Executive Summary of the 2020 Clinical Practice Guidelines for Sepsis and Septic Shock in Adults in the Philippines

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Summary

Sepsis is thought to affect over 30 million individuals all over the world annually, and puts at risk of death some six million of these people. The incidence of sepsis throughout the world had been reported to be 22 to 240 cases per 100,000 persons using the old sepsis definition. In February 2016, the Sepsis-3 definitions drastically changed the paradigm for sepsis. This 2020 Clinical Practice Guideline (CPG) adopted the new definitions and the latest evidence on sepsis and septic shock to (1) establish the definition and clinical criteria to be used in the Philippines, (2) present evidence-based recommendations with regard to screening, diagnosis, treatment, and prognostication of sepsis and septic shock in immunocompetent adults, and (3) aimed to reduce practice variability among healthcare practitioners and improve clinical outcomes in patients with sepsis and septic shock. The preparation of the guideline was spearheaded by the Steering Committee who selected the members of the multidisciplinary Technical Working Group (TWG) and the Consensus Panel. The TWG, composed of experts across various fields and specialties, conducted a comprehensive review of evidence relevant to each guideline question. The Consensus Panel consisted of different stakeholders who voted for the recommendations. The GRADE (Grades of Recommendation, Assessment, Development and Evaluation) Approach was used to determine the quality of evidence and guide the strength of recommendations. Publication of this CPG is part of the dissemination process, which will be followed later on by monitoring and updating.

Keywords: sepsis, septic shock, guideline, definition, criteria, diagnosis, treatment

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Introduction

This Clinical Practice Guideline is intended for the use of practicing clinicians in the Philippines who are involved in the care of adult patients with sepsis and septic shock. This document may be used by government and private practicing physicians, as well as trainors and trainees with respect to medical education, training, and mentoring.

This Philippine CPG for Sepsis and Septic Shock was developed because of (1) the significant burden of disease, (2) the confusion over the definitions, (3) the significant variability in clinical practice, (4) the availability of new evidence, and (5) the feasibility issues concerning cost, availability, and access to resources in the Philippines.

The Third International Consensus definitions drastically changed the paradigm for sepsis with its publication in February 2016.[1] It now defines "sepsis" as a life-threatening organ dysfunction caused by a dysregulated host response to infection. In this new definition, sepsis is now upgraded to what we previously knew as "severe sepsis." The updates were appreciated but certain quarters raised concerns about validity and applicability, leading to incomplete uptake of the definitions.

In recent years, there has been rapid turnover of evidence for sepsis which called for thorough review for validity and applicability in our setting. It is not only important that old and new evidence be considered, but cost, availability and access to resources in different settings as well. With the advent of the Universal Health Care Law, it is important to establish local guidelines that would set the standard of sepsis care in the Philippines.

This Clinical Practice Guideline aims (1) to establish the definition and clinical criteria to be used in diagnosing sepsis and septic shock in the Philippines, (2) to present evidence-based recommendations with regard to screening, diagnosis, treatment, and prognostication of sepsis and septic shock in immunocompetent adults, and (3) to reduce practice variability among healthcare practitioners and improve clinical outcomes in patients with sepsis and septic shock. The guideline will only cover sepsis in non-pregnant, immunocompetent adults.

Methodology

The Steering Committee examined the existing guidelines, identified problems which should be addressed in the current guidelines, projected the required budget and looked for funding sources, and selected the members of the Technical Working Group (TWG) and the Consensus Panel. The TWG assisted the Steering Committee in the formulation of the guideline questions structured in PICO format (population, intervention, control, and outcome. The TWG divided the questions and independent and comprehensive literature searches were performed. The GRADE (Grades of Recommendation, Assessment, Development and Evaluation) Framework/Approach[2] was used to determine the quality of evidence. The TWG prepared the evidence summaries that were presented to the Steering Committee and the Consensus Panel for finalization of the recommendations. The Consensus Panel voted on each recommendation and the strength of recommendations, taking into consideration (1) the quality of the evidence, (2) the value of the outcome, (3) the balance between benefit and harm, and (4) the cost and resource availability. Consensus required at least 75% of votes. If consensus was not reached, voters were allowed to share their perspective and provide feedback for a chance to revise the statement or ask for clarification. The voting process was repeated until a maximum of three rounds, at which unresolved questions were deliberated via Modified Delphi Technique. Publication of this CPG is part of the dissemination process, which will be followed later on by monitoring and updating. The development of this guideline was funded by the Philippine Department of Health (DOH) and the Philippine Society for Microbiology and Infectious Diseases (PSMID).

Summary of Recommendations

The full comprehensive manuscript of the CPG consists of 162 pages and can be accessed at the website of the Philippine Society for Microbiology and Infectious Diseases (PSMID).[3]

SEPSIS DEFINITION AND CRITERIA FOR DIAGNOSIS

Question 1 Should we use the Sepsis-3 definition over the old sepsis definition?

We recommend adoption of the Sepsis-3 definition of sepsis ("life-threatening organ dysfunction caused by a dysregulated host response to infection") ***(strong recommendation, moderate quality of evidence).***

The 2016 Sepsis-3 consensus revised the definition of sepsis making it equivalent to the severe sepsis of old. The new definition makes the condition more specific, as it removes those infections that are not life-threatening and present with at least two SIRS criteria, which could actually be just a normal host response to infection.[1]

Question 2 Should we use the quick Sequential Organ Failure Assessment (qSOFA) over the Systemic Inflammatory Response Syndrome (SIRS) as clinical criteria to identify patients with sepsis?

We recommend that qSOFA-based clinical criteria (at least two criteria in a patient suspected/proven infection) be used to identify patients with sepsis ***(strong recommendation, moderate quality evidence*****).**

We recommend that those with at least two (2) SIRS criteria plus suspected/proven infection but not meeting qSOFA≥2, be observed for progression to sepsis (***strong recommendation, moderate quality evidence*****).**

Foreign and local studies consistently demonstrated higher sensitivity of SIRS, but better specificity of qSOFA in terms of (1) predicting mortality, (2) predicting organ dysfunction, and (3) diagnosing sepsis.[4-16] The use of qSOFA appears to be attractive in terms of diagnosing

true, life-threatening infections, but the sensitivity of SIRS is difficult to ignore, given the fact that clinicians would not want to miss even a small number of cases at high risk of mortality.

To reconcile this, qSOFA and SIRS were included in the clinical algorithm for the diagnosis of patients suspected of sepsis. (*Figure 1)*The panel agreed to recommend the more specific qSOFA criteria to diagnose sepsis. But in recognition of SIRS' higher sensitivity, those with <2 qSOFA score should still be evaluated using the SIRS criteria. Patients who satisfy at least two SIRS criteria (but have qSOFA <2), should be monitored for progression to sepsis.

Question 3 Should the Sequential Organ Failure Assessment (SOFA) scoring-based clinical criteria be used instead of SIRS-based criteria in the diagnosis of sepsis in the Intensive Care Unit (ICU)?

We recommend the use of SOFA scoring-based clinical criteria instead of SIRS-based criteria in diagnosing sepsis in the ICU *(strong recommendation, high quality of evidence).*

Multiple studies demonstrated why SOFA scoring is preferred over qSOFA in the identification of sepsis inside the ICU.[4, 7, 17-18] Both qSOFA and SIRS can be used while waiting for the test results necessary to finalize the SOFA score. However, when used in this setting, the limitations of qSOFA and/or SIRS should be taken into consideration. *Figure 1* shows the clinical algorithm for the identification of patients with sepsis incorporating the use of the different clinical criteria discussed.

Question 4 Should we use the Sepsis-3 definition and clinical criteria to diagnose patients with septic shock?

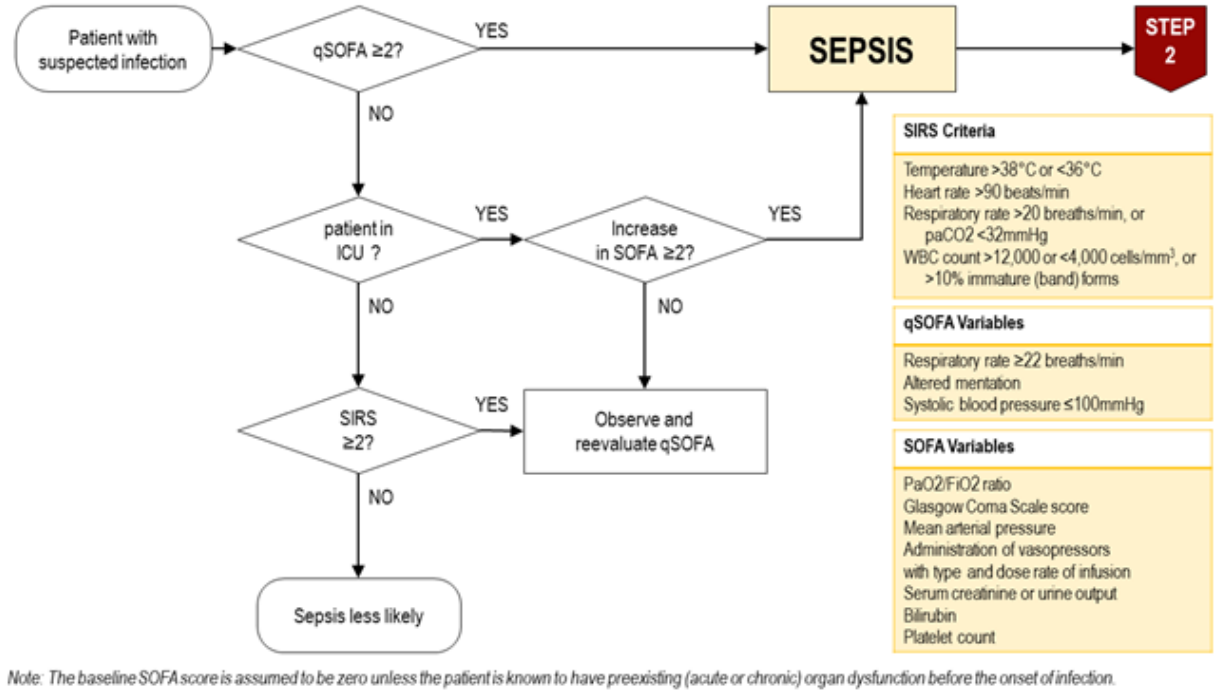
We recommend the adoption of the Sepsis-3 definition of septic shock - "a subset of sepsis with underlying circulatory, cellular and metabolic abnormalities that are profound enough to substantially increase mortality than sepsis alone" (*strong recommendation, moderate quality of evidence*).

When serum lactate is available, we recommend that the Sepsis-3 clinical criteria of (1) hypotension requiring vasopressor to maintain MAP ≥ 65mmHg, and (2) a serum lactate level >2mmol/L (18mg/dl) after adequate fluid resuscitation be used to identify patients with septic shock (*strong recommendation, moderate quality of evidence*)

Remark: A high lactate level further stratifies septic patients at higher risk of mortality.

When serum lactate is not available, we recommend that the previous clinical criteria of (1) hypotension that does not improve after adequate fluid resuscitation, and (2) needing vasopressor to maintain MAP of ≥65mmHg, be used at the minimum to identify patients with septic shock (*strong recommendation, moderate quality of evidence*).

In Sepsis-3, the task force agreed that septic shock is not cardiovascular dysfunction alone, and recognized the importance of cellular abnormalities. The clinical criteria for septic shock combined hypotension and



Note: The baseline SOFA score is assumed to be zero unless the patient is known to have preexisting (acute or chronic) organ dysfunction before the onset of infection.

