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

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Abbreviations

ACCP	American College of Chest Physicians
ACTH	Adrenocorticotropic hormone
AKI	Acute Kidney Injury
ARDS	Acute Respiratory Distress Syndrome
ATS	American Thoracic Society
AUC	Area Under the Curve
AUROC	Area Under the Receiver Operating Characteristic
AVP	Arginine vasopressin
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
CIRCI	Critical illness-related corticosteroid insufficiency
CIV	Continuous intravenous infusion
CO2	Carbon dioxide
COI	Conflict of Interest
CPG	Clinical Practice Guideline
CRT	Capillary Refill Time
CVP	Central Venous Pressure
CO	Cardiac Output
CRRT	Continuous Renal Replacement Therapy
DOH	Department of Health
ED	Emergency Department
EEO	End-expiratory occlusion
EGDT	Early Goal-Directed Therapy
EN	Enteral Nutrition
ESA	Erythropoiesis Stimulating Agent
ESICM	European Society of Intensive Care Medicine
GRADE	Grades of Recommendation, Assessment, Development and Evaluation
GRV	Gastric residual volume
HAP	Hospital-acquired pneumonia
H2R	Histamine 2 Receptor
HES	Hydroxyethyl Starch
Hgb	Hemoglobin
HPA	Hypothalamic-Pituitary-Adrenal
ICU	Intensive Care Unit
IDSA	Infectious Diseases Society of America
IHD	Intermittent Hemodialysis
IIV	Intermittent intravenous infusion
LGT	Lactate-guided Therapy
LMWH	Low-molecular weight heparin
MAP	Mean Arterial Pressure
MD	Mean Difference
MRSA	Methicillin-resistant *Staphylococcus aureus*
MSSA	Methicillin-susceptible *Staphylococcus aureus*

NLR	Negative likelihood ratio
NNT	Number needed to treat
OR	Odds Ratio
PA	Pulmonary Artery
PAC	Pulmonary Artery Catheter
PCT	Procalcitonin
PD	Peritoneal Dialysis
PEEP	Positive end-expiratory pressure
PICO	Population, Intervention, Control, Outcome
PK/PD	Pharmacokinetic/Pharmacodynamic
PLR	plain Lactated Ringer's solution
PLR	Positive likelihood ratio
PLR	Passive Leg Raise
PN	Parenteral Nutrition
POCL	Point-of-care Lactate
PPI	Proton pump inhibitor
PPV	Pulse pressure variation
qSOFA	Quick Sequential Organ Failure Assessment
RCT	Randomized controlled trial
RR	Risk Ratio / Relative Risk
RRT	Renal Replacement Therapy
SCCM	Society of Critical Care Medicine
SCVO2	Central venous oxygen saturation
SIRS	Systemic inflammatory response syndrome
SIS	Surgical Infection Society
Sn	Sensitivity
SOFA	Sequential Organ Failure Assessment
Sp	Specificity
SSC	Surviving Sepsis Campaign
SVV	Stroke volume variation
TTE	Transthoracic Echocardiogram
TWG	Technical Working Group
UFH	Unfractionated Heparin
VAP	Ventilator-associated pneumonia
VILI	Ventilator-induced Lung Injury
VTE	Venous Thromboembolism
VTI	Velocity time index
WBC	White blood cell

Introduction

This Clinical Practice Guideline (CPG) 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.

Disease Burden

While the World Health Organization (WHO) states that "the global epidemiological burden of sepsis is difficult to ascertain," the disease 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.[1] 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.[2] On the other hand, the incidence of septic shock was estimated at 11 per 100,000. It is one of the leading causes of death among hospitalized patients with case fatality rate of 30% for sepsis, and as high as 80% for septic shock.

Sepsis and Septic Shock Definitions

The Sepsis-3 definitions drastically changed the paradigm for sepsis with its publication in the Journal of the American Medical Association (JAMA) in February 2016.[3]

Old Definition

Before the Sepsis-3 publication, sepsis was known as a syndrome resulting from the host response to infection. Its definition was based on the systemic inflammatory response syndrome (SIRS) developing from documented or suspected infection.[2] The SIRS criteria needed to have at least two (2) of the following:
- Temperature >38°C or <36°C
- heart rate >90 beats per minute
- respiratory rate >20 breaths per minute or $PaCO_2$ <32 mmHg
- white blood cell (WBC) count >12,000 cells/mm^3 or <4,000 cells/mm^3, or >10% immature (band) forms

Severe sepsis was defined as sepsis with organ dysfunction, hypotension or signs of hypoperfusion, while septic shock was identified as sepsis occurring with acute circulatory failure, presenting with persistent hypotension even after adequate fluid resuscitation, and requiring vasopressor treatment.[2]

New Definition

The Third International Consensus 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." This new definition excludes a number of patients who were previously thought would be "septic." On the other hand, septic shock is now defined as a subset of sepsis with circulatory and cellular/metabolic dysfunction associated with a higher risk of mortality.

Issues on Sepsis Definition

The updates were appreciated but certain quarters raised concerns about the new definitions, including the lack of prospective validation in a "generalizable population," the fact that data were almost exclusively derived from high-income countries and adults, and the possibility of delayed diagnosis and treatment due to the focus on organ dysfunction. These concerns regarding validity and applicability, led to incomplete uptake of the definitions. A study conducted in a private tertiary teaching hospital in the Philippines showed that only 30% are using the Sepsis-3 criteria, with a large fraction (63%) still using the SIRS-based criteria.[4] The remaining number of respondents did not provide a definite response. Further assessment showed that three years after Sepsis-3 publication, only 26% of physician-respondents correctly defined sepsis, and less than 7% correctly defined septic shock.[4]

On the other hand, the SIRS criteria were also criticized because they were very non-specific, and bordering on unhelpful, inaccurate sepsis identification.[5] SIRS criteria was panned for being too focused on inflammation which may be present in many hospitalized patients, including those who never develop infection and never incur adverse outcomes.

Variations in Care

In reference to the multidisciplinary issues in sepsis and the slow catch-up in terms of medical practice, this guideline now aims to resolve the confusion that arose from the Sepsis-3 Consensus and to assist health care practitioners in the diagnosis and management of sepsis to reduce variations in practice. As an example, there is evidence that around 14% of 175 physicians surveyed in a private tertiary hospital admit to continue using hydroxyethylstarch (HES) even after the international Surviving Sepsis Campaign Guidelines recommended against its use.[4] A third of physicians do not even consider giving steroids to septic shock patients.

