CLINICAL PRACTICE GUIDELINES FOR SEPSIS AND SEPTIC SHOCK IN ADULTS IN THE PHILIPPINES 2020

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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.[3] It now defines "sepsis" as a life-threatening organ dysfunction caused by a dysregulated host response to infection.[3] 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.

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.

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 GRADE Evidence Profiles that supported these recommendations are listed in the Supplement 2 of the Clinical Practice Guidelines for Sepsis and Septic Shock in Adults in the Philippines 2020.

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).*

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*).

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).*

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*).

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).*

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.

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*).

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).*

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)*.

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).*

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).*

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

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. 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).

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.

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).*

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).*

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).*

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).*

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).*

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).*

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).*

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*).

Question 22: In patients with sepsis or septic shock, should low venoarterial 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.

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).*

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.

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).*

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).*

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).*

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; [1] or may temporarily suspend vancomycin infusion or switch to intermittent infusion method.

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).*

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).*

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.

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.

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*).

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).*

ACUTE RESPIRATORY FAILURE

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

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).*

Table Q36.1. 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 Q36.2. 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

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 inspiratory pause in a relaxed patient should be considered.

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).*

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).*

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)*.

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).*

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).*

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).*

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).*

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*).

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.

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.

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.

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*).

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.

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).*

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).*

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).*

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).*

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*).

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.

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).*

Remark: 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.

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).*

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*).

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).*

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*).

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).*

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*).

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).*

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*).

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*).

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).*

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).*

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).*

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

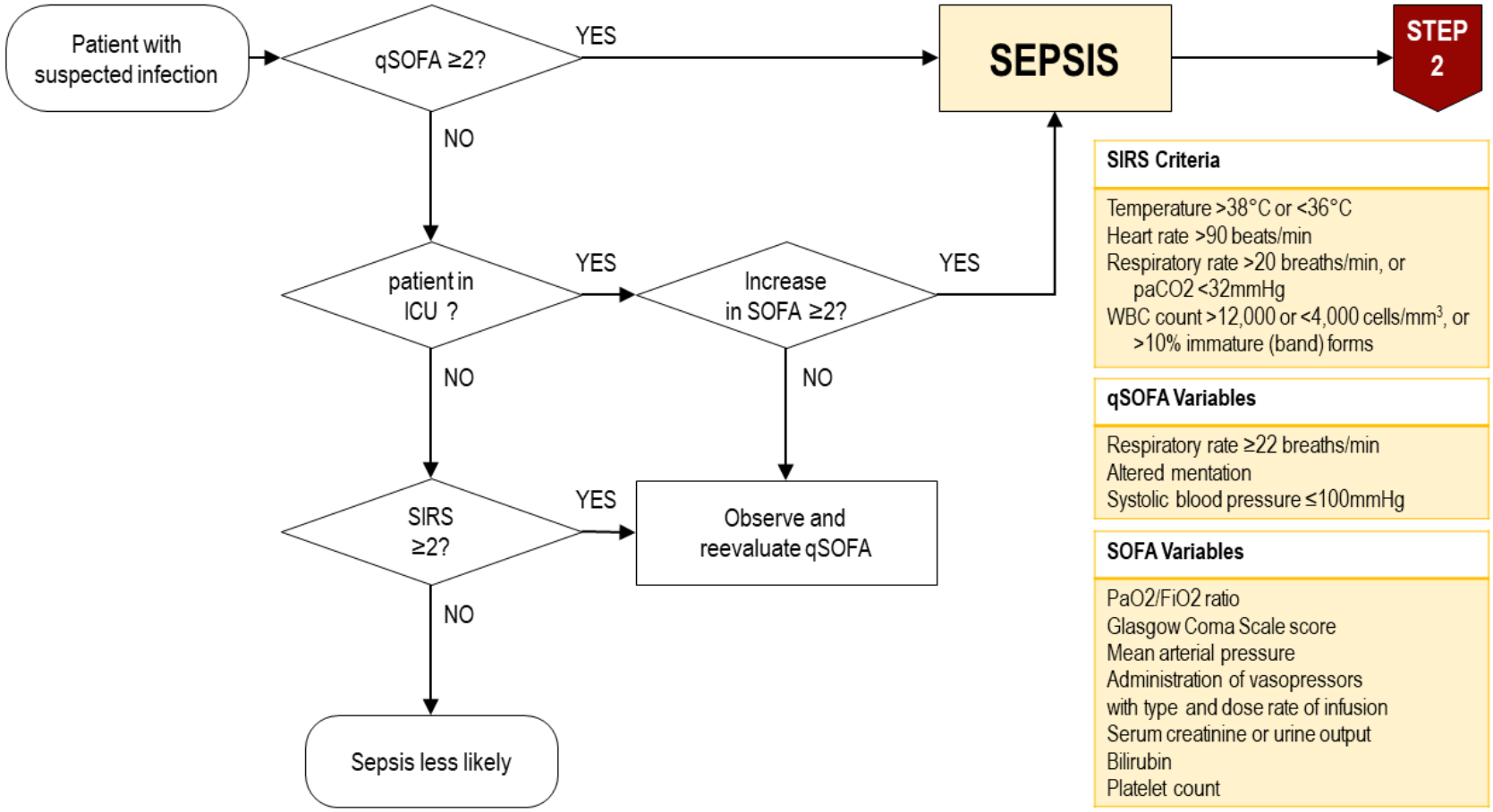
We suggest using either low-dose opioid or non-opioid analgesics in patients with sepsis or septic shock to achieve analgesia endpoints (*conditional recommendation, low quality of evidence*).