Figure 1. Identification of Patients with Sepsis

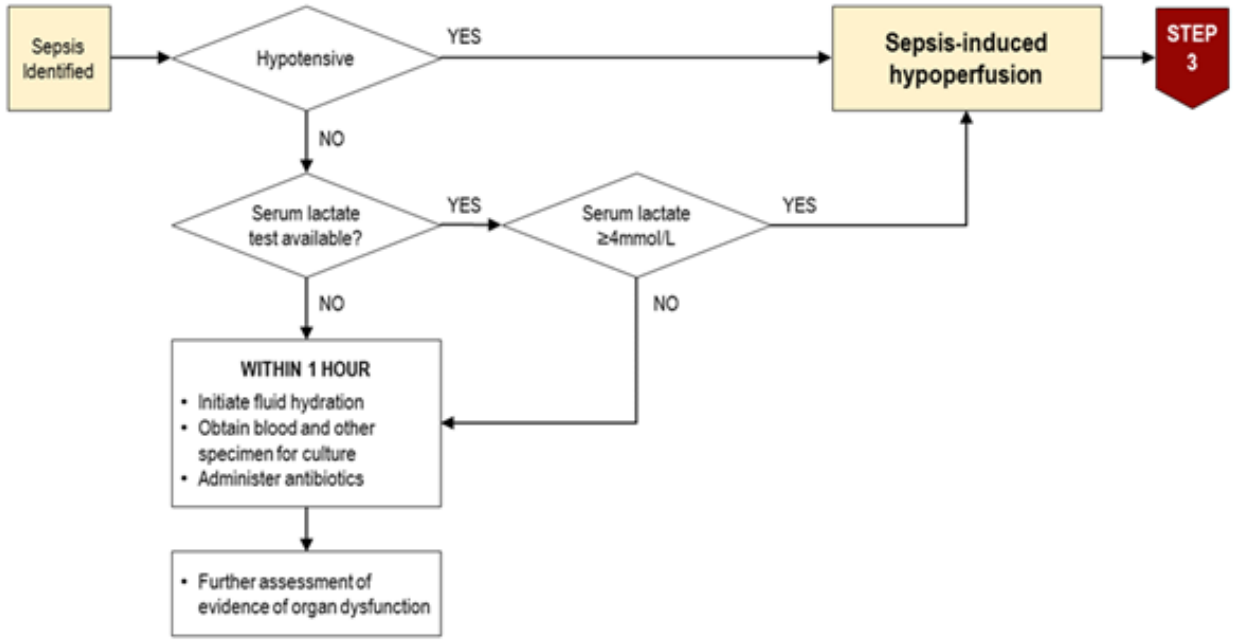


Figure 2. Initial Management of Patients with Sepsis and Identification of Patients with Sepsis

hyperlactatemia, representing both cardiovascular compromise and cellular dysfunction, since both have been uniformly associated with a significantly higher risk of mortality and organ dysfunction. Current evidence strongly supports the inclusion of hyperlactatemia, hence the adoption of the Sepsis-3 criteria for diagnosis of septic shock.[19-21]

However, the panel recognizes the potential limitation in terms of availability, accessibility and cost of serum lactate testing. Thus, the old criteria were recommended at a minimum for diagnosis of septic shock – though at the expense of lower prognostic accuracy. *Figure 2* shows the clinical algorithm for the identification of patients with sepsis-induced hypoperfusion based on serum lactate level, while *Figure 3* shows the algorithm in the diagnosis and initial management of septic shock.

DIAGNOSTIC TESTS

Question 5 Should we routinely request blood cultures from patients suspected with sepsis or septic shock?

Blood cultures should be obtained before administering antibiotics to patients suspected of sepsis or septic shock, if doing so will not result in substantial delay in the initiation of antibiotics ***(strong recommendation, low quality of evidence).***

Note: Antibiotics should be administered within an hour of sepsis recognition. The reader is directed to Question 27 for further information.

Blood cultures should be complemented by appropriate cultures taken from the suspected focus of infection ***(strong recommendation, low quality of evidence).***

Despite the limitations of blood culture, it has been consistently recommended in various sepsis clinical practice guidelines such as the Surviving Sepsis Campaign and the Japanese Clinical Practice Guidelines for the Management of Sepsis and Septic Shock.[22,23] Blood cultures do not only allow proper identification of the causative microorganism and targeted antimicrobial therapy but also support de-escalation of antibiotics to prevent unnecessary use of broad-spectrum antimicrobials. De-escalation is associated with less risk of developing resistant microorganisms, fewer antibiotic-related side effects, and lower costs.

The addition of specimen for culture from other potential sites of infection increased the sensitivity of the test to 68%.[24] Positivity rate was also higher with paired blood culture compared to single blood culture.[25] Unless there is clinically apparent focus of infection, culture from other sites apart from the suspected site(s) of infection should be discouraged as it could lead to inappropriate use of antibiotics.

Question 6 Should we use procalcitonin to diagnose adult patients with sepsis?

When there is uncertainty, procalcitonin may be used as an adjunct to support the diagnosis of sepsis in adults (*weak recommendation, low quality of evidence***).**

Note: Procalcitonin does not reliably rule out sepsis and should not be used solely to decide whether or not to start antibiotics.

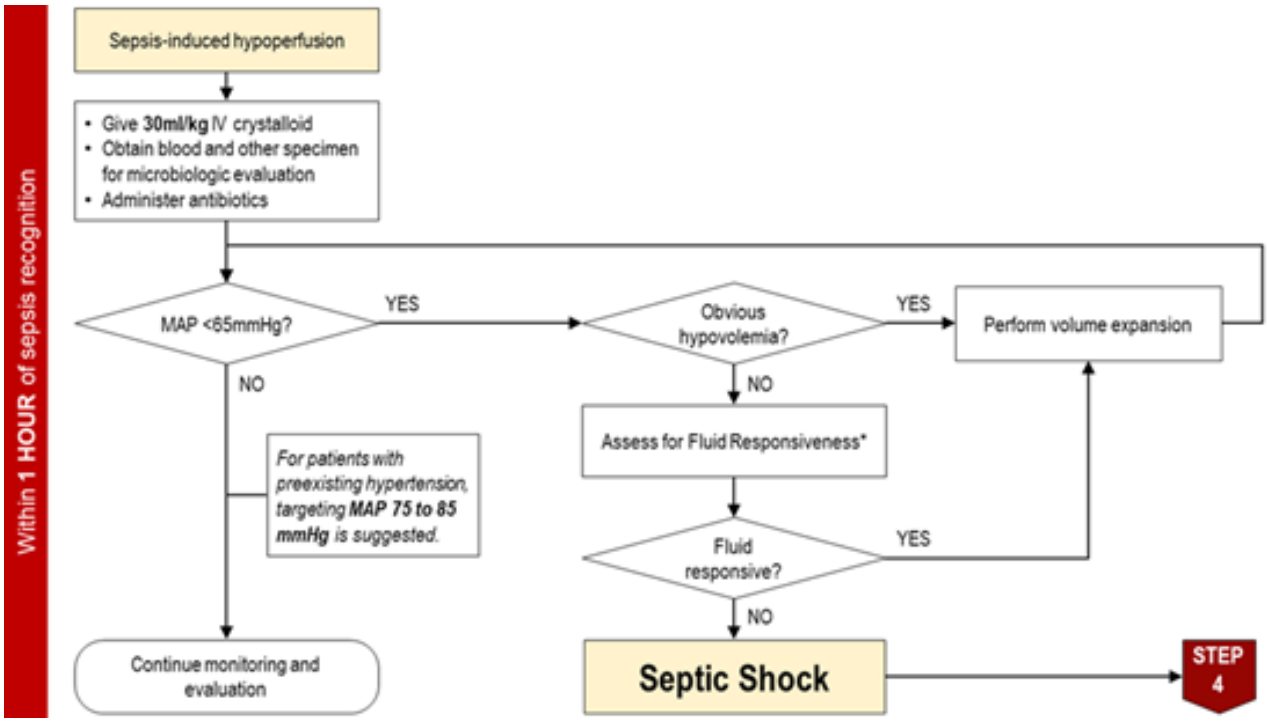


Figure 3. Initial Management of Patients with Sepsis-induced hypoperfusion and Identification of Patients with Septic Shock

A meta-analysis by Kondo and colleagues that included 1,377 patients showed moderate sensitivity (0.80, 95%CI 0.75, 0.84) and specificity (0.75, 95% CI 0.67, 0.81) of procalcitonin (PCT) in diagnosing patients with sepsis and septic shock.[26] Significant heterogeneity was observed across studies (Sn I^2=81.72, Sp I^2=87.13), and this was attributed to differences in the PCT cutoff values and the prevalence of sepsis.

Although the panel agreed to the adjunctive use of procalcitonin for patients whose diagnosis is uncertain, we would like to emphasize that PCT is not essential for sepsis diagnosis.

FLUID THERAPY

Question 7 In patients with sepsis or septic shock, should we use crystalloids for initial fluid resuscitation versus colloid solutions?

We recommend the use of crystalloids for initial fluid resuscitation of patients with sepsis or septic shock (*strong recommendation, moderate quality of evidence*).

We recommend against the use of hydroxyethylstarch (HES) for fluid resuscitation due to safety concerns (*strong recommendation, high quality of evidence*).

Current evidence show that crystalloids have the highest benefit-to-risk ratio among intravenous fluids for patients with sepsis or septic shock. Results showed no difference in mortality but lower risk for renal replacement therapy in favor of crystalloids over colloid solutions. Further analysis of colloids showed that this risk was associated with the use of hydroxyethyl starch (HES).[27-28] The latter was also associated with greater risk of acute kidney injury (RR 1.24, 95% CI 1.13 to 1.36) and renal replacement therapy.[29]

Question 8 In patients with sepsis or septic shock, should we use balanced crystalloids for initial fluid resuscitation versus normal saline solution?

We recommend the use of either balanced crystalloids or normal saline solution for initial resuscitation of patients with sepsis or septic shock *(strong recommendation, moderate quality of evidence).*

Studies showed marginal 30-day mortality benefit with the use of balanced crystalloids compared to saline solution among patients with sepsis (OR 0.74, 95%CI: 0.59, 0.93),[30] but no difference in the 90-day mortality (OR 0.98, 95%CI: 0.28, 3.42).[31] There was a trend toward benefit in terms of prevention of renal replacement therapy (OR 0.71, 95%CI: 0.48, 1.0) and acute kidney injury (OR 0.82, 95%: 0.66, 1.01) in favor of balanced crystalloids versus normal saline solution.

However, as we wait for the results of three trials, the consensus panel deems reasonable that either balanced crystalloids or normal saline solution be used for initial fluid resuscitation in patients with sepsis or septic shock.

Question 9 In patients with sepsis or septic shock, should we use crystalloids supplemented with albumin for initial fluid resuscitation versus crystalloids alone?

Addition of albumin to crystalloids may be considered in septic shock patients who are unresponsive to standard volume and vasopressor therapy or if with other indications ***(weak recommendation, moderate quality of evidence).***

Two meta-analyses showed a trend towards survival with the addition of albumin to crystalloids in patients with sepsis or septic shock. Use of hyperoncotic (20%) albumin solution resulted to lower mortality among septic shock patients (OR 0.88, 95%CI 0.79, 0.99).[32,33] With regard to adverse events, a meta-analysis found no increased risk for renal replacement therapy (RRT) with the use of albumin compared to crystalloids.[34]

At the moment, given the significant cost of albumin, we suggest that its use be considered only in septic shock patients who present with indications for its use and are unresponsive to standard volume therapy.

Question 10 In patients with sepsis or septic shock, should we initiate fluid resuscitation within an hour of sepsis recognition?

We recommend that fluid resuscitation be initiated immediately upon the recognition of sepsis or septic shock ***(strong recommendation, moderate quality of evidence).***

Best evidence came from a large prospective cohort study that included 11,182 adult patients with sepsis and septic shock. Fluid resuscitation initiated within 30 minutes was associated with reduced odds of mortality (OR 0.76, 95%CI 0.69, 0.84), decreased need for mechanical ventilation (OR 0.62, 95%CI 0.57, 0.68), lower need for vasopressor therapy (OR 0.77, 95%CI 0.71, 0.85), decreased refractory hypotension (OR 0.77, 95%CI 0.69, 0.87), and decreased ICU admission (OR 0.76, 95%CI 0.70, 0.82). When assessed as a continuous variable, time to crystalloid initiation was associated with 1.09 times greater odds of mortality (95%CI 1.03, 1.16) per hour of delay.[22]

Question 11 In patients with sepsis or septic shock, should we give 30ml/kg intravenous fluid bolus for initial fluid resuscitation?

We suggest initial resuscitation of 30ml/kg of intravenous fluids to patients with sepsis-induced hypoperfusion ***(conditional recommendation, low quality of evidence).***

Remarks: Patients with sepsis-induced hypoperfusion include those who are hypotensive or have lactate levels of >4mmol/L.

The SSC recommendation of 30ml/kg intravenous fluid bolus for initial resuscitation was adopted in our recommendation in recognition of its established precedence, in the context of the sepsis bundle, and in improving mortality among patients with sepsis and septic shock.[22, 35-37] Notwithstanding this, the absence of high- or even moderate-quality evidence supporting this fluid volume acknowledges the clinician's judgment and decision of the risk and benefit per individual patient. *Figure 3* shows the clinical algorithm for the identification and initial fluid management of patients with sepsis-induced hypoperfusion incorporating the 30ml/kg intravenous bolus of crystalloid.