In another study conducted in a tertiary teaching public hospital in the Philippines, compliance with the 2016 Surviving Sepsis Campaign (SSC) Guidelines was assessed in 224 patients admitted for sepsis and septic shock in 2017.[6] Of these, only 36% (81/224) were given initial bolus of intravenous fluid for resuscitation and only 52 of 81 (64%) were given the prescribed 30ml/kg volume. Less than a fourth (24%) of patients received empiric antibiotics within an hour of sepsis recognition.

New Evidence

In the recent years, there has been a rapid turnover of evidence for sepsis relating to the type of fluid for resuscitation, the volume of fluid for resuscitation, assessment of fluid responsiveness using dynamic parameters, the pharmacokinetic and pharmacodynamic optimization of antibiotic dosing, corticosteroids in septic shock, different strategies to address acute respiratory failure, and blood purification techniques, to name a few. The emergence of new information called for thorough review of new data for validity and applicability in our setting.

Feasibility Issues

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. It is not only important that old and new evidence be considered but cost, availability and access to resources in different settings as well.

Potential impact of the guideline

There is great possibility to reduce the baseline case-fatality rates for sepsis and septic shock with implementation of evidence-based recommendations. However, the wide variation in the current diagnosis and treatment of sepsis and septic shock poses a challenge to the attainment of these reductions. The inconsistency of therapeutic maneuvers, while largely supported by prior evidence, documentation and clinical experience, results in a wide range of outcomes and events. This 2020 clinical practice guideline for sepsis and septic shock reviewed and consolidated current best evidence for specific issues of concern in practice, towards the improvement of patient care and the constancy of management in sepsis and septic shock.

Objectives of the Clinical Practice Guideline

1. To establish the definition and clinical criteria to be used to diagnose 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
3. To reduce practice variability among healthcare practitioners and improve clinical outcomes in patients with sepsis and septic shock

Scope and Target Population

This clinical practice guideline will cover sepsis in non-pregnant, immunocompetent adults.

Target Audience and Users

In line with its purpose, this clinical practice guideline is intended for use among physicians of various disciplines, medical practitioners, mentors and trainees, to include the following:

1. Primary care physicians (general practitioners, general internists, family medicine practitioners)
2. Emergency medicine physicians
3. Intensivists
4. Relevant subspecialty physicians
5. Medical educators and mentors
6. Medical interns and students

Methodology

Selection and Organization of Committee Members

The preparation of the guidelines began with the formation of the Steering Committee that consisted of two co-chairpersons, both specialists in infectious diseases. Additional members in the committee included one Emergency Medicine physician, one Internal Medicine-Pulmonary Medicine specialist, and one Critical Care specialist. 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)/Evidence Review Experts and the Consensus Panel.

Formulation of Clinical Questions

Some of the questions from the 2016 SSC guidelines were selected for updating based on knowledge of new research data and publications. Controversial topics, and questions on diagnostic and therapeutic interventions which were considered challenging in terms of resource availability were also selected.

The TWG assisted the Steering Committee in the formulation of the guideline questions structured in PICO format (population, intervention, control, and outcome). A complete list of the guideline questions in PICO format is presented in **Supplementary Material 1**.

Search Strategy and Data Synthesis

A multidisciplinary TWG was formed to collect and synthesize data. The TWG divided the questions into several sections with at least two persons designated to work on each question. An independent literature search was performed for each guideline question. Electronic search was conducted in at least two databases such as Cochrane Database, MEDLINE, HERDIN, and clinical trial registries using the search terms *sepsis, severe sepsis,* and *septic shock,* combined with pertinent keywords based on the question (**Supplementary Material 2**). Related articles were also examined. Unpublished data were sourced, especially from local researches.   Assistance from librarians, clinical epidemiologists, and statisticians was sought.

It should be noted that for this guideline, the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) Framework/Approach was used to determine the quality of evidence (**Table 1**). This approach enabled the TWG to identify the strengths and limitations of the body of evidence, and prepare the evidence summaries that were presented to the Steering Committee and the Consensus Panel.

The synthesized data and initial draft of the recommendations were presented at the 49th Annual Convention of the Philippine Society for Microbiology and Infectious Diseases on November 14, 2019 at the SMX Convention Center to solicit public reaction, opinion and recommendations. The event was attended by Infectious Diseases specialists, internists, general practitioners, nurses, medical technologists, and other allied medical professionals.

Consensus Development

A multidisciplinary Consensus Panel was created to vote 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. Again, the GRADE Approach was used to guide the strength of recommendations (**Table 2**).

Table 1. Quality of Evidence using Grades of Recommendation, Assessment, Development and Evaluation (GRADE) Framework

QUALITY OF EVIDENCE		STUDY DESIGN	LOWER IF:	HIGHER IF:
High	Further research is very unlikely to change confidence in the estimate of effect	Randomized controlled studies (RCTs)	Study quality: Poor quality of implementation of RCT	Stronger association: Large magnitude effect, no plausible confounders
Moderate	Further research is likely to have impact in confidence in the estimate of effect	Downgraded RCTs or upgraded observational studies	Inconsistency of results: Indirectness: Different population, intervention, outcomes	Very large magnitude of effect, no major threats to validity
Low	Further research is very likely to have an important impact on the confidence in the estimate of effect	Observational studies	Imprecise results: High probability of reporting bias	Dose response gradient
Very low	Any estimate of effect is very uncertain	Case series or expert opinion		

Reference: Guyatt GH, OXman AD, Vist GE et al. GRADE: am emerging consensus on rating quality of evidence and strength of recommendations. BMJ, 2008;336:924-926.