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*).

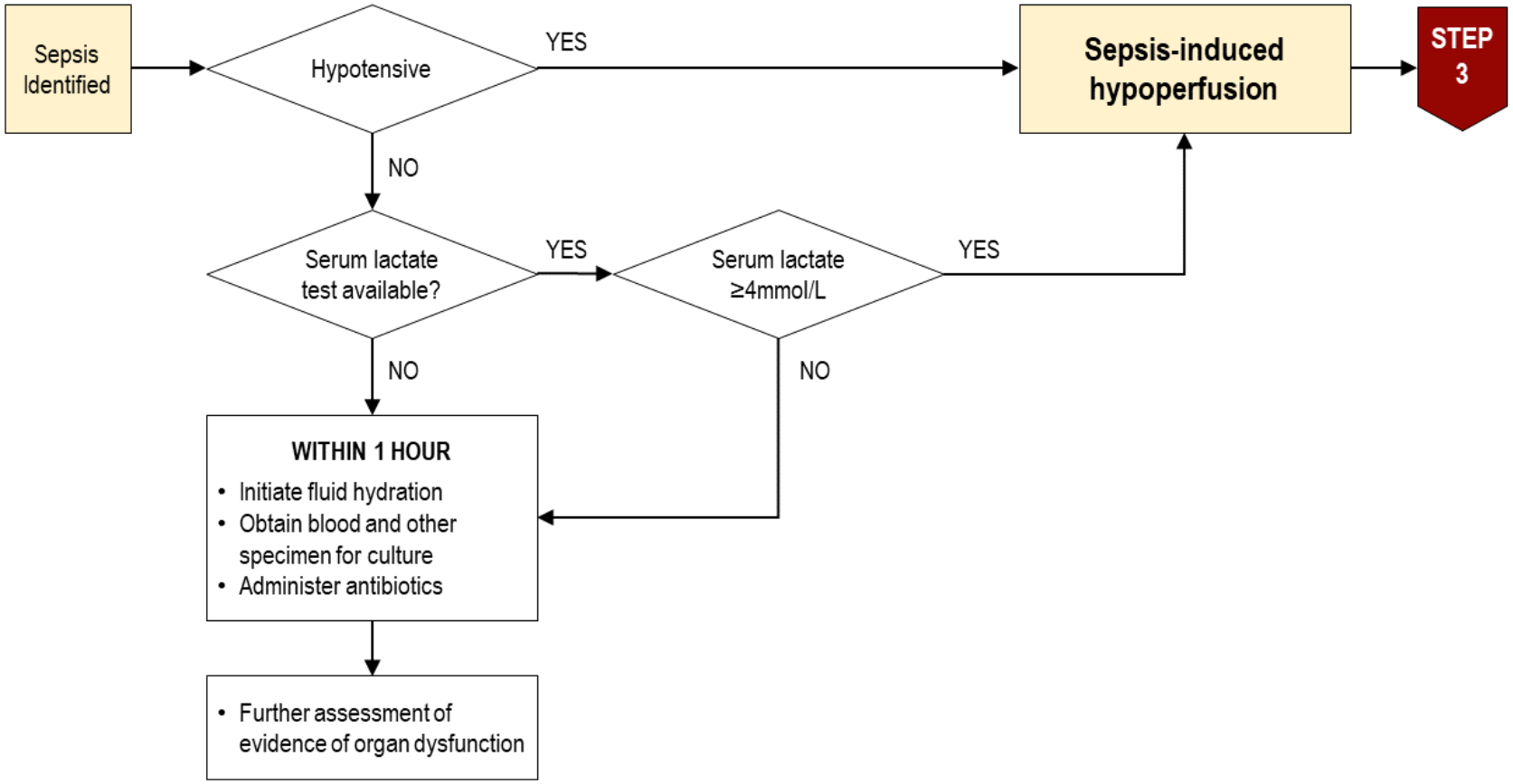
Clinical Algorithm for the Identification and Management of Sepsis and Septic Shock