Question 12 In patients with sepsis or septic shock, should we limit the volume of intravenous fluids?

We suggest not exceeding five (5) liters of total intravenous fluid volume in the first 24 hours of resuscitation (*conditional recommendation, moderate quality evidence***).**

Remark: Further fluid administration should be guided by hemodynamic targets, lactate levels, and repeated assessments of fluid responsiveness (*Table I*). Nonetheless, other measures to improve targets should be sought if total fluid volumes approach five (5) liters given the incremental increase in mortality associated per liter of fluid beyond five (5).

This recommendation is in consideration of the harm associated with overyhydration[38] especially in patients who are mechanically ventilated. Clinicians should be guided by repeated assessment of fluid responsiveness before additional fluids are administered. Early vasopressor therapy should be considered for fluid unresponsive patients.

Question 13 In patients with sepsis or septic shock, should deresuscitation be performed after hemodynamic stabilization?

We recommend deresuscitation by preventing positive cumulative fluid balance after stabilization of patients with sepsis or septic shock ***(strong recommendation, moderate quality evidence).***

Remarks: Fluid administration to improve end-organ perfusion is still recommended using hemodynamic targets. Limiting fluid administration to prevent positive fluid balance and attempting to achieve negative fluid balance once the patient is stabilized prevents adverse events and improves patient outcomes.

In a meta-analysis that included 2,051 patients with acute respiratory distress syndrome (ARDS), sepsis and SIRS in the post-resuscitation phase of critical illness, a trend toward lower mortality (OR 0.86, 95%CI 0.62, 1.17) and renal replacement therapy (OR 0.88, 95%CI 0.64, 1.22) was observed with conservative and deresuscitative fluid strategy.[39] Conservative and deresuscitative strategy also resulted to greater ventilator-free days (mean difference [MD] 1.82 days higher, 95%CI 0.53 to 3.1 days higher), shorter ICU stay (MD 1.88 days lower , 95%CI 0.12 to 3.64 lower), and better post-ICU cognitive function (MD 10.71 points higher, 95%CI 5.22 to 16.22 point higher QLQ-C30 cognitive domain).

Table I. Methods to predict fluid responsiveness[40,41]

Method	Variable	Threshold	Main limitations
Stroke volume variation (SVV)	Stroke volume	12%	Cannot be used in case of spontaneous breathing, cardiac arrhythmias, low tidal volume/lung compliance
Pulse pressure variation (PPV)	Pulse pressure	12%	Cannot be used in case of spontaneous breathing, cardiac arrhythmias, low tidal volume/lung compliance
Passive leg raising (PLR)	Stroke volume Pulse contour aortic blood flow	15% 15% 15%	Requires a direct measurement of cardiac output
Mini fluid challenge	SVV, PPV subaortic velocity time index	2% 10%	Requires a precise technique for measuring cardiac output
End-expiratory occlusion test (EOOT)	PPV, change in cardiac index subaortic velocity time index	5% 5%	Cannot be used in nonintubated patients and patients who cannot tolerate a 15-sec respiratory hold
Tidal volume challenge	SVV PPV	2.5% 3.5%	Requires a precise technique for measuring cardiac output

- Passive leg raise: From a semi-recumbent position the patient is placed to supine position and the lower limbs are elevated to 45 degrees for 2 minutes to mobilize blood from the lower extremities in order to create sufficient venous return to increase preload. Measurements of CO are taken at baseline and after PLR.
- Mini fluid challenge is performed by rapid infusion of 100ml intravenous fluid with measurements of CO before and after infusion.
- In end expiratory occlusion test, a 15 second end expiratory occlusion is applied among ventilated patients and cardiac output measured before and at the last 5 seconds of the test.
- Tidal volume challenge involves increasing the tidal volume from 6 ml/kg to 8 ml/kg (of predicted body weight) for one minute accompanied by measurements of CO before and after.

Question 14 In patients with sepsis and septic shock, should we use dynamic parameters versus static parameters to predict fluid responsiveness?

Following initial fluid resuscitation, we suggest assessment of fluid responsiveness using dynamic variables over static variables before administration of additional fluids *(weak recommendation, moderate quality of evidence).*

We suggest against the use of central venous pressure (CVP) to assess fluid responsiveness *(conditional recommendation, moderate quality of evidence).*

We recommend the use of non-invasive cardiac output monitor such as ultrasound or echocardiogram coupled with passive leg raise for assessing fluid responsiveness whenever possible *(weak recommendation, moderate quality of evidence).*

We recommend an individualized approach to the integration of various modalities and maneuvers to assess fluid responsiveness *(best practice statement).*

The use of dynamic variables for assessing fluid responsiveness involve maneuvers that increase preload, interpreted with concomitantly-measured variations in cardiac output. Each maneuver has its limitations and may be more applicable to certain patients than others. Therefore, an individualized approach to the integration of modalities and maneuvers to assess fluid responsiveness is recommended to guide fluid resuscitation in patients with sepsis. Current recommendations were similar to the Surviving Sepsis Campaign published in 2016.[22] We provided a clinical algorithm (*Figure 4*) to guide clinicians on the techniques, modalities and threshold used in assessing fluid responsiveness.[40-42]

VASOACTIVE AGENTS

Question 15 In patients with septic shock requiring vasopressors, should we use norepinephrine over other agents?

We recommend norepinephrine as a first-line agent in septic shock requiring vasopressors *(strong recommendation, high quality of evidence).*

The highest quality of evidence is given by the systematic review done by Avni and colleagues which reviewed 32 studies, including 14 randomized controlled trials involving 3544 patients.[43] Results showed a relative risk of 0.89 (95% CI 0.81-0.98) corresponding to an absolute risk reduction of 11% and a number-needed-to-treat (NNT) of nine (9) to prevent one mortality. This supports an early report by Vasu et al., where authors reviewed six randomized controlled trials involving 2043 participants. They compared norepinephrine with dopamine as first line agent in septic shock unresponsive to initial fluid resuscitation. The study reported a pooled relative risk of 0.91 (95% CI 0.83-0.99), with benefit favoring norepinephrine.[44]

Question 16. In patients with septic shock requiring a second vasopressor, which agent should be added to norepinephrine?

We recommend the use of vasopressin (titrated up to 0.03 U/min) as the second vasopressor of choice on top of norepinephrine in patients with septic shock, with the intent of raising mean arterial pressure to target or decreasing norepinephrine dosage *(conditional recommendation, low quality of evidence).*

There is a lack of evidence to support the use of an add-on vasopressor to norepinephrine with respect to mortality benefit. In real world practice, the decision to add a second vasopressor to norepinephrine for adult patients with septic shock will have to depend on mechanistic evidence in the absence of established mortality benefit based on clinical trials. Despite lack of mortality benefit, the potential of add-on vasopressin to improve mean arterial pressure and reduce norepinephrine requirement still makes it a viable option in selected clinical situations, taking into consideration its availability and accessibility in the local setting.

Question 17 In patients with septic shock and persistent hypoperfusion, should we use dobutamine?

We suggest using dobutamine in patients with persistent hypoperfusion and low cardiac index despite adequate fluid administration and the use of vasopressors *(weak recommendation, low quality of evidence).*

Current evidence supporting the use of dobutamine in septic shock was mainly physiologic in nature characterized by improved hemodynamics and perfusion indices. Importantly, inotropic therapy in septic shock is aimed at increasing oxygen delivery and improved tissue perfusion. In this case, dobutamine is considered as the inotrope-of-choice for patients with measured low cardiac index despite optimal left ventricular filling pressure and adequate mean arterial pressure.[45] A randomized controlled trial comparing dobutamine and epinephrine as add-on agent among patients with septic shock and myocardial dysfunction showed that the 28-day mortality was similar between treatment groups but resulted in significantly better arterial pH and lower serum lactate compared to epinephrine.[46]

HEMODYNAMIC MONITORING

Question 18 In patients with septic shock requiring vasopressors, should we target a mean arterial pressure (MAP) of at least 65mmHg versus higher MAP?

We recommend a target MAP of at least 65 mmHg in patients with septic shock ***(strong recommendation, moderate quality of evidence).***

We suggest targeting a higher MAP of 75mmHg to 85mmHg for patients with septic shock and preexisting hypertension (*weak recommendation, low quality of evidence).***

Asfar et al. showed that targeting a MAP of 80 to 85 mmHg, as compared to 65 to 70 mmHg, in patients with shock undergoing resuscitation, did not result in significant differences in mortality at either 28 or 90 days.[47] However, targeting higher blood pressure may increase mortality in patients who have been treated with vasopressors for more than six hours.[48]

Cecconi et al. suggest a higher MAP in septic patients with history of hypertension and in patients who show clinical improvement with higher blood pressure.[49] A cohort study by Lee and colleagues in 2019 showed that in patients with previously known high blood pressure

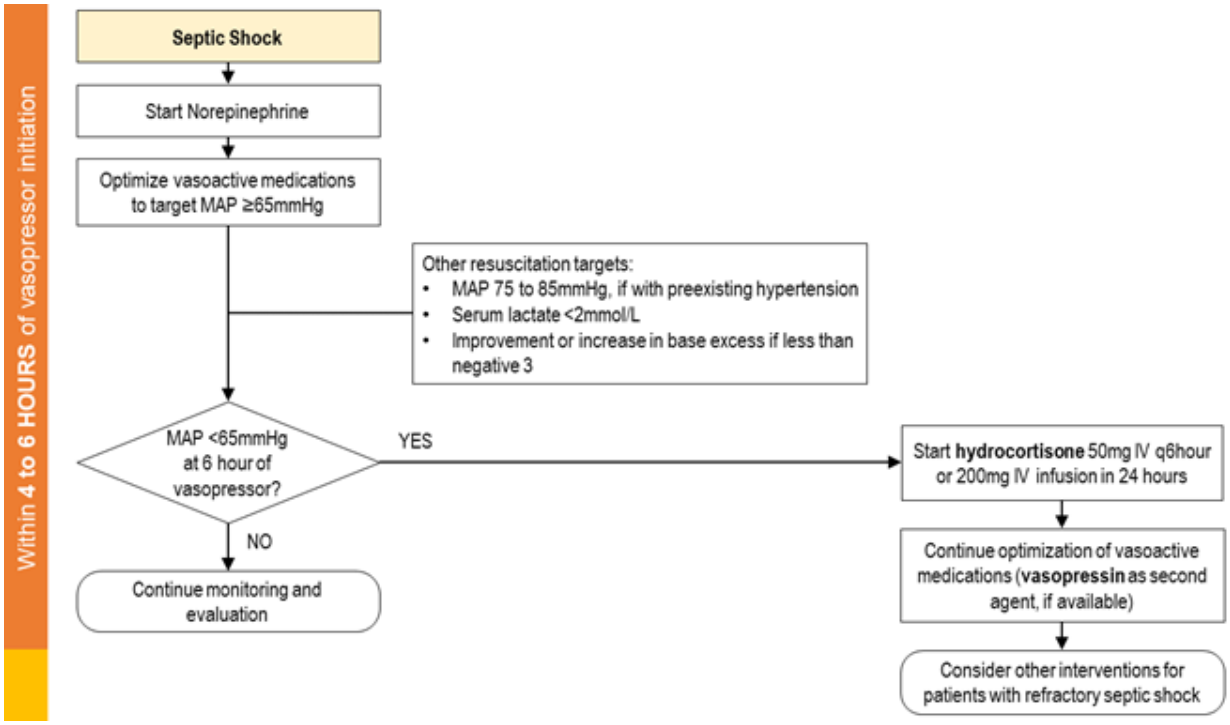


Figure 4. Management of Patients with Septic Shock

trends, targeting a MAP of 75-85mmHg improved survival, however, the mortality risk starts to increase at MAP >85mmHg.[50]

Question 19 Should we aim for normalization of lactate levels during resuscitation of patients with sepsis?

We suggest the use of lactate as guide to hemodynamic resuscitation, with the goal of normalizing serum lactate levels ***(weak recommendation, moderate quality of evidence).***

However, persistent hyperlactatemia may be related to causes other than tissue hypoperfusion.[54] Moreover, lactate kinetics is relatively slow even in survivors,[52,53] and measurements of lactate levels are not universally available, especially in resource-poor areas. Despite this, lactate-guided therapy (LGT) is recommended since high lactate levels among septic patients are associated with higher risk of organ failure and mortality.[51]

Question 20 Can we use base excess (as surrogate) to diagnose hyperlactatemia?

