis or septic shock.

13. MECHANICAL VENTILATION

Use a target tidal volume of 6 mL/kg predicted body weight (PBW) compared with 12 mL/kg in adult patients with sepsis induced ARDS (strong recommendation, high quality of evidence). Use an upper limit goal for plateau pressures of 30 cmH2O over higher plateau pressures in adult patients with sepsis-induced severe ARDS (strong recommendation, moderate quality of evidence). Use higher PEEP over lower PEEP in adult patients with sepsis-induced moderate to severe ARDS (weak recommendation, moderate quality of evidence). Use recruitment maneuvers in adult patients with sepsis-induced, severe ARDS (weak recommendation, moderate quality of evidence). (time to change this recommendation?) Guidelines recommend using prone over supine position in adult patients with sepsis-induced ARDS and a Pao2/Fio2 ratio <150 (strong recommendation, moderate quality of evidence) and also recommend against using high-frequency oscillatory ventilation (HFOV) in adult patients with sepsis-induced ARDS (strong recommendation, moderate quality of evidence).

No recommendation regarding the use of noninvasive ventilation (NIV) for patients with sepsis-induced ARDS. Use neuromuscular blocking agents (NMBAs) for ≤48 h in adult patients with sepsis induced ARDS and a Pao2/Fio2 ratio <150 mm Hg(weak recommendation, moderate quality of evidence). A conservative fluid strategy for patients with established sepsis-induced ARDS who do not have evidence of tissue hypoperfusion (strong recommendation, moderate quality of evidence). Do not use β-2 agonists for the treatment of patients with sepsis-induced ARDS without bronchospasm (strong recommendation, moderate quality of evidence). Do not use of the PA catheterroutinely for patients with sepsis-induced ARDS (strong recommendation, high quality of evidence). Use lower tidal volumes over higher tidal volumes in adult patients with sepsis induced respiratory failure without ARDS (weak recommendation, low quality of evidence). Mechanically ventilated sepsis patients be maintained with the head of the bed elevated between

30° and 45° to limit aspiration risk and to prevent the development of VAP (strong recommendation, low quality of evidence). Use spontaneous breathing trials in mechanically ventilated patients with sepsis who are ready for weaning (strong recommendation, high quality of evidence). Use a weaning protocol in mechanically ventilated patients with sepsis induced respiratory failure who can tolerate weaning (strong recommendation, moderate quality of evidence).[14]

14. SEDATION AND ANALGESIA

Minimize continuous or intermittent sedation in mechanically ventilated sepsis patients, targeting specific titration end points (BPS).

15. GLUCOSE CONTROL

A protocolized approach to blood glucose management in ICU patients with sepsis, commencing insulin dosing when two consecutive blood glucose levels are >180 mg/dL. Target an upper blood glucose level ≤180 mg/dL rather than an upper target blood glucose level ≤110 mg/dL (strong recommendation, high quality of evidence). Blood glucose values be monitored every 1–2 h until glucose values and insulin infusion rates are stable, then every 4 h thereafter in patients receiving insulin infusions (BPS). Glucose levels obtained with point-of-care testing of capillary blood be interpreted with caution because such measurements may not accurately estimate arterial blood or plasma glucose values (BPS). Use arterial blood rather than capillary blood for point-of-care testing using glucose meters if patients have arterial catheters (weak recommendation, low quality of evidence).[15,16]

16. RENAL REPLACEMENT THERAPY

Use either continuous RRT (CRRT) or intermittent RRT in patients with sepsis and acute kidney injury (weak recommendation, moderate quality of evidence). Use CRRT to facilitate management of fluid balance in hemodynamically unstable septic patients (weak recommendation, very low quality of evidence). Do not use RRT in patients with sepsis and acute kidney injury for increase in creatinine or oliguria without other definitive indications for dialysis (weak recommendation, low quality of evidence).

17. BICARBONATE THERAPY

Do not use sodium bicarbonate therapy to improve hemodynamics or to reduce vasopressor requirements in patients with hypoperfusion-induced lactic acidemia with pH ≥ 7.15 (weak recommendation, moderate quality of evidence).

18. VENOUS THROMBOEMBOLISMPROPHYLAXIS

Use pharmacologic prophylaxis [unfractionated heparin (UFH) or low-molecular- weight heparin (LMWH)] against venous thromboembolism (VTE) in the absence of contraindications (strong recommendation, moderate quality of evidence). Use LMWH rather than UFH for VTE prophylaxis in the absence of contraindications (strong recommendation, moderate quality of evidence). Combine pharmacologic VTE prophylaxis and mechanical prophylaxis, whenever possible (weak recommendation, low quality of evidence).