STEP 1: Identification of Patients with Sepsis

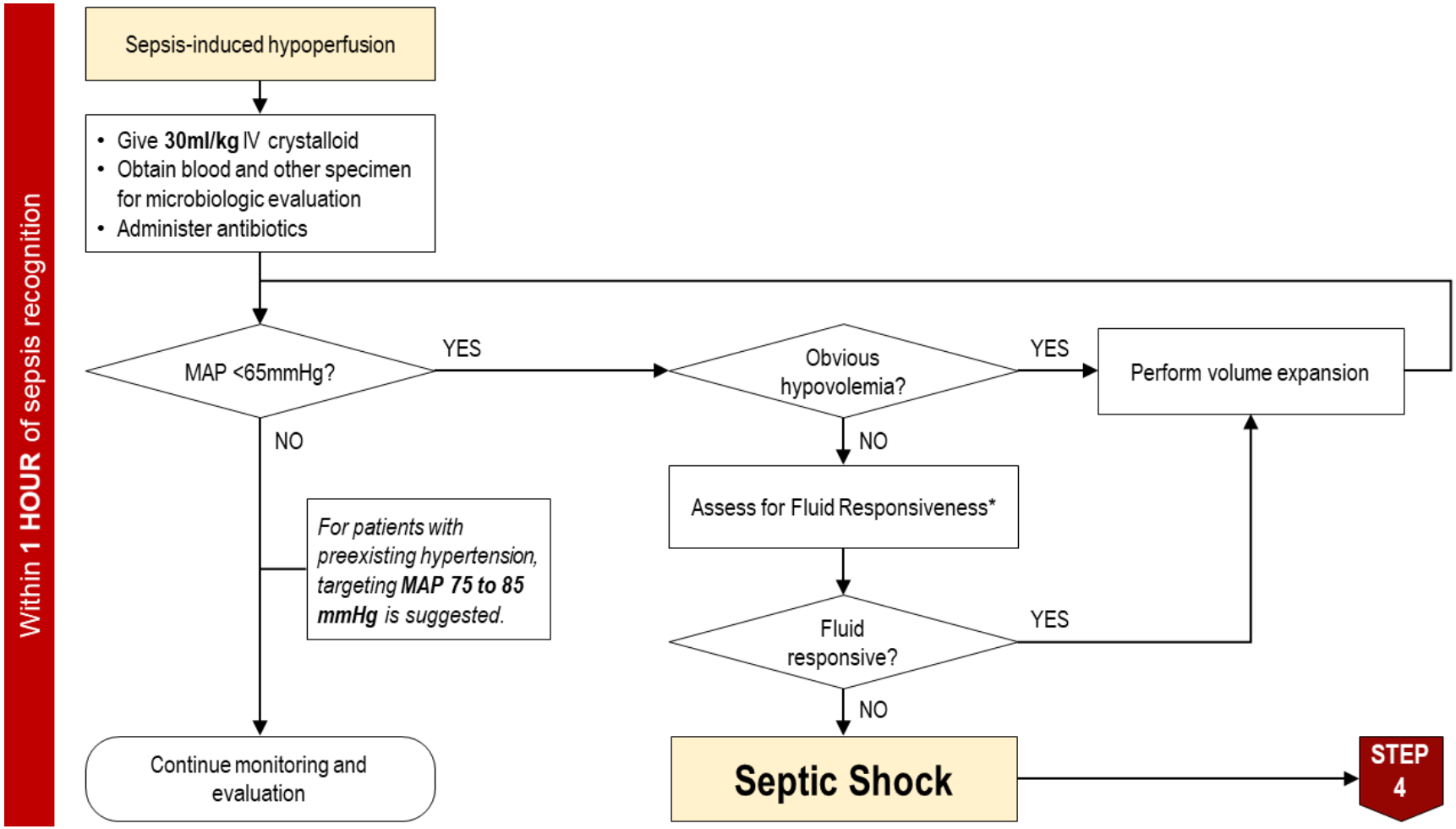


Note: The baseline SOFA score is assumed to be zero unless the patient is known to have preexisting (acute or chronic) organ dysfunction before the onset of infection.