An initial base excess value < (-3) is moderately predictive of hyperlactatemia (>4mmol/L), and should prompt immediate fluid resuscitation ***(weak recommendation, low quality of evidence).***

Montassier and colleagues showed that base excess levels may predict elevated lactate levels among septic patients in the emergency department.[55] This suggests the availability of a quick marker in assessing the severity of hypoperfusion.

Question 21 Should we use base excess to monitor fluid resuscitation?

Base excess may be used to monitor fluid resuscitation by targeting an improvement or increase from baseline (*weak recommendation, low quality of evidence*).

Single center studies have showed that targeting improvement in base excess from baseline measurements revealed lower mortality rates compared to septic patients who were noted to have further decreases in base excess levels.[56-58]

Question 22 In patients with sepsis or septic shock, should low veno-arterial CO_2 gap be used as a goal for resuscitation?

We suggest using venoarterial carbon dioxide gap as adjunct to serum lactate to monitor response to fluid resuscitation (*weak recommendation, low quality of evidence*).

Remarks: In order to measure venoarterial carbon dioxide gap, arterial and central venous blood gas samples should be taken. We do not recommend insertion of central venous catheters for the sole purpose of obtaining central venous blood gas.

Studies have consistently proposed that a low CO2 gap was associated with a higher cardiac index, and a lower lactate level. They have noted that patients with lower CO_2 gap levels – less than or equal to 6 mmHg had higher survival rates compared to those with higher CO_2 gap levels.[59-61]

Question 23 In patients with sepsis or septic shock, should we use a pulmonary artery catheter (PAC)?

The routine use of a pulmonary artery catheter alone for hemodynamic monitoring in patients with sepsis and septic shock is not recommended ***(strong recommendation, moderate quality of evidence).***

The use of a pulmonary artery catheter may be reserved for the management of severe multifactorial shock conditions, and to be used with other hemodynamic monitoring parameters ***(weak recommendation, low quality of evidence).***

Due to numerous large trials that have shown lack of mortality benefit with the use of the PA catheter, its indications for use have been put to question. A meta-analysis comparing the use versus non-use of a PA catheter among ICU patients revealed that there was no significant difference in mortality between the group managed with a PA catheter versus the group without PA catheter use.[22, 62-63] As a result, the general use of PA catheter declined and no longer routinely recommended.

ANTIMICROBIAL THERAPY

Question 24 In patients with sepsis or septic shock, should we use empiric broad-spectrum antibiotic(s)?

We recommend broad-spectrum antimicrobial therapy targeted to the site of infection based on existing recommendations ***(strong recommendation, moderate quality of evidence).***

Remark: The reader is directed to Question 25 and the accompanying table for the updated recommendations for empiric antimicrobial therapy for the most common infections.

The systematic review and meta-analysis of Paul et al.[64] provides the most robust evidence in favor of giving broad-spectrum antimicrobials at the onset of treatment for sepsis or septic shock. The adjusted multivariable analysis of risk factors done showed a two-fold increase in 30-day all-cause mortality when inappropriate empiric therapy was given, compared to appropriate empiric therapy (OR 2.05, 95% CI 1.69-2.49, p<0.001). Among all clinical variables, only septic shock resulted in higher ORs. Similarly, the one by Marquet et al.[65] investigated the outcomes of inappropriate empiric antibiotics on hospital mortality, reviewing studies published between 2004 to 2014. It included the study by Kumar et al.,[66] perhaps the largest single study on outcomes of inappropriate empiric antibiotics in septic shock patients that demonstrated a 5-fold reduction in survival of patients who received inappropriate empiric antibiotics). Certainly, knowledge of the most common pathogens associated with the suspected infection site plays the greatest role in determining the best empiric regimen,

while also considering whether the infection is community-acquired or nosocomial, with shock or not, device-related or not, while considering patient age and other patient-related factors. Knowledge of local antimicrobial susceptibility rates and probability of multidrug-resistant organisms are also important.

Question 25 In patients with sepsis or septic shock, should we use empiric combination antimicrobial therapy versus monotherapy?

Among adults with septic shock, empiric combination therapy (i.e. the use of two antibiotics from different mechanistic classes) is suggested over monotherapy *(weak recommendation, low quality of evidence).*

The conflicting results on the benefits of combination therapy in sepsis might be explained by the heterogeneous nature and structural bias of the different studies. There is also variation in the site and severity of infection and antibiotic treatment. It is important to note at this point that most randomized studies are designed to assess noninferiority. Also, these studies often do not compare the same antibiotic in monotherapy and in combination with a second agent. Thus, synergy is difficult to assess rigorously in many individual studies.[66-68] The decision to give empiric combination antibiotic therapy or monotherapy should be individualized and based on the suspected site of infection, disease severity, likely pathogen, renal function, and local/institutional microbiological and resistance patterns.[69-70]

Question 26 In patients with sepsis or septic shock, should we empirically start antibiotics for methicillin-resistant Staphylococcus aureus (MRSA)?

We recommend empiric MRSA coverage on septic shock patients who have invasive vascular catheters, previous intravenous antibiotics in the past 90 days, and previous MRSA infection or colonization. We do not recommend routine use of empiric MRSA coverage for all patients with sepsis and septic shock *(strong recommendation, low quality of evidence).*

We suggest infectious diseases referral for septic patients with MRSA risk factors *(best practice statement).*

The identified risk factors that are most common and most highly associated with MRSA infections based on high odds ratio are septic shock, previous extensive intravenous antibiotic use in the past 90 days, previous MRSA colonization or infection, and presence of intravascular devices.[71-75] The presence of urinary catheter was not included as a risk factor because prevalence of MRSA, especially as a pathogen, in the urinary tract is low.

Question 27 In patients with sepsis or septic shock, should empiric antibiotics be administered within the first hour of sepsis recognition?

We recommend that empiric antimicrobials be given within an hour after recognition of sepsis or septic shock *(strong recommendation, moderate quality of evidence).*

An hourly delay of effective antimicrobial therapy was associated with mean decrease in survival of 7.6%, as shown in the study done by Kumar et al.[76] Appropriate antibiotic therapy complements early administration of antibiotics. It is therefore important that clinicians be updated of the most common pathogens for a given infection along with their local antimicrobial sensitivity pattern in order to select the most appropriate empiric antibiotic and not just rely on the rapidity of antibiotic administration. In relation to this, the value of sending blood and other relevant cultures cannot be overemphasized. Microbiologic data enables clinicians to streamline and optimize antimicrobial treatment, that is very crucial in patients with high risk of mortality as defined by sepsis and septic shock.

Question 28 In patients with sepsis, should we implement pharmacokinetic dosing optimization for each antimicrobial?

If the following antibacterial agents are to be used for empiric therapy:

We recommend administering piperacillin-tazobactam by extended or continuous infusions in patients with sepsis to improve clinical outcomes *(strong recommendation, moderate quality of evidence).*

We recommend administering meropenem by extended or continuous infusions in patients with sepsis to improve clinical outcomes *(strong recommendation, moderate quality of evidence).*

We recommend either prolonged or intermittent dosing of cephalosporins in patients with sepsis or septic shock *(strong recommendation, low quality of evidence).*

We recommend continuous infusion of vancomycin in patients with sepsis and septic shock *(strong recommendation, low quality of evidence).*

Remarks:

- Loading dose of antibiotics should be administered before proceeding with extended or continuous infusion on the succeeding doses.
- Independent lines or multiple catheters should be considered during continuous intravenous infusion (CIV) in instances where incompatible medications (i.e., beta-lactams, moxifloxacin, dexamethasone, furosemide, heparin, propofol, phenobarbital) are administered with vancomycin during critical care setting; [77] or may temporarily suspend vancomycin infusion or switch to intermittent infusion method.

In sepsis, there is increased volume of distribution, changes in protein binding and clearance of drugs. These changes may cause the concentration of unbound drug to fall to subtherapeutic level and potentially cause treatment failure. Utilizing knowledge on altered drug pharmacokinetics during sepsis in order to optimize

antimicrobial administration may improve outcomes in critically-ill patients.[78-93]

Question 29 In patients with sepsis or septic shock who are receiving antimicrobial agents, should we de-escalate antimicrobial therapy once culture sensitivities are determined?

Among adults with sepsis and septic shock, de-escalation of antimicrobials is recommended over continuation of empiric therapy *(strong recommendation, moderate quality of evidence).*

De-escalation can be more safely done once there are positive signs of recovery such as stable normotension and resolution of fever. Moderate quality evidence suggests no difference in mortality between de-escalation and no de-escalation, but the panel considered potential benefits such as reduction in antimicrobial exposure (in effect reduction in risk of development of antimicrobial resistance) and reduced cost related to hospitalization and antibiotic therapy.[94-96]

Question 30 In patients with sepsis or septic shock, should we recommend longer versus shorter duration of antibiotic therapy?

The duration of antibiotic for septic patients will depend on the focus of infection and the pathogen.

Shorter duration of antibiotic therapy of seven (7) days should be considered for cases of hospital-acquired pneumonia, uncomplicated urinary tract infection, and intra-abdominal infection with rapid clinical improvement and in patients who received adequate source control (*strong recommendation, moderate quality of evidence).*

Longer courses of antibiotic are recommended in patients with non-fermenting Gram-negative pneumonia, inadequate source control, anatomically-complicated pyelonephritis, and *Staphylococcus aureus* **bacteremia** *(strong recommendation, moderate quality of evidence).*

Pugh and colleagues conducted a Cochrane review with six relevant studies involving 1088 participants with hospital-acquired and ventilator-associated pneumonia. Similar to older studies, it revealed that a course of seven or eight days of antibiotics was associated with an overall decrease in antibiotic administration and reduced the recurrence of pneumonia due to resistant organisms when compared to a longer, 10- to 15- day course.[97] Furthermore, this was achieved without any significant effect on mortality. Nevertheless, in cases when VAP was due to a particular type of organism ("non-fermenting Gram-negative bacilli" and MRSA), which can be difficult to eradicate with antibiotics, the risk of recurrent pneumonia appeared higher after a short course of treatment.

Traditionally, practitioners have treated patients until all evidence of SIRS has resolved, typically for seven to 14 days. More recently, it has been suggested that with adequate source control, a shorter course of three to five days should suffice for cure and could decrease the risk of antimicrobial resistance.[98-99] A systematic review and meta-analysis of randomized controlled trials on acute pyelonephritis and septic urinary tract infection also showed that seven days of treatment for acute pyelonephritis was equivalent to longer treatment, even in bacteremic patients.[100] But in patients with urogenital abnormalities, longer treatment is required. Low quality of evidence also shows no significant differences in clinical cure, microbiologic cure and survival among those receiving shorter versus longer duration antibiotic therapy except for those with *Staphylococcus aureus*.[101]

Question 31 In patients with sepsis or septic shock, should we use procalcitonin to support discontinuation or de-escalation of antibiotic therapy?

Procalcitonin may be used as an adjunct to other clinical parameters, to guide antibiotic discontinuation among patients with sepsis and septic shock *(weak recommendation, low quality evidence).*

Remarks: In order to guide therapy, serial measurements should be taken. A procalcitonin level below 0.5 µg/L, or a decline by 80% from the peak level, allows for shorter antibiotic duration.

The meta-analysis of 11 randomized controlled trials by Wirz et al. that in patients who met the Sepsis-3 criteria, procalcitonin (PCT) guidance resulted in better survival (OR 0.86, 95%CI 0.76, 0.98) and shorter duration of antibiotic therapy (mean difference [MD] -1.22 days, 95%CI -1.82, -0.62).[102]

Respiratory infections were the ones who benefited from reduced antibiotic exposure with PCT guidance and consistent with a larger meta-analysis (26 trials, n=6708) showing lower mortalities (adjusted OR 0.83, 95% CI 0.70 to 0.99), and shorter antibiotic exposures (2.4-day reduction in antibiotic exposure, 95% CI -2.71 to -2.15) among patients with acute respiratory tract infections.[103] The PCT algorithms employed in the trials focused on early discontinuation of antibiotics if levels dropped below 0.5 µg/L or by 80% from the peak level.

SOURCE CONTROL

Question 32 In patients with sepsis or septic shock, should we attempt early source control?

Early, adequate source control of infection is imperative in control of sepsis and septic shock (*best practice statement***).**

The specific source of infection must be identified, as the infection source may impact outcome.