Table 2. Implications of Strength of Recommendations to Patients, Clinicians and Policy Makers using GRADE Approach

STRENGTH OF RECOMMENDATION		IMPLICATIONS OF THE RECOMMENDATIONS		
		TO PATIENTS	*TO CLINICIANS*	*TO POLICY MAKERS*
Strong	The benefits outweighed the harm. There are no cost or access issues for the general population.	Most people in the situation would want the recommended course of action and only very few would not; request for discussion if the intervention is not offered	Most patients should receive the recommended course of action	The recommendation can be adopted as a policy in most situations
Weak	Best available evidence is very low to low quality; Magnitude of benefits or risks is uncertain or closely balanced for the general population and applicable to a specific group, population or setting; Benefits may not warrant the cost or resource requirements in all settings	Most people in the situation would want the recommended course of action, but many would not	Different choices are appropriate for different patients, and clinician must help patients arrive at a management decision consistent with patient's values and preferences	Policy making will require substantial debate and involvement of any stakeholders

Reference: Guyatt GH et al. Going from evidence to recommendations. BMJ. 2008 May 10;336(7652):1049-1051.

Representatives from relevant groups and societies participated in a two-day meeting held on November 23 and 30, 2019 in order to discuss controversial topics and questions with new recommendations. A copy of the evidence summaries and draft recommendations were sent through email at least a week before the meetings. The voting process was conducted manually using flags to indicate agreement, disagreement, or abstention. Consensus required at least 75% of votes. Each participating society or group was entitled to one vote, even if it had two or more representatives. 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.

The rest of the guideline questions, together with unresolved ones were sent for voting via the Modified Delphi Technique. A copy of the evidence summaries and draft recommendations were sent through email and voting was accomplished using Google forms. A tally of the votes was generated and downloaded to an excel spreadsheet. Consensus for this part was agreement of at least 75%.

Guideline Dissemination

The final recommendations are to be presented in scientific fora (including the annual conventions in 2020 of the Philippine College of Physicians and Philippine College of Emergency Medicine) to target the expected end-users of the guidelines. Printed copies of the guidelines will be distributed to medical societies and posted online for wider coverage.

Guideline Monitoring and Updating

The impact of this Clinical Practice Guideline will be assessed by monitoring adherence to the recommendations, and more importantly, evaluate clinical outcomes such as reduction in mortality. In order to achieve this, PSMID will continue to spearhead the process and collaborate with societies, institutions, and hospitals in the country, and will use a modified version of the Center for Disease Control and Prevention (CDC)'s March 2018 "Hospital Toolkit for Adult Sepsis Surveillance."[9] The Steering Committee plans to update the guideline after five (5) years, or earlier, considering new evidence, availability of resources and interventions, and the results of the monitoring.

Sponsorship and Funding

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Management of Conflicts of Interest (COI)

All members of the Steering Committee, Technical Working Group, and the Consensus Panel were asked to disclose all potential conflicts of interest (COIs), including financial. Identified COIs were adjudicated by the Steering Committee, and the TWG chair and co-chair. COIs were managed by limiting the discussion and voting ability of panel members with relevant COI to a particular question or topic. Likewise, TWG members with relevant COI to a particular topic were re-assigned to work on another question.

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Health Questions Covered by this Guideline

A complete list of PICO – formatted questions is included in **Supplementary Material 1**.

1. Should we use the Sepsis-3 definition over the old sepsis definition?
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?
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)?
4. Should we use the Sepsis-3 definition and clinical criteria to diagnose patients with septic shock?
5. Should we routinely request blood cultures from patients suspected with sepsis or septic shock?
6. Should we use procalcitonin to diagnose adult patients with sepsis?
7. In patients with sepsis or septic shock, should we use crystalloids for initial fluid resuscitation versus colloid solutions?
8. In patients with sepsis or septic shock, should we use balanced crystalloids for initial fluid resuscitation versus normal saline solution?
9. In patients with sepsis or septic shock, should we use crystalloids supplemented with albumin for initial fluid resuscitation versus crystalloids alone?
10. In patients with sepsis or septic shock, should we initiate fluid resuscitation within an hour of sepsis recognition?
11. In patients with sepsis or septic shock, should we give 30ml/kg intravenous fluid bolus for initial fluid resuscitation?
12. In patients with sepsis or septic shock, should we limit the volume of intravenous fluids?
13. In patients with sepsis or septic shock, should deresuscitation be performed after hemodynamic stabilization?
14. In patients with sepsis and septic shock, should we use dynamic parameters versus static parameters to predict fluid responsiveness?
15. In patients with septic shock requiring vasopressors, should we use norepinephrine over other agents?
16. In patients with septic shock requiring a second vasopressor, which agent should be added to norepinephrine?
17. In patients with septic shock and persistent hypoperfusion, should we use dobutamine?
18. In patients with septic shock requiring vasopressors, should we target a mean arterial pressure (MAP) of at least 65mmHg versus higher MAP?
19. Should we aim for normalization of lactate levels during resuscitation of patients with sepsis?
20. Can we use base excess (as surrogate) to diagnose hyperlactatemia?
21. Should we use base excess to monitor fluid resuscitation?
22. In patients with sepsis, should low venoarterial CO2 gap be used as a goal for resuscitation?
23. In patients with sepsis, should we use a pulmonary artery catheter (PAC)?
24. In patients with sepsis, should we use empiric broad-spectrum antibiotic(s)?
25. In patients with sepsis, should we use empiric combination antimicrobial therapy versus monotherapy?