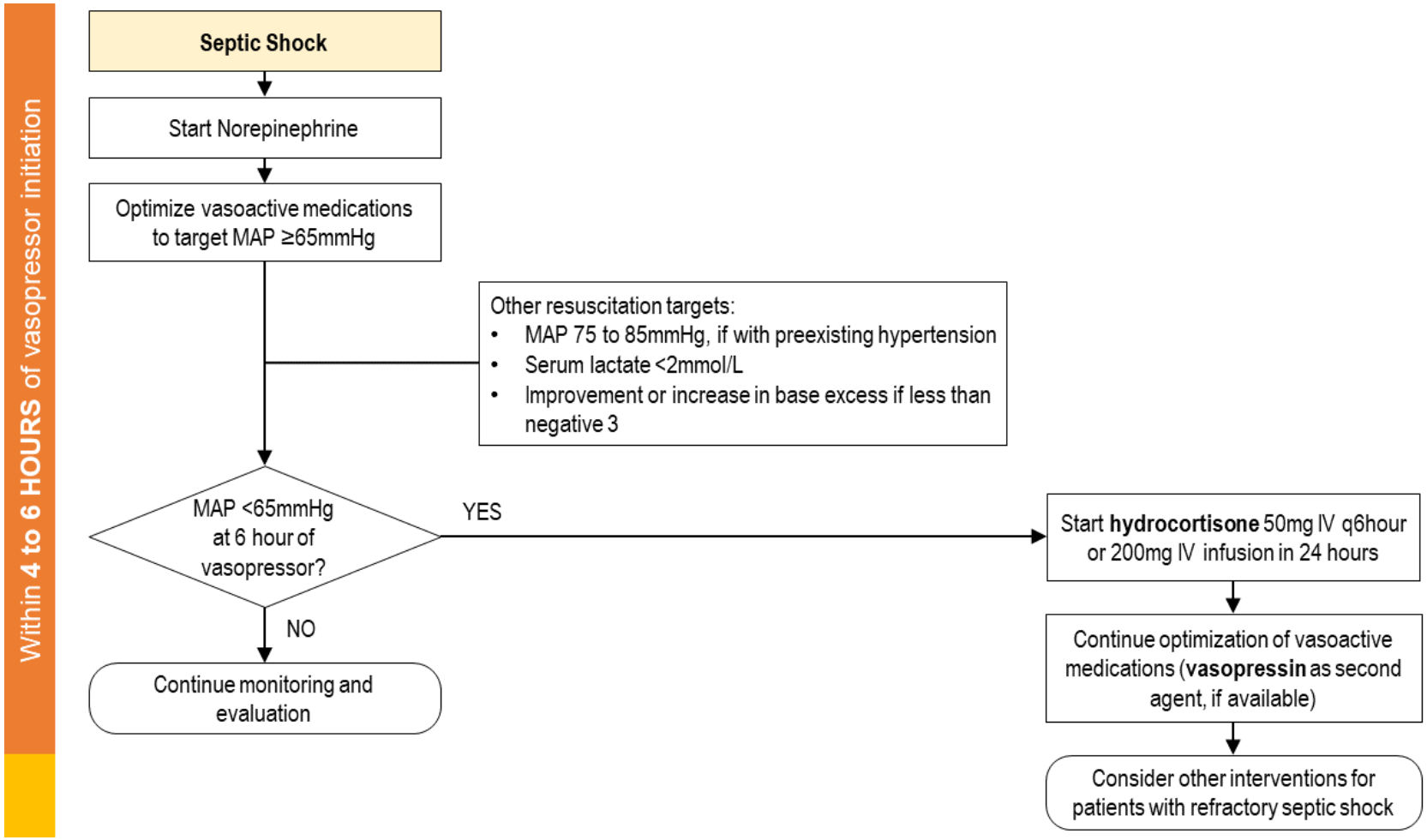
STEP 2: Initial Management of Patients with Sepsis and Identification of Patients with Sepsis