- **We recommend that a specific anatomical diagnosis of infection requiring consideration for emergent source control (e.g., necrotizing soft tissue infection, complicated intra-abdominal infection) be sought and diagnosed or excluded as rapidly as possible, and intervention be undertaken for source control within the first 6-12 h after the diagnosis is made, if feasible.**

- **When source control in a severely septic patient is required, the most effective intervention associated with the least physiologic insult should be used (e.g., percutaneous, rather than surgical, drainage of an abscess).**
- **If intravascular access devices are a possible source of severe sepsis or septic shock, they should be removed promptly.**

Measures of source control include all actions taken in the process of care to contain the foci of infection and to restore optimal function of the site of infection[104]. Often it involves early diagnosis, drainage of infected fluids, debridement of infected soft tissues, removal of infected devices or foreign bodies. It can be summed up in two ways: to correct anatomic derangements that result in ongoing microbial contamination, and to restore optimal function.[105]

Compared to patients who did not have source control, patients who underwent source control had lower crude ICU mortality rates (21.2% vs 25.1%; p = 0.010). Hospital mortality was also lower (Odds Ratio, 0.809 [95% CI, 0.658–0.994]; *p = 0.044*), after statistical adjustment for confounding factors was performed.

The evidence regarding timing of source control is limited to intra-abdominal infections, and based on results of several studies which showed that early intervention improved outcome.[106-110]

There is insufficient evidence to recommend a specific method of source control – whether minimally invasive, or open surgery.[111]

The immediate removal of central venous catheters (CVC) remains controversial. To date, evidence from randomized controlled trials is lacking.[112]

CORTICOSTEROIDS

Question 33 In adult patients with septic shock, should we use intravenous corticosteroids?

Question 34 In adult patients with septic shock, should we use intermittent (bolus) versus continuous intravenous corticosteroids?

Among septic shock patients, we recommend administration of intravenous hydrocortisone either as 50 mg bolus every six (6) hours or a 200mg daily continuous infusion initiated within six (6) hours of vasopressor therapy (*strong recommendation, moderate quality of evidence*).

The survival benefit of corticosteroids to treat sepsis and septic shock continues to be controversial but the latest meta-analyses were consistent in some reduction in mortality, higher rates of shock reversal at day 7 and lower SOFA scores at day 7, with majority using low-dose hydrocortisone (<400 mg/day or equivalent), without any severe adverse events or superinfections apart from increase in risk of hyperglycemia and hypernatremia.[113-116] The recommendation to give giving the corticosteroids within 6 hours, came from the latest 2 large RCTs[117-118].

GLYCEMIC CONTROL

Question 35 In patients with sepsis, should we aim for intensive glycemic control?

We recommend to aim for blood glucose levels of ≤ 180mg/dl but not less than 110mg/dl among adult patients with sepsis or septic shock *(strong recommendation, moderate quality evidence)*

Meta-analyses which included the NICE-SUGAR trial confirm findings that intensive insulin treatment is not associated with mortality benefit in critically ill patients and is associated with an increased incidence of hypoglycemia.[119-121] One meta-analysis that included only septic patients found that intensive insulin treatment did not significantly reduce overall mortality (RR 0.98, 95% CI [0.85, 1.15], P = 0.84), severity of illness and length of ICU stay.[120] On the contrary, there was a greater incidence of significant hypoglycemia among patients given intensive insulin treatment (RR 2.93, 95% CI [1.69, 5.06], *p = 0.0001*)

ACUTE RESPIRATORY FAILURE

We suggest referral to Pulmonary or Critical Care specialist, when available, for patients with sepsis and ARDS *(best practice statement).*

ARDS is a life-threatening form of respiratory failure. At present, there are limited therapeutic options directed towards the underlying pathology. Supportive care with mechanical ventilation remains the cornerstone of the management with the attempt to improved oxygenation through lung recruitment with minimizing ventilator associated lung injury. Ventilatory strategies to provide an adequate balance of these conditions have been the focus of decades of research. Adequate training on these ventilator maneuvers cannot be overemphasized. Monitoring response and need for further intervention may also seem complicated for some generalists and internists, thus necessitating referral to trained or specialized physicians.

Question 36 In patients with sepsis-induced acquired respiratory distress syndrome (ARDS), should we use lung protective ventilation strategy?

36.1. In patients with sepsis-induced ARDS, should we use low tidal volume ventilation?

36.2. In patients with sepsis-induced ARDS on mechanical ventilation (MV), should we use high- versus low-positive end-expiratory pressure (PEEP) strategy?

36.3. In patients with sepsis-induced ARDS who are mechanically ventilated, should we use plateau pressures less than 30 mmHg?

We recommend a bundle of lung protective ventilation strategy in ventilating patients with sepsis-induced ARDS. This includes the following:

1. **We recommend use of low tidal volumes (6ml/kg) using Predicted Body Weight (PBW)**

(strong recommendation, high quality of evidence).

Remark: Predicted body weight is calculated as 50 + 0.91 (centimeters of height-152.4) for males and45.5 + 0.91 (centimeters of height-152.4) for females.

2. **We recommend providing PEEP as guided by the PEEP/ FiO2 table of the ARDSNET (2000) and ALVEOLI studies (2004) to target PaO2 between 55 mmHg and 80 mmHg or peripheral O2 saturation between 88% to 95%** *(strong recommendation, moderate quality of evidence).*

3. **We recommend targeting a plateau pressure of <30cm H_2O (***strong recommendation, quality of evidence).*

Remarks: Plateau pressure should be measured and recorded at least one minute after changing of PEEP or tidal volume taken in a relaxed patient. A plateau pressure recorded after a 0.5-second inspiratory pause in a relaxed patient should be considered.

There are no large RCT's that specifically investigate the effects of mechanical ventilation on sepsis-induced ARDS. As shown in *Tables II, and III*, most of the studies that exist look into the benefit of lung protective strategies which include giving low tidal volume, high PEEP and limiting plateau pressure during ventilation in ARDS. These studies involve a significant population of patients with pneumonia and sepsis, and include the landmark trial ARDSNET.[122] Following the ARDSNET trial, studies often bundle the strategies of low TV, high PEEP and plateau pressure targeting, which made it difficult to attribute the effect of each individual ventilator maneuver to measured clinical outcomes.[123-131] This is highlighted in the 2017 meta-analysis of Petrucci and colleagues. We therefore recommend to use a bundle of lung protective strategies in sepsis-induced ARDS utilizing (1) low tidal volume of 6ml/kg PBW; (2) high PEEP and (3) limiting plateau pressure of <30cm H_2O.

Question 37 In sepsis patients who are mechanically ventilated but without ARDS, should we use lung protective ventilation strategies?

We suggest using low tidal volume in ventilating patients with sepsis without ARDS *(weak recommendation, low quality of evidence).*

Table II. Lower PEEP / higher FIO2 table. Adapted from the ARDS NET Protocol 2000.

FiO_2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0
PEEP	5	5-8	8-10	10	10-14	14	14-18	18-24

Table III. Higher PEEP / lower FIO2 table. Adapted from the ARDS NET Protocol 2000

FiO_2	0.3	0.4	0.5	0.5 – 0.8	0.8	0.9	1.0
PEEP	5-14	14- 16	16-18	20	22	22	22- 24

The three studies exploring the use of low tidal volume in ventilating patients without ARDS included results that showed that those who received the low TV/ high PEEP intervention had an adjusted mortality OR of 0.47 (0.35 – 0.63).[132-134] More studies are needed to provide better quality evidence of benefit in using lung protective strategies in patients with sepsis who do not have ARDS.

Question 38 In patients with sepsis- induced ARDS, should we use conservative fluid strategy?

We recommend using conservative/deresuscitative fluid management for sepsis-induced ARDS after the resuscitative phase *(strong recommendation, moderate quality of evidence).*

Even without a mortality benefit, the strong evidence suggesting decrease in ventilator dependency[135] and ICU stay as well as a good safety profile of a fluid conservative strategy mandate a recommendation.[135-136]

Question 39 In patients with sepsis-induced ARDS on MV, should we do recruitment maneuvers?

We suggest recruitment maneuvers in patients with sepsis-induced ARDS under the care of a Pulmonary or Critical Care specialist (*conditional recommendation, low quality of evidence).*

Recruitment maneuvers (RMs) in ARDS represent one of the classic strategies to ventilate atelectatic lung segments and raise oxygenation of those with refractory hypoxemia. However, there is no consistent evidence on the proper recruitment maneuver strategy as well as the contemplated level of PEEP needed after a RM, plus issues of indirectness in the available studies.

The latest meta-analysis, in 2017, of six trials with varied RMs showed that RMs are associated with reduced mortality, improved oxygenation, and lesser need for rescue therapy.[137] There was no increase in the incidence of barotrauma with RMs on the pooled analysis.

In contrast, a study published after - the Alveolar Recruitment Trial - showed that in patients with moderate to severe ARDS, a strategy with lung recruitment and titrated PEEP compared with low PEEP increased 28-day all-cause mortality[138]. On review of this trial, we deemed it to be more of a PEEP titration study rather than a recruitment maneuver trial. Hence this was removed from the pooled analysis included in this part of the guidelines.

Question 40 In patients with sepsis-induced ARDS on MV, should we use prone positioning?

We suggest early proning of at least 12 hours/day in severe ARDS *(weak recommendation, moderate quality of evidence).*

The PROSEVA landmark trial as well as the other prone positioning studies on ARDS involved centers with high experience in conducting the maneuver showed mortality benefit.[139-144]

Question 41 In patients with sepsis-induced ARDS on MV, should we use neuromuscular blocking agents?

We recommend early use of neuromuscular (NM) blockade within 48 hours of ARDS diagnosis in moderate to severe ARDS *(weak recommendation, very low quality of evidence).*

We did a meta-analysis on NM blockade in ARDS which included the ROSE study and other studies published after the 2013 meta-analysis of Alhazzani which showed a cumulative RR of 0.87 (CI 0.76.1.0) in favor of NM blockade in ARDS. The updated meta-analysis also showed that NM blocker use in ARDS increases mean difference of ventilator-free days at 0.57 (-0.48 – 1.62).[145-147]

Question 42 In patients with sepsis-induced ARDS, should we use extracorporeal membrane oxygenation (ECMO) treatment?

We suggest early ECMO as a salvage therapy for sepsis-induced ARDS refractory to optimal conventional mechanical ventilation management and recruitment maneuvers *(conditional recommendation, moderate quality of evidence).*

A 2017 meta-analysis concluded that there is still limited evidence on the use of ECMO in ARDS patients.[148]

Due to inconsistent results of the two large trials on mortality, effect of technological advancements, need for expertise and high costs, we provide a conditional recommendation for the early use of ECMO for severe ARDS patients refractory to conventional ventilation therapy.[149-150]

At present, ECMO centers in the Philippines have invested in expensive equipment, facility, as well as in training personnel for cannulation, monitoring and performance of this therapy. To date, there are eight centers in the Philippines capable of conducting ECMO. These are the National Kidney and Transplant Institute, the Lung Center of the Philippines, the Philippine Heart Center, St. Luke's Medical Center, Asian Hospital and Medical Center, Makati Medical Center, The Medical City and Southern Philippines Medical Center.

Question 43 In patients with sepsis induced ARDS, should we use high frequency oscillatory ventilation (HFOV)?

We recommend against the use of high frequency oscillatory ventilation (HFOV) in sepsis-induced ARDS *(strong recommendation, moderate quality of evidence).*

The latest meta-analysis published in the American Thoracic Society (ATS) involving six trials supports the premise that HFOV does not reduce 30-day hospital mortality due to ARDS.[151]

Question 44 In patients with sepsis-induced ARDS, should we use non-invasive positive pressure ventilation (NPPV)?

Question 45 In patients with sepsis and hypoxic respiratory failure, should we use non-invasive ventilation (NIV)?

We recommend the use of non-invasive positive pressure ventilation (NPPV) in sepsis-induced mild ARDS (*strong recommendation, moderate quality of evidence***).**

We recommend the use of NPPV in early non-cardiogenic, hypoxic respiratory failure (*strong recommendation, moderate quality of evidence***).**

Prospective and retrospective cohort studies all corroborated that the success of NIV – measured as outcomes of decreasing invasive ventilation rates and shortening the length of ICU stay - is manifest only in mild ARDS.[152-156] NPPV should not be used as a means to delay intubation and mechanical ventilation in moderate to severe ARDS where invasive positive pressure ventilation is likely to improve outcomes

ACUTE KIDNEY INJURY

Question 46 In patients with sepsis and indication for renal replacement therapy, should we use hemodialysis versus peritoneal dialysis?

We suggest that either hemodialysis or peritoneal dialysis be used in patients with sepsis requiring acute renal replacement therapy (*conditional recommendation, very low quality of evidence).*

Remarks: Current literature does not support any significant difference in outcomes between peritoneal and hemodialysis or other extracorporeal blood purification techniques. This suggests that either peritoneal dialysis or hemodialysis may be a viable option. The choice remains to be individualized to the patient and the setting, largely based on availability of dialysis modality in the unit and the trained staff.