Mechanical VTE prophylaxis require when pharmacologic VTE is contraindicated (weak recommendation, low quality of evidence).[16,13]

19. STRESS ULCER PROPHYLAXIS

Give stress ulcer prophylaxis to patients with sepsis or septic shock who have risk factors for gastrointestinal (GI) bleeding (strong recommendation, low quality of evidence).Use either proton pump inhibitors (PPIs) or histamine-2 receptor antagonists (H2RAs) when stress ulcer prophylaxis is indicated (weak recommendation, low quality of evidence).Do not give stress ulcer prophylaxis in patients without risk factors for GI bleeding (BPS).

20. NUTRITION

Do not administer early parenteral nutrition alone or parenteral nutrition in combination with enteral feedings (but rather initiate early enteral nutrition) in critically ill patients with sepsis or septic shock who can be feed enterally (strong recommendation, moderate quality of evidence). Try not to administer parenteral nutrition alone or in combination with enteral feeds (but rather to initiate IV glucose and advance

enteral feeds as tolerated) over the first 7 days in critically ill patients with sepsis or septic shock for whom early enteral feeding is not feasible (strong recommendation, moderate quality of evidence).

Initiate early enteral feeding rather than a complete fast or only IV glucose in critically ill patients with sepsis or septic shock who can be fed enterally (weak recommendation, low quality of evidence).

Either early trophic/hypocaloric or early full enteral feeding in critically ill patients with sepsis or septic shock; if trophic/hypocaloric feeding is the initial strategy, then feeds should be advanced according to patient tolerance (weak recommendation, moderate quality of evidence).

Do not use omega-3 fatty acids as an immune supplement in critically ill patients with sepsis or septic shock (strong recommendation, low quality of evidence). Avoid routine monitoring of gastric residual volumes (GRVs) in critically ill patients with sepsis or septic shock (weak recommendation, low quality of evidence). However, it is suggested that measure gastric residuals in patients with feeding intolerance or who are considered to be at high risk of aspiration (weak recommendation, very low quality of evidence). This recommendation refers to nonsurgical critically ill patients with sepsis or septic shock. Use of prokinetic agents in critically ill patients with sepsis or septic shock and feeding intolerance (weak recommendation, low quality of evidence). Place post-pyloric feeding tubes in critically ill patients with sepsis or septic shock with feeding intolerance or who are considered to be at high risk of aspiration (weak recommendation, low quality of evidence). Do not use of IV selenium to treat sepsis and septic shock (strong recommendation, moderate quality of evidence). Do not use arginine to treat sepsis and septic shock (weak recommendation, low quality of evidence). Do not use glutamine to treat sepsis and septic shock (strong recommendation, moderate quality of evidence). No recommendation about the use of carnitine for sepsis and septic shock.[17]

21. SETTING GOALS OF CARE

Discuss goals of care and prognosis with patients and families (BPS). Incorporate goals of care into treatment and end-of-life care planning, utilizing palliative care principles where appropriate (strong recommendation, moderate quality of evidence). Address goals of care as early as feasible, but no later than within 72 h of ICU admission (weak recommendation, low quality of evidence). For adults with sepsis or septic shock, we recommend discussing goals of care and prognosis with patients and families over no such Discussion. For adults with sepsis or septic shock, we suggest addressing goals of care early (within 72 h) over late Weak recommendation, low-quality evidence. There is insufficient evidence to make a recommendation for any specific standardised criterion to trigger goals of care discussion. Despite lack of evidence, the panel recognised that discussion of prognosis and exploration of goals of care with patients and/or family is a necessary precondition to determine patient treatment preferences and providing value-concordant care.

22. PALLIATIVE CARE

For adults with sepsis or septic shock, we recommend integrating principles of palliative care (which may include palliative care consultation based on clinician judgement) into the treatment plan, when appropriate, to address patient and family symptoms and suffering. For adults with sepsis or septic shock, we suggest against routine formal palliative care consultation for all patients over palliative care consultation based on clinician judgement Weak recommendation, low-quality evidence.

Inclusion criteria for ICU patients consisted of mechanical ventilation for 7 days, high risk on a palliative care screen, physician determination that care should not be escalated or care should be withdrawn, physician belief that the patient would die in a few days or death in the ICU or within 30 h of transfer out of the ICU

Interventions comprised formal palliative care consultation, a complex quality improvement project to improve end-of-life care and a planned end-of-life conference conducted by intensivists according to specific guidelines along with a bereavement brochure. Overall evidence for routine formal palliative care.

Interventions in ICU patients is of low quality and provides mixed evidence of benefit. Thus, the panel suggests against routine formal palliative care consultation for all patients with sepsis or septic shock, instead using clinician judgment to determine which patients and families may benefit from a palliative care consultation.[18]

23. PEER SUPPORT GROUPS

For adult survivors of sepsis or septic shock and their families, we suggest referral to peer support groups over no such referral. Weak recommendation, very low quality of evidence.