STEP 3: Initial Management of Patients with Sepsis-induced hypoperfusion and Identification of Patients with Septic Shock



STEP 4: Management of Patients with Septic Shock



Guide to Assessment of Fluid Responsiveness

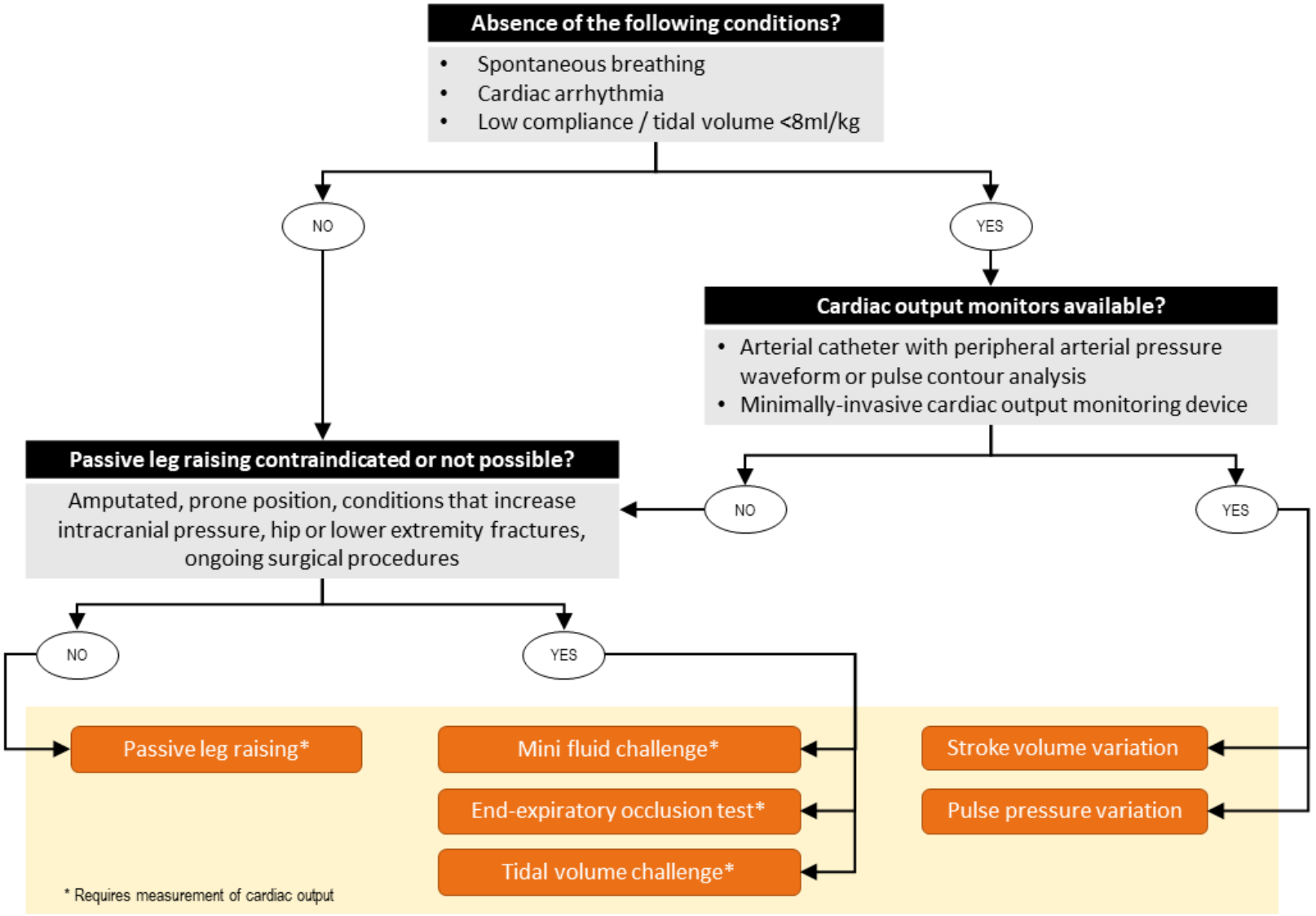


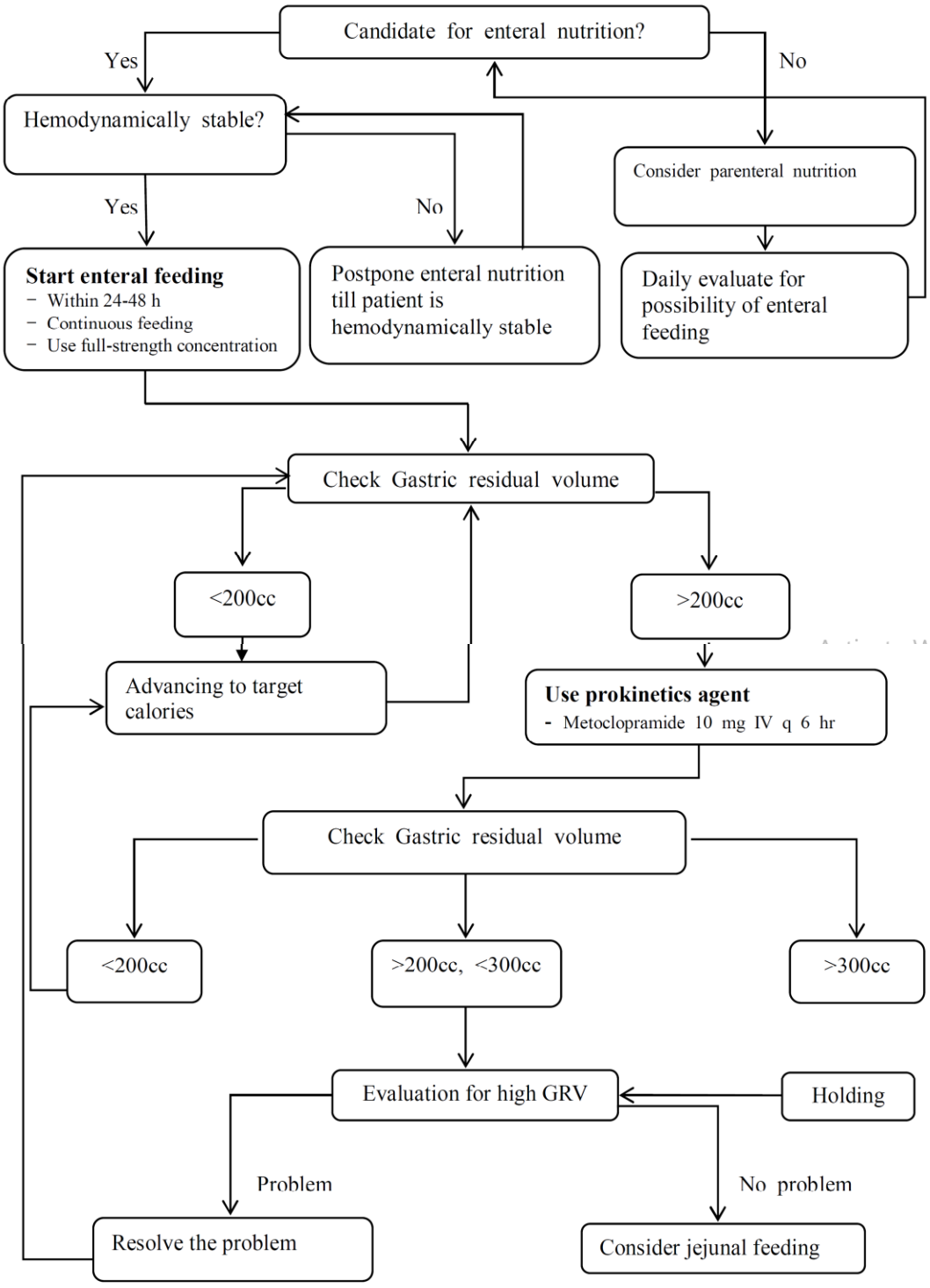
Table 1. Summary of Methods predicting Fluid Responsiveness with diagnostic threshold and limitations

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 semirecumbent 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.

References:
Monnet X, Teboul JL. Assessment of fluid responsiveness: recent advances. Current opinion in critical care. 2018 Jun 1;24(3):190-5.4.
Georges D, de Courson H, Lanchon R, Sesay M, Nouette-Gaulain K, Biais M. End-expiratory occlusion maneuver to predict fluid responsiveness in the intensive care unit: an echocardiographic study. Critical Care. 2018 Dec;22(1):32.
Jalil BA, Cavallazzi R. Predicting fluid responsiveness: a review of literature and a guide for the clinician. The American journal of emergency medicine. 2018 Nov 1;36(11):2093-102.

Sample Standard Feeding Protocol



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