Current literature shows that either hemodialysis or peritoneal dialysis may be used in the setting of acute kidney injury in sepsis.[157-165] Therefore, the choice remains to be individualized to the patient and the local setting, stressing importance on cost, convenience, feasibility, availability of medical staff and equipment, as well as local expertise.

Question 47 In patients with sepsis and indication for renal replacement therapy, should we use continuous renal replacement therapy (CRRT) versus intermittent hemodialysis?

In patients with sepsis and acute kidney injury requiring acute renal replacement therapy, we suggest the use of intermittent hemodialysis. In facilities where continuous renal replacement therapy (CRRT) is available, this modality may be offered in particular to patients who are hemodynamically unstable *(conditional recommendation, low quality of evidence).*

Remarks: With the lack of difference in mortality between the two modalities, IRRT was favored over CRRT due to better access, available expertise, and lower cost.

For patients with sepsis and hemodynamic instability, we suggest the use of CRRT. If CRRT is unavailable in the unit, the use of sustained low efficiency dialysis may be considered in this population *(conditional recommendation, low quality of evidence).*

Remarks: CRRT and prolonged intermittent renal replacement therapy modalities such as sustained low efficiency dialysis (SLED) were considered for septic shock patients due to better hemodynamic tolerance.

Continuous renal replacement therapy (CRRT) has been proposed as an alternative to intermittent renal replacement therapy because of its theoretical advantage in the management of fluid balance in hemodynamically unstable patients due to slower rate of fluid removal[1]. Several studies[166-174] have shown an association with improved survival but the evidence is not robust and lacks statistical significance.

In the light of the markedly higher costs of CRRT, it was therefore suggested that in the absence of a survival benefit, intermittent hemodialysis or prolonged intermittent renal replacement therapies such as sustained low efficient dialysis (SLED) may be a suitable, more cost-effective treatment modality for AKI in critically ill patients.

Question 48 In patients with sepsis and acute kidney injury, should we initiate renal replacement therapy early (versus delayed renal replacement therapy)?

We suggest that initiation of renal replacement therapy be based on the presence of definitive indications for dialysis *(weak recommendation, low quality of evidence)*

Remarks: There is no clear advantage of early dialysis initiation versus late initiation in the setting of acute kidney injury. The potential harm related to secondary infections and additional cost pushes the balance of risk and benefit in favor of initiating RRT only when definitive indications are present in septic patients with AKI such as uremia, refractory acidosis, severe hyperkalemia, oliguria/anuria, and volume overload unresponsive to diuretic therapy.

The possibility of harm from increased risk of infection and catheter-related bleeding complications, plus the increased cost, pushes the balance of risk and benefit in favor of initiating RRT only when definitive indications are present.[175-186]

Question 49 In patients with sepsis and septic shock and hypoperfusion-induced lactic acidosis, should we use sodium bicarbonate therapy?

We do not recommend the routine use of sodium bicarbonate among septic patients with hypoperfusion-induced lactic acidosis (*strong recommendation, low quality of evidence***).**

Three recent studies failed to prove that sodium bicarbonate therapy offered any significant benefit in mortality or time to reversal of shock in patients with sepsis or septic shock[187-189]. The current evidence is of low quality. Larger randomized controlled studies are still needed.

BLOOD PURIFICATION

Question 50 In adult patients with sepsis, should we use hemoperfusion or other blood purification techniques?

We cannot recommend at this time any of the blood purification modalities (hemoperfusion, plasmapheresis, hemofiltration) for patients with sepsis or septic shock.

At this time, the panel cannot recommend any of the blood purification techniques due to their unclear benefit, the significant cost, and the limited access to these treatment modalities in the country.[190-192]

BLOOD TRANSFUSION

Question 51 In adult patients with sepsis, should we use restrictive transfusion strategy versus liberal transfusion?

We recommend restrictive transfusion strategy (transfusion threshold of Hgb of 7-8g/dL) over liberal transfusion strategy (Hgb of 9-10g/dL) *(strong recommendation, moderate quality of evidence).*

There is a limited number of studies on the use of a liberal versus restrictive transfusion strategy among adult patients with sepsis who have anemia. The latest Cochrane review on liberal versus restrictive transfusion included patients who were admitted at the ICU for sepsis or septic shock, however no subgroup analysis was done for this subset of patients.[193-195] Current evidence shows that a restrictive transfusion strategy is associated with neither benefit nor harm when compared to a liberal transfusion strategy in terms of mortality. Given the risk of infection, need for resources (e.g., blood products), as well as the additional costs, a restrictive transfusion strategy is preferred.

Question 52 In adult patients with sepsis, should we use erythropoiesis-stimulating agent (ESA) to treat anemia?

We cannot recommend the use of erythropoiesis-stimulating agent (ESA) to treat anemia among patients with sepsis *(weak recommendation, moderate quality of evidence).*

Studies on the use of erythropoiesis-stimulating agents (ESA) among septic patients with anemia are limited. Available evidence were from critically-ill patients which included a mix of medical and surgical patients.[196-200] Studies also differ on what type of ESA is used, with most of the studies using erythropoietin alpha or erythropoietin beta. There is also not enough evidence to clearly assess the benefit or harm with the use of erythropoietin among septic patients with anemia. Studies on critically-ill patients showed no advantage in terms of reducing transfusion requirements as well as mortality.

Question 53 In nonbleeding patients with sepsis and coagulation abnormalities, should we use prophylactic fresh frozen plasma (FFP)?

We cannot recommend the use of prophylactic fresh frozen plasma transfusion in adult patients with sepsis and coagulation abnormalities. *(weak recommendation, low quality of evidence).*

For patients with sepsis and abnormal coagulation test results who will undergo an invasive procedure but with no active bleeding, use of prophylactic frozen plasma transfusion should be guided by pre-procedure transfusion guidelines *(weak recommendation, very low quality of evidence).*

There is a paucity of studies investigating the use of prophylactic fresh frozen plasma transfusion among nonbleeding adult patients with sepsis and coagulation abnormalities.[201-203]

Question 54 In nonbleeding patients with sepsis and thrombocytopenia, should we use prophylactic platelet transfusion based on specific platelet levels?

For septic patients with no bleeding, we suggest prophylactic platelet transfusion (1) when counts are < 10,000 per cubic millimeter (10 × 10^9/L) in the absence of apparent bleeding, or (2) when counts are < 20,000 per cubic millimeter (20 × 10^9/L) if the patient has a significant risk of bleeding (*weak recommendation, very low quality of evidence).***

For septic patients with no bleeding and with platelet count < 150,000 per cubic millimeter (150 × 10^9/L) who will undergo an invasive procedure, use of prophylactic platelet transfusion should be guided by pre-procedure transfusion guidelines *(weak recommendation, very low quality of evidence).*

We found no studies which looked into the use of prophylactic platelet transfusion among patients with sepsis and septic shock. Existing data were from patients who will undergo invasive procedure, or have existing hematopoietic malignancies.[204-207]

IMMUNOGLOBULINS

Question 55 In adult patients with sepsis or septic shock, should we use intravenous immunoglobulins?

We do not recommend the use of standard polyclonal intravenous immunoglobulins in sepsis and septic shock (*strong recommendation, high quality of evidence***).**

The use of IgM-enriched intravenous immunoglobulins may be considered in patients with sepsis or septic shock with SOFA score of 12 or higher (*conditional recommendation, low quality of evidence***).**

The systemic inflammatory response linked to sepsis can cause a cascade of harmful effects, hypothesized to be brought about by the lipid-A component of the endotoxin molecule in gram-negative bacteremia. Intravenous immunoglobulin – both polyclonal and monoclonal – have been investigated to neutralize and inactivate toxins, and increase bactericidal activity.[208] Immunoglobulins have been proposed to have both inflammatory and immune properties that target the host response to infection.[209]

A meta-analysis and systematic review in 2013 using immunoglobulins investigated the all-cause mortality with the use of polyclonal IVIg. Among the low-risk of bias studies that included 945 patients, there was no difference in mortality among patients given immunoglobulin and those given placebo.[208] A 2019 study by Cui et al. focused on the use of IgM-enriched immunoglobulin, and results showed reduction in mortality, length of mechanical ventilation and ICU length of stay. Further subgroup analyses highlighted this benefit especially in patients with SOFA score of at least 12 or APACHE II score of at least 15.[209]

At present, only standard polyclonal IVIg is available in the Philippines. With cost of 5grams of IVIg varying from PhP12,000.00 to PhP28,000.00., a full three-day course for sepsis would range from PhP 36,000.00 to PhP 84,000.00. IgM-enriched IVIg is currently not available in the Philippines but may be imported under compassionate use.

ANTICOAGULANT THERAPY

Question 56 In adult patients with sepsis or septic shock, should we use anticoagulants as adjunctive treatment?

We cannot make any recommendation on the use of heparin for sepsis and septic shock.

A 2015 meta-analysis of nine randomized controlled trials (RCT) that used anticoagulants in sepsis did not demonstrate a significant difference in mortality. However, a shortened length of stay in the ICU and decreased duration of mechanical ventilation was reported among patients who received anticoagulation.[210] A 2016 multicenter prospective cohort study investigated if an effect would be observed in those with increased severity and in the presence of disseminated intravascular coagulation (DIC). In 505 patients with SOFA score of 13-17 and at high risk for DIC, there was decreased in-hospital mortality. No difference in mortality outcomes were observed for those with lower or higher SOFA scores. This data suggests that anticoagulants may be effective in sepsis among patients with DIC.[211] Additional studies are required to clarify the role of anticoagulation in the management of sepsis. Currently there is one such ongoing – the Heparin Anticoagulation in Septic Shock (HALO) trial.[212]

VENOUS THROMBOPROPHYLAXIS

Question 57 In adult patients with sepsis, should we use pharmacologic venous thromboembolism (VTE) prophylaxis?

We suggest the use of either pharmacologic or non-pharmacologic VTE prophylaxis in patients with

sepsis or septic shock *(strong recommendation, moderate quality of evidence).*

Remarks: Pharmacologic interventions were found to be more efficacious in preventing VTE among critically-ill patients, but with potential risk for bleeding. The decision to choose one over the other in patients with sepsis or septic shock should take into consideration other factors that could increase the patient's risk for bleeding.

The interaction between systemic inflammation and coagulation in sepsis may predispose patients with sepsis to venous thromboembolism (VTE). Both pharmacologic (i.e. UFH or LMWH) and non-pharmacologic/mechanical (i.e., intermittent pneumatic compression [IPC] or gradual compression stockings) thromboprophylaxis are used as prevention for VTE in sepsis. Currently, there are no RCTs directly comparing these interventions among septic patients.[213-214]

A meta-analysis by Alhazzani et al. in 2013 showed no difference in the rates of major bleeding and mortality with the use of heparin for thromboprophylaxis in the ICU setting.[213] However, the study did not compare pharmacologic versus non-pharmacologic VTE prophylactic interventions.

A network meta-analysis of RCTs by Park et. al in 2016[214] comparing UFH, LMWH, and IPC in both medical and surgical critically-ill patients showed lower risks for DVT in LMWH and UFH than IPC. Based on this analysis, pharmacological thromboprophylaxis seems more efficacious than mechanical thromboprophylaxis in critically-ill patients with a potential risk of bleeding.

Question 58 In patients with sepsis, should we use low molecular weight heparin (LMWH) versus unfractionated heparin (UFH) for VTE prophylaxis?

We recommend the use of LMWH over UFH for VTE prophylaxis in patients with sepsis or septic shock *(strong recommendation, moderate quality of evidence).*

In a meta-analysis by Wang et al. in 2014, heparin therapy was found to reduce 28-day mortality in adult patients with severe sepsis, with no increased risk of bleeding.[215] Similarly, the efficacy and safety of LMWH treatment in sepsis was evaluated in another meta-analysis by Fan et al. It showed that LMWH significantly reduced 28-day mortality and APACHE II score among septic patients. However, LMWH also significantly increased the bleeding events.[216]

Few studies compared LMWH with UFH as thromboprophylaxis in critically-ill patients, but data on patients with sepsis remain limited.[213,214,217,218]

In one meta-analysis that included adult medical or surgical critically-ill patients, results showed that compared to UFH, LMWH reduced rates of pulmonary embolism (PE) and symptomatic PE but not deep vein thrombosis (DVT), symptomatic DVT, major bleeding or mortality.[213] Results were consistent with another meta-analysis which showed that LWMH, compared with UFH, reduced the risk of any DVT.[217] Safety of LMWH was equal to UFH with no significant difference in the occurrence of major bleeding.[213,214,217,218] A prospective study was done on VTE incidence and risk factors in patients with severe sepsis and septic shock. Results suggest that sepsis may predispose patients to VTE. Acute VTE occurred in 42 of 113 (37.2%) patients with sepsis. All-cause 28-day mortality was 21.2%. The incidence of VTE did not differ between patients receiving LMWH compared with UFH.[214]

STRESS ULCER PROPHYLAXIS

Question 59 In adult patients with sepsis, should we use stress ulcer prophylaxis?