26. In patients with sepsis or septic shock, should we empirically start antibiotics for methicillin-resistant *Staphylococcus aureus (MRSA)*?
27. In patients with sepsis or septic shock, should empiric antibiotics be administered within the first hour of sepsis recognition?
28. In patients with sepsis, should we implement pharmacokinetic dosing optimization for each antimicrobial?
29. In patients with sepsis or septic shock who are receiving antimicrobial agents, should we de-escalate antimicrobial therapy once culture sensitivities are determined?
30. In patients with sepsis or septic shock, should we recommend longer versus shorter duration of antibiotic therapy?
31. In patients with sepsis or septic shock, should we use procalcitonin to support discontinuation or de-escalation of antibiotic therapy?
32. In patients with sepsis or septic shock, should we attempt early source control?
33. In adult patients with septic shock, should we use intravenous corticosteroids?
34. In adult patients with septic shock, should we use intermittent (bolus) versus continuous intravenous corticosteroids?
35. In patients with sepsis, should we aim for intensive glycemic control?
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?
37. In sepsis patients who are mechanically ventilated but without ARDS, should we use lung protective ventilation strategies?
38. In patients with sepsis-induced ARDS, should we use conservative fluid strategy?
39. In patients with sepsis-induced ARDS on MV, should we do recruitment maneuvers?
40. In patients with sepsis-induced ARDS on MV should we use prone positioning?
41. In patients with sepsis-induced ARDS on MV should we use neuromuscular blocking agents?
42. In patients with sepsis-induced ARDS, should we use extracorporeal membrane oxygenation (ECMO) treatment?
43. In patients with sepsis induced ARDS, should we use high frequency oscillatory ventilation (HFOV)?
44. In patients with sepsis-induced ARDS, should we use non-invasive positive pressure ventilation?
45. In patients with sepsis and hypoxic respiratory failure, should we use non-invasive ventilation (NIV)?
46. In patients with sepsis and indication for renal replacement therapy, should we use hemodialysis versus peritoneal dialysis?
47. In patients with sepsis and indication for renal replacement therapy, should we use continuous renal replacement therapy (CRRT) versus intermittent hemodialysis?
48. In patients with sepsis and acute kidney injury, should we initiate renal replacement therapy early (versus delayed renal replacement therapy)?
49. In patients with sepsis and septic shock and hypoperfusion-induced lactic acidosis, should we use sodium bicarbonate therapy?

50. In adult patients with sepsis, should we use hemoperfusion or other blood purification techniques?
51. In adult patients with sepsis, should we use restrictive transfusion strategy versus liberal transfusion?
52. In adult patients with sepsis, should we use erythropoiesis-stimulating agent (ESA) to treat anemia?
53. In nonbleeding patients with sepsis and coagulation abnormalities, should we use prophylactic fresh frozen plasma (FFP)?
54. In nonbleeding patients with sepsis and thrombocytopenia, should we use prophylactic platelet transfusion based on specific platelet levels?
55. In adult patients with sepsis or septic shock, should we use intravenous immunoglobulins?
56. In adult patients with sepsis or septic shock, should we use anticoagulants as adjunctive treatment?
57. In adult patients with sepsis, should we use pharmacologic venous thromboembolism (VTE) prophylaxis?
58. In patients with sepsis, should we use low molecular weight heparin (LMWH) versus unfractionated heparin (UFH) for VTE prophylaxis?
59. In adult patients with sepsis, should we use stress ulcer prophylaxis?
60. In adult patients with sepsis, should we use proton pump inhibitor (PPI) versus histamine 2 (H2) receptor antagonist for stress ulcer prophylaxis?
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)?
62. In adult patients with sepsis or septic shock who can be fed enterally, should we give early enteral feeding (versus delayed enteral feeding)?
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?
64. In adult patients with sepsis who are fed enterally, should we give prokinetic agents to prevent feeding intolerance?
65. In adult patients with sepsis or septic shock who are fed enterally, should we give prokinetic agents to manage/treat feeding intolerance?
66. In adult patients with sepsis who have enteral tubes, should we use post-pyloric tube feeding versus gastric tube feeding?
67. In adult patients with sepsis, should we follow a standard feeding protocol?
68. In mechanically-ventilated patients with sepsis or septic shock who require sedation, should we use continuous versus intermittent sedation?
69. In patients with sepsis or septic shock, should we give nonbenzodiazepines (versus other agents) for sedation?
70. In patients with sepsis or septic shock who are in pain, should we give opioids (versus other agents) for analgesia?

SEPSIS DEFINITION AND CRITERIA FOR DIAGNOSIS

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

Recommendation

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).*

Summary of Evidence

Before the Sepsis-3 definitions of sepsis and septic shock were published, the old definition of sepsis consisted of at least two criteria of the systemic inflammatory response syndrome (SIRS) plus infection, whether suspected or proven. The term "severe sepsis" was previously defined as sepsis that was complicated by organ dysfunction, hypotension responsive to fluids, or signs of hypoperfusion. Similarly, the term septic shock used to refer to sepsis with acute circulatory failure, particularly with a persistence of hypotension that was unresponsive to adequate fluid resuscitation, and needing vasopressor treatment.[1]

The 2016 Sepsis-3 consensus revised the definition of sepsis to "a life-threatening organ dysfunction caused by a dysregulated host response to infection," which was actually 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.[2]

The new sepsis definition has led to the formulation of new clinical criteria for sepsis, again by the 2016 Sepsis-3 Consensus. Because there is no gold standard for it, patient cases with infection but were "really sick" were used as the proxy for "septic" patients, as recently defined. In the study of Seymour, twenty-one (21) variables that were clinically relevant and assessible, tested for association with in-hospital mortality, were statistically analyzed by multivariable logistic regression.[3] This led to the new criteria for sepsis outside of the intensive care unit (ICU) and was called the quick sequential organ failure assessment (qSOFA) score, which consisted of: (1) respiratory rate $\geq$ 22 breaths per minute, (2) altered mentation, and (3) systolic blood pressure $\leq$ 100 mmHg. Outside the ICU, the presence of two or more qSOFA points would be a reasonable prompt to consider sepsis.   On the other hand, the SOFA score was much better in the ICU, particularly a change of $\geq$ 2 from the baseline SOFA score. These criteria would prompt one to consider sepsis in ICU patients.

It is important to note that because sepsis has no gold standard diagnostic test, Question 1 was answered by testing the sensitivity and specificity of the clinical criteria that represented the new sepsis definition, particularly the components of the qSOFA or the SOFA in those patients with suspected or proven infection. Simply put, the summaries of evidence for Questions 2 and 3 were used to support the recommendation for Question 1.

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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?

Recommendations

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$\geq$2, be observed for progression to sepsis *(strong recommendation, moderate quality evidence.)*

Summary of Evidence

Sepsis definition of a life-threatening infection prompted search for studies that looked into the ability of qSOFA and SIRS to predict mortality among patients suspected of infection. A meta-analysis that included 38 studies demonstrated qSOFA sensitivity of 51.2% outside the ICU, and 46.7% in the emergency department (ED).[1] On the other hand, specificity was 79.6% outside the ICU, and 81.3% in the ED. In contrast, SIRS had a sensitivity of 82.2% outside the ICU, and 83.6% in the ED. The specificity of SIRS criteria though was only 34.2% outside the ICU, and 30.6% in the ED. The above evidence shows that SIRS is more sensitive but less specific in predicting mortality compared to qSOFA. This means that the use of the SIRS criteria for sepsis screening identifies a significant number of cases that were not at high risk of mortality, and were probably infections exhibiting appropriate inflammatory response.