Peer support groups have been used to enhance recovery from illness when survivors have long-lasting disability but have only recently been used in critical care and sepsis. With increased recognition of post-intensive care syndrome (PICS) in survivors of critical illness and their families, peer support represents a patient-centered approach to improve long-term outcomes. Models of peer support are numerous and include community-based in person or virtual peer support; outpatient ICU follow-up clinics (with or without psychologist support); within-ICU peer support; and individual peer mentors. For adults with sepsis or septic shock, we suggest using a handoff process of critically important information at transitions of care, over no such handoff process .Weak recommendation, very low-quality evidence. There is insufficient evidence to make a recommendation for the use of any specific structured handoff tool over usual handoff processes. Structured handoff interventions for critically ill patients have been evaluated at many transitions of patient care ED/ICU, OR/ICU, ICU/ward, and hospital/home and it appear to result in more complete and accurate transfer of information, without any undesirable effects.[18]

24. SHARED DECISION MAKING

For adults with sepsis or septic shock and their families, we recommend the clinical team provide the opportunity to participate in shared decision making in post-ICU and hospital discharge planning to ensure discharge plans are acceptable and feasible.

Shared decision making (SDM) is a process in which health professionals, patients and their caregivers collaborate in making decisions about a patient's care options. It is associated with lower rate of anxiety and depression and improve support for family.

25. DISCHARGE PLANNING

For adults with sepsis and septic shock and their families, we suggest using a critical care transition programme, compared to usual care, upon transfer to the floor . Weak recommendation, very low-quality evidence.

Transfer from ICU to general floor and discharge from the hospital are both vulnerable periods for patients, with high frequency of medication errors and information loss Sepsis patients, with longer than average hospitalisations and higher co-morbidity burden, may be at particular risk for poor outcomes with transitions.

For adults with sepsis and septic shock, we recommend reconciling medications at both ICU and hospital discharge.

Hospitalisation and ICU admission are high-risk periods for unintentional medication error—both continuations of medications for temporary indications and unintentional discontinuations of chronic medications. Medication reconciliation has been associated with fewer medication errors and may help reduce hospital readmission. For adult survivors of sepsis and septic shock and their families, we recommend including information about the ICU stay, sepsis and related diagnoses, treatments, and common impairments after sepsis in the written and verbal hospital discharge summary. For adults with sepsis or septic shock who developed new impairments, we recommend hospital discharge plans include follow-up with clinicians able to support and manage new and long-term sequelae. There is insufficient evidence to make a recommendation on early (7 to 14 days) post-hospital discharge follow-up compared to routine post hospital discharge follow-up.

26. COGNITIVE THERAPY

There is insufficient evidence to make a recommendation on early cognitive therapy for adult survivors of sepsis or septic shock.

Sepsis is associated with newly acquired cognitive impairment and functional disability amongst survivors. Long-term impairments in memory, attention, verbal fluency, decision-making and executive functioning may be linked to a variety of mechanisms such as metabolic derangements, cerebral ischaemia, overwhelming inflammation, disrupted blood–brain barrier, oxidative stress, and severe microglial activation, particularly within the limbic system.

27. Post Discharge follow-up

For adult survivors of sepsis or septic shock, we recommend assessment and follow-up for physical, cognitive, and emotional problems after hospital discharge.There are insufficient data to suggest any specific tool to assess for these problems, and the optimal approach will vary by patient and setting.

For adult survivors of sepsis or septic shock, we suggest referral to a post-critical illness follow-up programme if available.

Weak recommendation, very low-quality evidence.

Post-critical illness programmes have been developed as a means of screening for and addressing the multi-faceted issues faced by ICU survivors. These programmes are consistently well-liked by patients and offer an environment to learn about challenges sepsis survivors face, as well as to pilot and test interventions for enhancing recovery.

For adult survivors of sepsis or septic shock receiving mechanical ventilation for > 48 h or an ICU stay of > 72 hr, we suggest referral to a post-hospital rehabilitation programme. (Weak recommendation, very low-quality evidence) .[18]

Conclusion

In cases with sepsis or septic shock, a better understanding of the host response leading to the clinical course, a briskly discovery of high- threat cases, and an earlier and further standardized approach in managing sepsis are the crucial challenges in current clinical practice. On the one hand, the recent findings of host defense mechanisms on the cellular position, the new Sepsis- 3 description, and the current developments after probing the goods of obligatory care of cases with sepsis are significant and promising way in sepsis exploration. On the other hand, these steps are tracking new ways which in some cases may lead to unknown destinations. At present, it's too early to risk a clear prognostic; we all hope that the sum effect of these new developments will be a positive bone . At least it was demonstrated that advances in sepsis exploration are possible! Maybe this will foster exploration engagement by clinicians and scientists in this instigative field of drug and will bring further attention and support from artificial as well as public institutions.

List of Abbreviation

1. HR- Heart Rate
2. RR- Respiratory Rate
3. WBC- White Blood Cells
4. ICU- Intensive Care Unit

Conflict of Interest

None declared

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