We recommend providing stress ulcer prophylaxis to patients with sepsis and septic shock (*strong recommendation, moderate quality of evidence***).**

Most of the published data on stress ulcer were on critically-ill patients or patients admitted in the intensive care unit rather than septic patients specifically.

Although the incidence of GI bleeding in the critically-ill is low, mortality in this population is high. In one study, the all-cause mortality rate was 48.5% ($p<0.001$).[219] Mortality attributable to GI bleeding among critically-ill patients was found to be 3.54%.[220]

Stress ulcer prophylaxis is the use of antacids, histamine-2 receptor antagonists (H2RAs), proton pump inhibitors and sucralfate to prevent GI bleeding. In a meta-analysis that included 20 trials (n= 1,971), the use of stress ulcer prophylaxis has been shown to reduce the risk of GI bleeding compared to no prophylaxis (RR 0.44; 95% CI: 0.28 to 0.68, p= 0.01, i^2= 48%).[221] There was no statistically significant difference in mortality (RR 1.00, 95% CI: 0.84 to 1.20, p= 0.87; i^2= 0%).[10]

There was only one study that included severe sepsis patients. This retrospective cohort study involving 70,862 severe sepsis patients in Japan showed that there were no significant differences in gastrointestinal bleeding (0.6% vs 0.5%; p = 0.208) and 30-day mortality (16.4% vs 16.9%; p = 0.249) between the stress ulcer prophylaxis group and control. However, the quality of evidence is low.[222]

Question 60 In adult patients with sepsis, should we use proton pump inhibitor (PPI) versus histamine 2 (H2) receptor antagonist for stress ulcer prophylaxis?

We suggest the use of proton pump inhibitors over histamine 2-receptor antagonists for stress ulcer prophylaxis *(weak recommendation, low quality of evidence).*

There were five meta-analyses published that compared proton pump inhibitors PPIs) to histamine 2 receptor antagonists (H_2RAs) in stress ulcer prophylaxis. Four meta-analyses concluded that PPIs are more efficacious than H_2RAs in reducing GI bleeding in critically-ill patients.[223-226] The most recent meta-analysis in 2017 included 14 trials and concluded that PPIs lowered the

risk of clinically important GI bleeding compared to H_2RAs (OR 0.38, 95% CI: 0.20, 0.73, p= 0.002, i2= 0%).[226] It was also found that PPIs probably increase pneumonia compared with H_2RAs (OR 1.27; 95% CI 0.96, 1.68). There was no significant difference in terms of mortality (OR = 0.83, 95% CI: 0.63, 1.10).

One earlier meta-analysis in 2010 that included seven randomized controlled trials (RCTs) with 936 patients concluded that there was no significant difference in stress-related upper GI bleeding, pneumonia and mortality among patients admitted in intensive care units.[227]

FEEDING AND NUTRITION

Question 61 In adult patients with sepsis or septic shock who can be fed enterally, should we use enteral feeding versus early total parenteral nutrition (TPN)?

We recommend the use of enteral nutrition in patients with sepsis who are hemodynamically stable and can be fed enterally (*strong recommendation, moderate quality of evidence*).

Overall, earlier studies did not show a clear benefit for EN over PN.[228-231] Two early systematic reviews, showed no difference in mortality and that EN was associated with less infectious complications.[232-233] EN was associated with fewer intra-abdominal infections (RR 0.26, 95% CI 0.07 to 0.89) and reduced sepsis (RR 0.59, 95% CI 0.37 to 0.95).[234] Only one study reported data for number of ventilator-free days. For gastrointestinal events, there was less vomiting (RR 3.42, 95% CI 1.15 to 10.16) and diarrhea (RR 2.17, 95% CI 1.72 to 2.75) with the use of PN but the evidence for this was low. No difference in incidence of abdominal distention was reported (RR 1.53, 95% CI 0.34 to 6.96).[234]

Current guidelines recommend the use of EN over PN in the critically-ill adult patient as summarized in Table 3. Both the American Society for Parenteral and Enteral Nutrition (ASPEN, McClave 2009) and the Surviving Sepsis Campaign (Singer 2016) recommend use of EN over PN due to the reduced infectious morbidity.[235-236] PN was not recommended alone or in conjunction with enteral feeding within the first seven days after the diagnosis of severe sepsis or septic shock. Rationale includes the potential risk of infection, and extra cost for PN in the absence of clinical benefit.[206] In the recent European Society of Parenteral and Enteral Nutrition (ESPEN, Singer 2018) guidelines, EN is recommended in septic patients who are hemodynamically stable. Advantages of EN include preserving gut integrity. If oral intake or EN is contraindicated - such as in ileus, or gastrointestinal bleeding - PN may be initiated within three to seven days day of admission. In the presence of shock, which may impair gut perfusion and potentially lead to bowel ischemia, EN is not recommended and should be delayed until the patient is more stable.[236] Based on the above evidence, we recommend EN over PN in septic patients who are hemodynamically stable and can be fed enterally. This is due primarily to the evidence on lower rates of infectious complications. However, in the presence of shock, where vasopressors or inotropes are administered, EN should be used with caution or even avoided until hemodynamics are stable. When EN is deemed not feasible within 3-7 days, PN may be considered after three days from admission in patients with sepsis or septic shock.

Question 62 In adult patients with sepsis or septic shock who can be fed enterally, should we give early enteral feeding (versus delayed enteral feeding)?

We suggest initiation of early enteral feeding within 24 to 48 hours in adult patients with sepsis or septic shock *(weak recommendation, low quality of evidence).*

Early enteral feeding is the initiation of feeding within the first 24 or 48 hours of ICU admission or injury. A meta-analysis by Doig et al. in 2009 involving 234 critically-ill patients showed that initiation of early enteral feeding is associated with a significant reduction in mortality (OR 0.34, 95% CI 0.14-0.85) and in the incidence of pneumonia (OR 0.31, 95% CI 0.12-0.78).[237]

However, only two studies were done to evaluate the impact of early enteral feeding among adult patients with sepsis and septic shock. A retrospective analysis was done by Koga et al. (2018) concluded that early enteral feeding is associated with reduced in-hospital mortality in septic sarcopenic patients (OR 0.18, 95% CI 0.05-0.71).[238]

Liu et al. in 2018 showed significantly lower levels of endotoxin and Th17 cells and significantly higher Treg cells (anti-inflammatory cells) in the early enteral feeding group, compared to the delayed enteral feeding group. The study also showed decreased length of hospital stay (17.94 days vs 22.04 days, P<0.05), decreased length of ICU stay (12.89 days vs 15.89 days, P<0.05) and shorter duration of mechanical ventilation (9.49 days vs 11.61 days, P<0.05). However, the 28-day mortality was the same between the early enteral feeding and the delayed enteral feeding group (RR 0.87, 95% CI 0.47- 1.59).[239]

The following are the posited physiologic effects that may also benefit septic patients when early enteral feeding is initiated: modulation of insulin resistance and inflammatory response, prevention of intestinal permeability and maintenance of gut integrity.[240-241]

The major guidelines recognize the importance, and recommend the use, of early enteral feeding. The ASPEN guidelines (2016) recommend that early enteral feeding should be initiated within 24–48 hours in the critically-ill patient who is unable to maintain volitional intake.[242] In addition, the ESPEN guidelines (2018) recommend initiation of early enteral feeding in critically-ill adult patients when oral intake is possible within 48 hours.[236] Lastly, the Surviving Sepsis Campaign (2016) also suggests starting early enteral feeding in patients with sepsis or septic shock .[206]

Question 63 In adult patients with sepsis or septic shock who can be fed enterally, should we give supplemental parenteral nutrition on top of enteral feeding?

We suggest against routine supplemental parenteral nutrition on top of in patients on enteral nutrition in patients with sepsis or septic shock (*weak recommendation, very low quality of evidence*).

For patients who are not able to meet their requirements fully through the enteral route for a week, we suggest supplemental parenteral nutrition to increase caloric and protein delivery (*weak recommendation, low quality of evidence*).

Given the uncertain mortality benefit and the potential risk for infection, we recommend against the routine administration of supplemental PN on patients already on enteral feeding.

Then again, there may be special situations when the addition of PN may be considered. It has been established in studies that patients who have calorie deficits, such as critically-ill patients, will have more mechanical ventilator days, ICU stay and mortality as shown in the study by Villet in 2005.[243] A high-calorie deficit was also shown to have increased incidence of ARDS, sepsis and pressure sores in the 2006 study by Dvir.[244] The study by Faisy in 2011 showed that a greater calorie deficit was related to staphylococcal ventilator-acquired pneumonia.[245]

As to the timing of supplemental PN, a study by Casaer in 2011 showed that late-initiation of PN was associated with greater likelihood of early ICU discharge (OR 1.06; 95% CI, 1.00 to 1.13), hospital discharge (OR 1.06; 95% CI, 1.00, 1.13), and also exhibited fewer ICU infections (22.8% vs. 26.2%, *p=0.008*), and lower incidence of cholestasis (P<0.001).[246] The late-initiation group had a relative reduction of 9.7% in the proportion of patients requiring more than two days of mechanical ventilation (P=0.006), a median reduction of three days in the duration of renal-replacement therapy (P=0.008), and a mean reduction in health care costs of €1,110 (about US$1,600) (P=0.04). Mortality rates were similar with both early and late initiation of PN.

The American Society for Parenteral and Enteral Nutrition (ASPEN) and Society of Critical Care Medicine (SCCM) recommends that in patients with low or high nutrition risk, the use of supplemental PN should be considered after 7–10 days if the patient is unable to meet >60% of energy and protein requirements by the enteral route alone. Initiating supplemental PN prior to this 7- to 10-day period in critically-ill patients does not improve outcomes and may in fact be detrimental to the patient, with the evidence for this at moderate quality. On the other hand, the Surviving Sepsis Campaign Guidelines recommend against the administration of parenteral nutrition alone or in combination with enteral feeds. Rather, SSC strongly recommends initiation of IV glucose and advance enteral feeds as tolerated over the first seven days in patients with sepsis or septic shock for whom early enteral feeding is not feasible. Similarly, European Society of Clinical Nutrition and Metabolism (ESPEN) strongly recommends (96% agreement) initiating PN on a case-by-case basis for critically-ill adult patients who do not tolerate full dose EN during the first week in the ICU.

Question 64 In adult patients with sepsis who are fed enterally, should we give prokinetic agents to prevent feeding intolerance?

We do not recommend the use of prokinetics for prevention of feeding intolerance in patients with sepsis or septic shock *(strong recommendation, low quality of evidence).*

Intolerance to enteral nutrition or feeding intolerance (FI) may be seen in the critically-ill patient. Prevalence of FI ranges from 2% to 75% with a pooled proportion of 38.3%.[247] The most recent definition of FI came from the European Society of Parenteral and Enteral Nutrition guidelines, wherein a cumulative value of >500ml GRV in a six-hour period is the threshold for delaying feeding due to intolerance.[236]

A 2016 meta-analysis by Lewis et al. included 13 trials on prokinetics (both erythromycin and metoclopramide) compared to placebo in critically-ill adult patients.[248] In this review, the included RCTs defined FI as GRV of greater than 150 ml, to 250 ml. Ten of the trials included critically-ill patients who did not have FI at baseline while the remaining three studies looked at patients with pre-existing FI. When all studies are included, the use of prokinetics decreased FI (RR 0.73, 95% CI 0.55 to 0.97) and reduced the risk of developing high GRV (RR 0.69 95% CI 0.52 to 0.91).[9] Subgroup analysis to detect efficacy for prevention of FI alone, however, showed no significant benefit (RR 0.62 95% CI 0.31 to 1.22). No effect on risk of pneumonia (RR 1.00, 95% CI 0.76 to 1.32), ICU length of stay (MD 1.24, 95% CI 5.21 to 7.68), diarrhea (RR 1.82, 95% CI 0.67 to 4.91), vomiting (RR 0.74, 95% CI 0.49 to 1.12) or mortality (RR 0.97, 95% CI 0.81 to 1.16) was observed for prokinetics in general.[248]

It is important to note that prokinetics should be used with caution in patients with potential underlying gut obstruction. Other drawbacks with the use of erythromycin include tachyphylaxis, antibiotic resistance and cardiac toxicity. Erythromycin may also interact with warfarin, digoxin, theophylline, carbamazepine and cyclosporine, and is contraindicated in patients with macrolide allergy.[249] Adverse effects of metoclopramide use include extrapyramidal symptoms, nausea and cardiac arrythmia.[249, 250]

Question 65 In adult patients with sepsis or septic shock who are fed enterally, should we give prokinetic agents to manage/treat feeding intolerance?