The same meta-analysis also looked into more clinically useful positive and negative likelihood ratios. The positive likelihood ratio (PLR) for mortality was 2.50 outside the ICU and 2.49 in the ED, when using qSOFA. This is much higher compared to PLR values 1.25

and 1.20 outside the ICU and in the ED, respectively using the SIRS criteria. A higher PLR means that the probability of dying is higher for patients with qSOFA score ≥2 compared to patients who satisfy at least two SIRS criteria. On the other hand, the negative likelihood ratio (NLR) for mortality using qSOFA was 0.61 outside the ICU, and 0.66 in the ED. The NLR of SIRS criteria was lower at 0.52 outside the ICU, and 0.54 in the ED. This means that the probability of dying is lower for patients who do not meet at least two of the SIRS criteria compared to those whose qSOFA scores are <2.

Another meta-analysis of ten studies which included a total of 229,480 patients showed similar results.[2] The sensitivity in predicting mortality ranged from 19.9% (n=184,875) to 97.4% (n=214) for SIRS, and 22.8% (n=184,875) to 90.0% (n=152) for qSOFA, in favor of SIRS. Then again, specificity ranged from 2.3% (n=214) to 90.2% (n=184,875) for SIRS, and 27.4% (n=214) to 91.3% (n=8,871) for qSOFA, in favor of qSOFA.

In terms of predicting risk for organ dysfunction, several studies showed sensitivities ranging from 71% to 91% for SIRS, and 28% to 66% for qSOFA.[3-7] Conversely, specificities were only 29% to 69% for SIRS, and 88% to 97% for qSOFA. This only shows that qSOFA more reliably predicts organ dysfunction compared to SIRS.

For sepsis diagnosis, a systematic review by Serafim and colleagues investigated the diagnostic accuracy of both SIRS and qSOFA using a combination of clinical, laboratory and microbiologic criteria as gold standard.[2] Included studies reported sensitivities of 39.5% (n=152) to 88.3% (n=30,677) for SIRS, and 10.2% (n=8,871) to 54.4% for qSOFA, again favoring the old SIRS criteria. Only one study that included 152 patients reported specificity at 84.4% for SIRS and 97.3% for qSOFA, in favor of the new Sepsis-3 clinical criteria.

A study conducted in a tertiary teaching private hospital in the Philippines also looked into the diagnostic accuracy of both SIRS and qSOFA for predicting mortality and diagnosing sepsis in 295 subjects. SIRS was found to be more sensitive in diagnosing sepsis at 73.7% versus 46.3%, while qSOFA was more specific at 95.5% versus 60%.[8]

Foreign and local studies consistently demonstrate higher sensitivity of SIRS, but better specificity of qSOFA in terms of (1) predicting mortality, (2) predicting organ dysfunction, and (3) diagnosing sepsis.[1-13] For either SIRS or qSOFA, mortality increase progressively with each criterion satisfied or point increased.[3,14] The use of qSOFA appears to be attractive in terms of diagnosing true, life-threatening infections – as the third International Consensus defined Sepsis. 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. Using qSOFA as a primary clinical tool will allow clinicians to easily identify patients at high risk of mortality using only four clinical variables. 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.
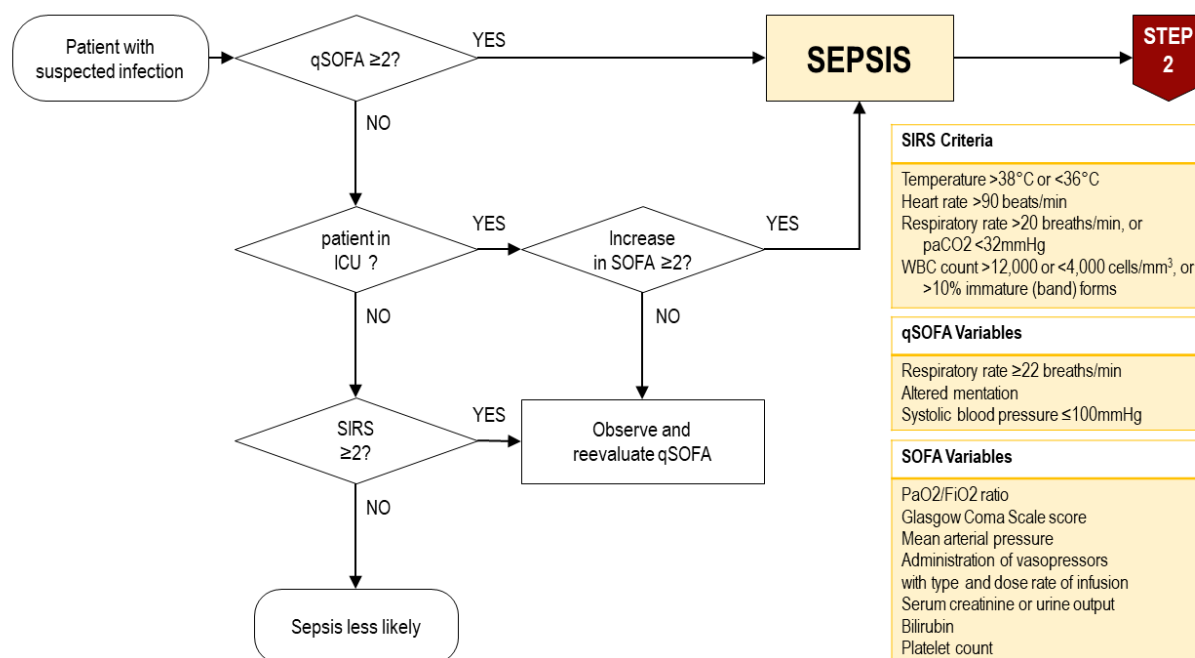
Note: The baseline SOFA score is assumed to be zero unless the patient is known to have preexisting (acute or chronic) organ dysfunction before the onset of infection.

Figure 1. Identification of patients with sepsis

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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)?

Recommendation

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).*

Summary of Evidence

The Sequential Organ Failure Assessment (SOFA) is a mortality prediction score that is based on the degree of dysfunction of six organ systems. The SOFA score can be used to determine the level of organ dysfunction and mortality risk in ICU patients. The scores can be used in several ways, including (1) as individual scores for each organ to determine the progression of organ dysfunction, (2) as a sum of scores on a single intensive care unit (ICU) day, or (3) as a sum of the worst scores during the ICU stay.[1]

The SOFA variables were selected by a working group of the European Society of Intensive Care Medicine in the 1990s.[1] In the initial validation study, 1449 patients from 40 ICUs in 16 countries were enrolled over a period of one month. The study found that the SOFA score had a good correlation to organ dysfunction/failure in critically-ill patients.[2]

In a retrospective cohort analysis done in 182 Australian and New Zealand ICUs, SOFA score demonstrated significantly greater discrimination (crude AUROC 0.753 [99& CI 0.750-0.757]) for in-hospital mortality than SIRS (crude AUROC 0.589 [99% CI 0.585-0.593]) criteria, and even qSOFA (crude AUROC 0.607 [99% CI 0.603-0.611]).[3] It also outperformed SIRS and qSOFA in terms of the composite secondary outcome of in-hospital mortality or ICU length of stay of three days or longer. Findings were consistent for both outcomes in multiple sensitivity analyses. These findings suggest that compared to SOFA, SIRS criteria and qSOFA have inferior utility for predicting mortality in an ICU setting.

It is important to note that the meta-analysis of 38 studies showed that when qSOFA was used in the ICU, its sensitivity for mortality was 87.2%, better than when it was used outside the ICU, where its sensitivity was only 51.2%.[4] Conversely, the specificity of qSOFA for mortality in the ICU was inferior at only 33.3% compared to outside the ICU, where it was 81.3%. Similarly, the sensitivity of the SIRS criteria for mortality was 93.9% in the ICU, which was slightly better than the 82.2% when it was used outside the ICU. The specificity of SIRS criteria for mortality though was only 13% in the ICU, and was much better at 34.2% outside the ICU.

A ten-year retrospective cohort study conducted in a teaching hospital in Thailand involved 2350 mixed sepsis patients, and it compared the performance of SOFA, qSOFA and SIRS for predicting mortality and organ failure.[5] The SOFA score presented the best discrimination with an AUROC of 0.839. The AUC of SOFA score for hospital mortality was significantly higher than qSOFA (AUC 0.814, p=0.003) and SIRS (AUC 0.587, p<0.0001). It was shown that SOFA is a superior prognostic tool for predicting mortality and organ failure than qSOFA and SIRS criteria among sepsis patients admitted to the ICU.

Seymour et al., on the other hand, conducted a retrospective study to assess the clinical criteria for sepsis for the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3).[6] This involved 148,907 electronic health records encounters with suspected infection from January 2010 to December 2012 at 12 hospitals in southwestern Pennsylvania. Their findings showed that among ICU encounters with suspected infection, the predictive validity for in-hospital mortality of SOFA was statistically greater than SIRS and qSOFA, supporting its use in clinical criteria for sepsis.

All of the above demonstrate why SOFA scoring is preferred over qSOFA in the identification of sepsis inside the ICU. 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.

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

Recommendations

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*).

Summary of Evidence

In the 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference, septic shock was described as "a state of acute circulatory failure" or hypotension (SBP <90 mmHg) after fluid resuscitation or the initiation of vasopressor infusion.[1] The Sepsis-3 defines septic shock as "a subset of sepsis in which underlying circulatory and cellular metabolism abnormalities are profound enough to substantially increase mortality."[2] In Sepsis-3, the operational criteria for septic shock include (1) persisting hypotension requiring vasopressors to maintain a mean arterial pressure (MAP) of ≥65mmHg, and (2) serum lactate level >2 mmol/L (18mg/dL) despite adequate volume resuscitation. 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 hyperlactatemia, representing both cardiovascular compromise and cellular dysfunction, since both have been uniformly associated with a significantly higher risk of mortality and organ dysfunction.[3-6] The addition of hyperlactatemia of > 2 mmol/liter to hypotension was seen to increase hospital mortality from 30.1% to 42.3%, which signifies that a serum lactate of that level is clinically relevant.[7] Nonetheless, patients who met only the old definition still demonstrated significant organ failure and mortality.[4-6]

Hyperlactatemia has been a reasonable marker of illness severity in patients with sepsis reflecting cellular dysfunction. Some may argue that lactate may rise with other conditions, but studies have shown that higher lactate levels predict mortality. A prospective observational study that included 985 patients with sepsis show high predictive value for clinical deterioration with lactate values greater than 4mmol/L (Sensitivity [Sn] 27.4%, 95% confidence interval [CI] 18.2, 38.2; Specificity [Sp] 97.5%, 95%CI 96.2, 98.4).[8] In this study, clinical deterioration was a composite of death, endotracheal intubation, vasoactive medication administration for a minimum of 1 hour, noninvasive positive pressure ventilation for a minimum of 1 hour, or ICU admission for a minimum of 24 hours. Other studies which analyzed large datasets from statewide (n=12,349) and international reporting systems (n=28,150) that prospectively collected data from participating sites show similar results, with elevated lactate levels found to be strongly associated with mortality.[9,10] Lactate values greater than 4mmol/L, with or without hypotension, were associated with higher mortality than intermediate levels (2-3 and 3-4mmol/L).

The addition of lactate to the existing clinical criteria of septic shock was found to be associated with consistently higher mortalities, that is 42%, 54%, and 35% in three large databases.[2] These databases include the SSC multicenter registry (n=28,150), the University of Pittsburgh Medical Center with 12 participating hospitals (n=5,984), and the Kaiser Permanente Northern California with 20 participating hospitals (n=54,135). Exclusion of lactate revealed varying mortality rates from as high as 30% to as low as 8%. Indeed, lactate is a useful marker that discriminates the subset of patients that have higher mortality than sepsis alone.