We suggest the use of prokinetics (intravenous metoclopramide) to treat feeding intolerance in patients with sepsis or septic shock (*conditional recommendation, low quality of evidence*).

In the context of treating pre-existing feeding intolerance (FI), the use of prokinetics was studied in a meta-analysis by Lewis et al. where three RCTs were included in a subgroup analysis. The study on Metoclopramide, however, did not specify the dose and duration of Metoclopramide. In the two remaining studies, erythromycin 200mg IV single dose was used while in the other RCT, 250mg IV of erythromycin every 6 hours was given. The use of prokinetics combined did reduce FI in those with pre-existing gastroparesis (RR 0.70, 95 % CI 0.52, 0.96; P = 0.03).[248] As mentioned in the previous, there was no significant benefit with the use of prokinetics on risk of pneumonia, ICU length of stay, mortality, diarrhea nor vomiting.[248]

Question 66 In adult patients with sepsis who have enteral tubes, should we use post-pyloric tube feeding versus gastric tube feeding?

We recommend that enteral nutrition be initiated via the gastric route (*strong recommendation, moderate quality of evidence*).

Post-pyloric tube feeding may be considered in patients with feeding intolerance not improved with prokinetics, those with documented aspiration, or are at high risk for aspiration (*weak recommendation, moderate quality of evidence*).

Both the American Society for Parenteral and Enteral Nutrition (ASPEN, 2016) and European Society of Parenteral and Enteral Nutrition (ESPEN, 2018) recommend that enteral nutrition be initiated via gastric route as standard approach. Although post-pyloric feeding was associated with a decrease in ventilator-associated pneumonia, there was no benefit in mortality. Additionally, post-pyloric tube insertion may be associated with time delay, and requires expertise. Gastric EN is also considered more physiologic. In the presence of feeding intolerance not improved with prokinetics, as well as for patients with high risk of aspiration, post-pyloric feeding is recommended.[235,236] In the Surviving Sepsis Campaign, the placement of post-pyloric feeding tube in septic patients with feeding intolerance is considered for patients at high risk for aspiration: these include patients with history of recurrent aspiration, severe gastroparesis, feeding intolerance, on mechanical ventilation, neurologic deficits, or refractory to medical treatment.[235,236] A systematic review and meta-analysis done by the authors showed that post-pyloric tube feeding reduced the risk of pneumonia compared to gastric tube feeding (RR = 0.75, 95% CI 0.59–0.94) with a 2.5% absolute risk reduction.[206]

Question 67 In adult patients with sepsis, should we follow a standard feeding protocol?

We suggest implementation of standard feeding protocols to improve delivery of target calories and protein to patients with sepsis and septic shock *(conditional recommendation, very low quality of evidence).*

A feeding protocol refers to an algorithm enabling the bedside nurse to start, monitor and adjust the delivery of enteral tube feedings to patients not capable of oral food intake.[251] The benefits of enteral nutrition are often faced with the challenges of actual delivery. Feeding protocols have been proposed to initiate and increase nutrient delivery for patients, since calorie and protein deficits are related to adverse outcomes. Clinicians often may overlook nutritional management in patients with sepsis/septic shock, hence a protocol may provide an action to manage feeding issues.

Evidence-based algorithms are used as basis for selection of standards for feeding protocols. In the studies reviewed, protocols usually employ one or more of the following: volume-based feeding (versus rate-based feeding) or compensatory feeding, top-down management (nurse or dietitian-driven, computerized protocol), increasing or supplementing protein, initiation of supplemental parenteral nutrition, provision of prokinetics, or advancement to post pyloric feeding.

One algorithm employed multiple evidence-based components (*Figure 6*).[252] In terms of outcomes- in-hospital mortality, 28-day mortality, 60-day mortality and ICU mortality were decreased by feeding protocols. There is also a significant decrease in diarrhea and GI bleeding with feeding protocol. [252]

In the ASPEN SCCM Guideline (2016), it is recommended that enteral feeding protocols be designed and implemented to increase the overall percentage of goal calories provided (Quality of Evidence: Moderate to High). [242] Based on expert consensus, it is suggested that use of a volume-based feeding protocol or a top-down multi-strategy protocol be considered (Quality of evidence: Moderate).

SEDATION AND ANALGESIA

Question 68 In mechanically-ventilated patients with sepsis or septic shock who require sedation, should we use continuous versus intermittent sedation?

We suggest either continuous or intermittent sedation in mechanically-ventilated patients with sepsis or septic shock to achieve protocol-based sedation targets *(conditional recommendation, low quality of evidence).*

The 2018 Clinical Practice Guidelines[253] for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU (PADIS) has been endorsed by multiple international societies.

A prospective cohort study by Shehabi et al. found that early deep sedation was an independent predictor of delayed time to extubation and increased long-term mortality.[206] This supports the use of strategies to reduce sedative use and the duration of mechanical ventilation. Bedside protocols that incorporate sedation scales likely result in improved outcomes; however, the benefit depends on the existing local culture and practice.

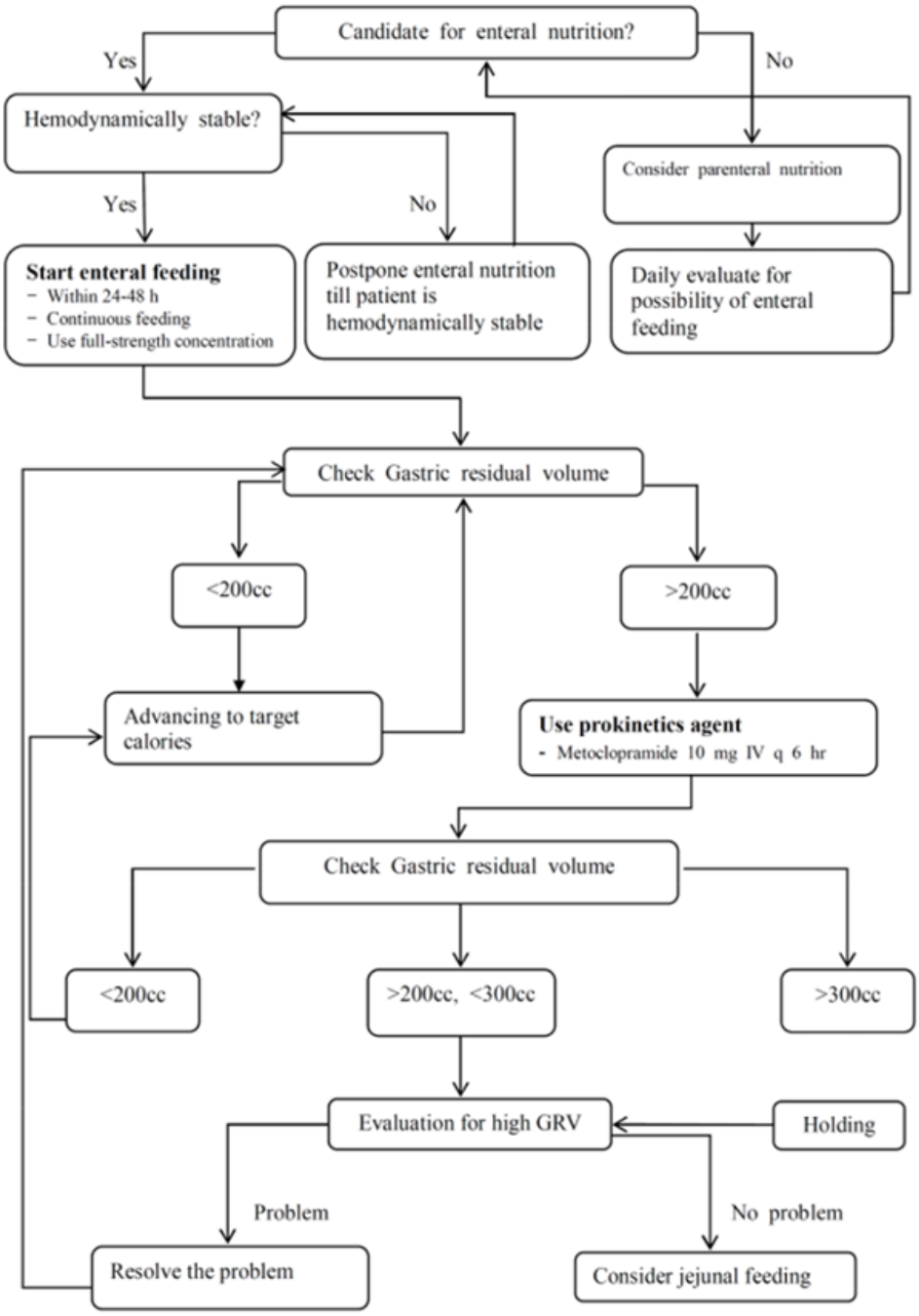


Figure 6. Enteral Feeding Protocol (from reference 252)

In a multicenter RCT study by Mehta et al., where protocolized sedation with daily sedation interruption (DSI) was compared with usual protocolized sedation, authors found no advantage to DSI when patients were managed with a sedation protocol. DSI did not reduce the duration of mechanical ventilation and offered no additional benefits for patients. In fact, the study suggested that DSI may have increased both sedation and analgesic use and a higher perceived nurse workload.[254]

Question 69 In patients with sepsis or septic shock, should we give nonbenzodiazepines (versus other agents) for sedation?

We suggest the use of short-acting non-benzodiazepine sedatives to address agitation and the need for adequate sedation, to achieve protocol-based sedation targets *(conditional recommendation, low quality of evidence).*

Fraser et al. compared the use of different benzodiazepines and non-benzodiazepines of ICU patients in a meta-analysis[255] of six RCTs in 2012. They reported that compared to a benzodiazepine sedative strategy, a non-benzodiazepine sedative strategy was associated with a shorter ICU length of stay (mean difference [MD] 1.64 days lower, 95% CI 2.57 to 0.7 days lower) and duration of mechanical ventilation (MD 1.87 days lower, 95% CI 2.51 to 1.22 days lower) but a similar prevalence of delirium and short-term mortality rate. The non-benzodiazepines reviewed in the meta-analysis were dexmedetomidine and propofol.

Question 70 In patients with sepsis or septic shock who are in pain, should we give opioids (versus other agents) for analgesia?

We suggest using either low-dose opioid or non-opioid analgesics in patients with sepsis or septic shock to achieve analgesia endpoints (*conditional recommendation, low quality of evidence***).**

We suggest following an individualized approach to pain management in patients with sepsis or septic shock (*best practice statement***).**

We suggest referral to a pain management specialist as needed (*best practice statement***).**

There is a lack of studies on the use of analgesics for patients with sepsis or septic shock, so the recommendations for general ICU patients were

adopted. In the 2018 PADIS guidelines[253], opioid analgesics like fentanyl, morphine and meperidine are still the mainstay for addressing pain in the general ICU despite the numerous potential side effects they carry and the safety concerns that surround their use.

Zhang et al. conducted a retrospective cohort study on hospitalized patients with sepsis in 2017 and reported a crude 28-day mortality rate of 10.35% (Hazard Ratio 6.239; 95% Hazard Ratio Confidence Limits 4.407–8.831) for patients treated with opioids during their hospitalization compared to non-opioids patients (2.40%).[256] Their study suggested that opioid use in hospitalized patients with a diagnosis of sepsis is associated with increased mortality but randomized clinical studies are still warranted. Thus, it is ideal to adopt a multimodal analgesia approach that may reduce opioid use.

CONCLUSION

This first Philippine Sepsis & Septic Shock Guidelines document has established the definition and clinical criteria to be used in diagnosing sepsis and septic shock in the Philippines. It has presented comprehensive, well-researched, evidence-based recommendations with regard to screening, diagnosis, treatment, and prognostication of sepsis and septic shock in immunocompetent adults, and is expected to reduce practice variability among healthcare practitioners and improve clinical outcomes in patients with sepsis and septic shock.

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