Several studies further support the ability of the Sepsis-3 septic shock criteria in discriminating patients at higher risk of mortality. A secondary analysis of two clinical trials that included 470 patients showed higher SOFA score (9 versus 5; p < 0.001) and mortality (29% vs 14%; p < 0.001) of patients labeled as septic shock by the Sepsis-3 compared to the old definition.[4] In a prospective multicenter study in Korea (n=1,028), those who met the Sepsis-3 septic shock criteria demonstrated higher morbidity (83.1% vs. 75.3%), SOFA scores (6.5±3.1 vs. 5.0±2.9), acute physiology scores (9.3±3.8 vs. 6.6±3.4) and chronic health evaluation II scores (20.0 [15.0–26.0] vs. 15.0 [10.0–20.3]) compared to when the old criteria was used.[11] Furthermore, mortality rates in the hospital, at 28 days, and at 90 days were also higher at 26.8% vs. 17.1%, 25.1% vs. 16.5%, and 32.1% vs. 23.3%, respectively. A third study by Driessen and colleagues prospectively collected data from a cohort of 632 septic patients in the ICU, 482 (76.3%) of which had septic shock according to Sepsis-2 and 300 patients (48.4%) according to Sepsis-3 definition.[6] Patients meeting Sepsis-3 definition had a higher mortality than patients meeting Sepsis-2 definition (38.9 vs. 34.0%).

Current evidence strongly supports the inclusion of hyperlactatemia, hence the adoption of the Sepsis-3 criteria for diagnosis of septic shock. However, the panel recognizes the potential limitation in terms of availability, accessibility and cost of serum lactate testing. Thus, the old criteria was 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.

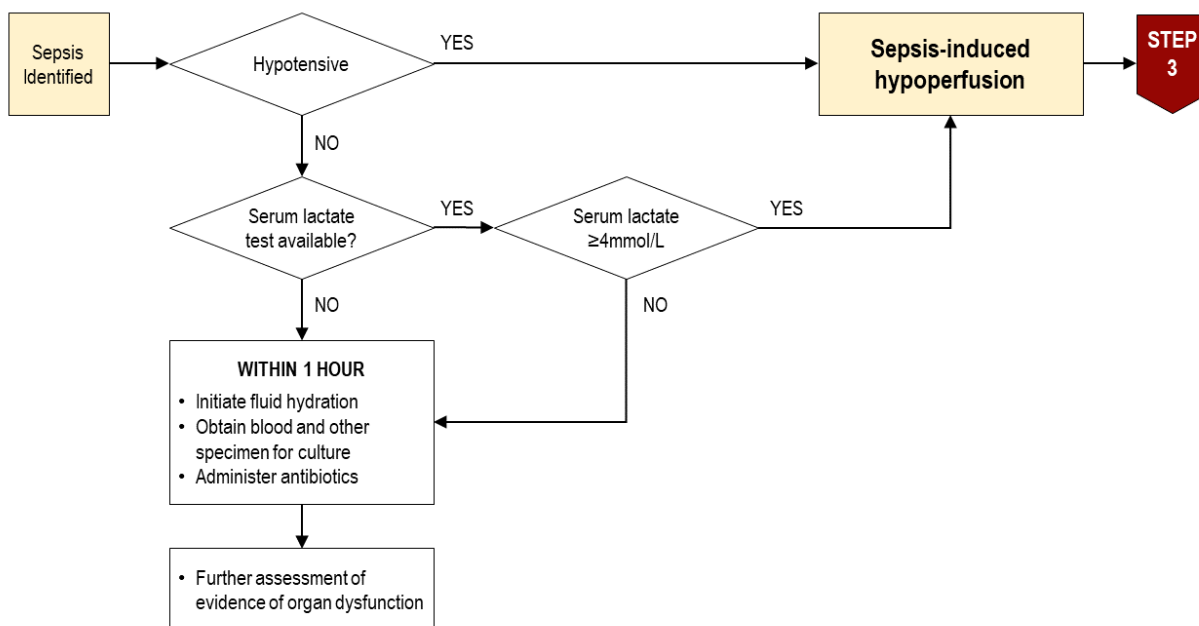-remainder of page left blank-

Figure 2. Initial Management of Patients with Sepsis and Identification of Patients with Sepsis-induced hypoperfusion
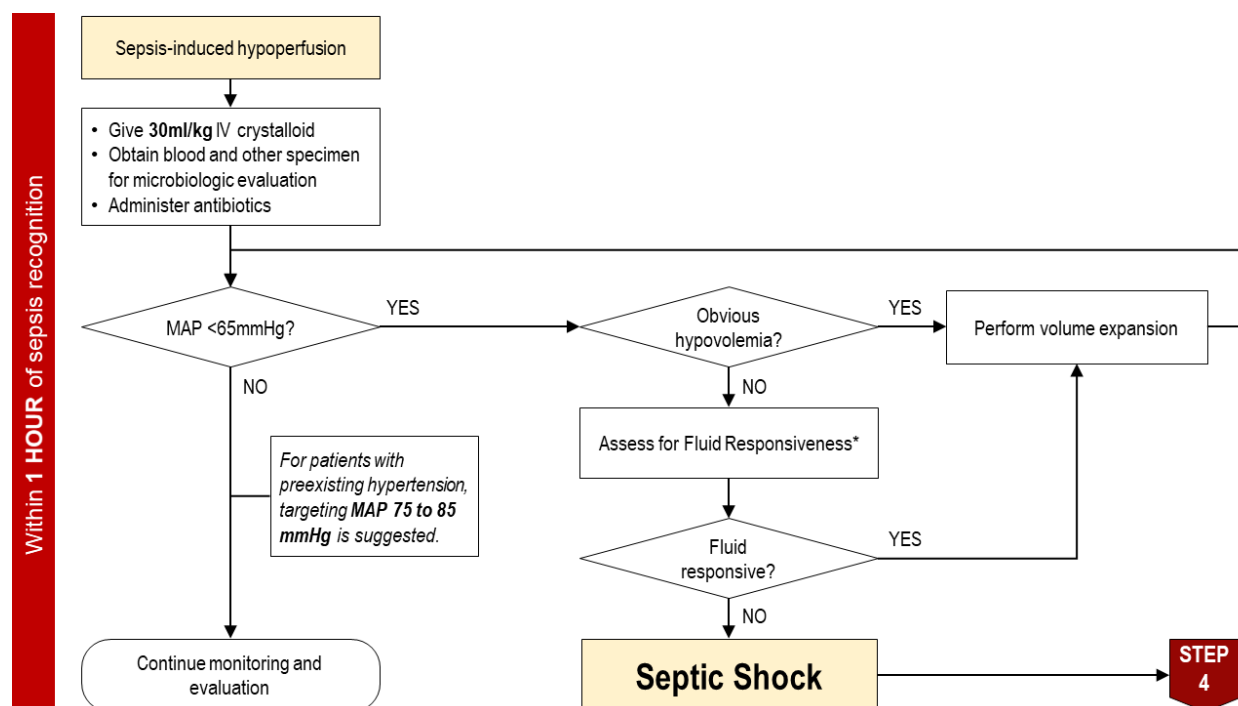

Figure 3. Initial Management of Patients with Sepsis-induced hypoperfusion and Identification of Patients with Septic Shock

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DIAGNOSTIC TESTS

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

Recommendations

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).*

Summary of Evidence

The diagnosis of sepsis remains a challenge due to lack of unambiguous clinical criteria or laboratory features that would clearly identify patients with sepsis. Most physicians rely on their clinical skills and experience to diagnose sepsis, and both clinical and microbiologic criteria are often used as reference standard in diagnostic studies. In some scenarios, bacterial cultures are still considered as reference standard for detection of infection. However, the low pathogen yield, as well as the waiting time for results continue to be a stumbling block in the efficient and accurate diagnosis of sepsis. A review by Coburn and colleagues revealed that blood culture positivity varied depending on the clinical context.[1] Microbiological yield is low among patients with cellulitis (2%), community-acquired pneumonia (7%), community-onset fever (13%), and ambulatory patients (2%), and high among those with acute bacterial meningitis (53%), severe sepsis (38%), and septic shock (69%). A trend showing greater probability of bacteremia with increasing illness severity was also observed in a prospective observational study that included 2,527 patients presenting with SIRS.[2] Microbiologic yield was 25.4% among patients with severe sepsis, and 69.1% among those with septic shock.

Culture positivity or bacteremia among patients with sepsis was found to be associated with increased mortality in various prospective cohort studies. Two large prospective, multicenter cohort studies that included 3,147 and 11,828 patients showed increased odds of mortality among bacteremic patients with sepsis, Odds Ratios (OR) 1.7 (95% CI 1.2, 2.4) and 1.7 (95% CI 1.1, 2.8), respectively.[3,4] This finding was also observed in a cohort of 3,588 patients with either community- or hospital-acquired infections, with mortalities of 48.5% (vs 40.3%) and 43% (vs 36.9%), respectively.

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.[5,6] 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.

Blood cultures obtained after initiation of antibiotics demonstrated reduction in microbiologic yield, from 31.4% pre- to 19.4% post-antibiotic administration.[7] On the average, cultures obtained after antibiotics took longer to grow organisms. The rational desire to obtain cultures should be balanced against the risk of delaying antimicrobials. A study by Kumar and colleagues showed that every hour of delay in administration of antimicrobials increases the risk of mortality among patients with sepsis and septic shock.[8] Therefore, the need for blood cultures must not delay initiation of antibiotics beyond the first hour of sepsis recognition.

The addition of specimen for culture from other potential sites of infection increased the sensitivity of the test to 68%.[7] Positivity rate was also higher with paired blood culture compared to single blood culture.[9] 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.

Consensus Panel Issues. The panel would like to emphasize the importance of timely administration of antibiotics in improving the survival of patients with sepsis and septic shock. If blood cultures cannot be obtained within an hour, administration of antibiotics should be prioritized. Nonetheless, every effort to immediately obtain blood cultures should be sought to assist clinicians in making decisions related to optimal antimicrobial therapy. Targeted focused investigation is the key to treatment, complemented by the proper manner of specimen collection.

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

Recommendation

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.

Summary of Evidence

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.[1]   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. Sensitivity analysis showed results to be significantly different between studies having high and low risk of bias (Sn 0.79, 95%CI 0.72-0.86 vs 0.79, 95%CI 0.59-0.99; Sp 0.79, 95%CI 0.69-0.89 vs 0.74, 95%CI 0.38-1.00), as well as those conducted before and after 2015 (Sn 0.75, 95%CI 0.65-0.86 vs 0.82, 95%CI 0.74-0.90; Sp 0.72, 95%CI 0.57-0.87 vs 0.83, 95%CI 0.73-0.94).

Additional information from observational studies also showed that PCT values varied depending on sepsis severity, the causative organism, and the site of infection.[2,3] PCT concentration increased with greater sepsis severity as shown in Figure Q6.3 (Supplementary Material 2).[2] Patients with gram-negative bacteremia had distinctly higher PCT values (26ng/ml, 95%CI 7.7, 63.1), compared to those with gram-positive bacteremia

(7.1ng/ml, 95%CI 2.0, 23.3) and candidemia (4.7ng/ml, 95%CI 1.9, 13.7). The area under the curve (AUC) was 0.69 (95%CI 0.67–0.72) for the differentiation of Gram-negative bacteremia from Gram-positive bacteremia or candidemia, and 0.72 (95% CI 0.71–0.74) for the prediction of Gram-negative bacteremia compared to all other blood culture results, including those read as negative.[3] AUC is a reflection of how good the test is in distinguishing between patients with the condition and those without. In general, the closer the AUC is to 1, the better overall diagnostic performance of the test. In this case, PCT had moderate diagnostic accuracy in predicting gram-negative infection compared to those caused by other organisms.

A systematic review and meta-analysis of 58 studies that included 16,514 patients studied the diagnostic accuracy of PCT in predicting bacteremia.[4] Similar to sepsis studies, the sensitivity and specificity of PCT for bacteremia was only moderate at 0.76 (95% CI: 0.72 to 0.80) and 0.69 (95% CI: 0.64 to 0.72), respectively. A PCT value of less than 0.5ng/ml had low positive predictive value (17% to 28%) but high negative predictive value for bacteremia (95 to 98%) across different clinical settings: in the ED, ICU, or wards. In another prospective observational study that included 106 patients with sepsis, PCT values >4.68ng/ml were found to have high positive predictive value for bacteremia (97%).[2]

Current evidence show that among numerous biological markers which have been examined to date, PCT had the best diagnostic value in predicting sepsis. The rapid rise of plasma PCT concentration within 6 to 12 hours of infection, as well as its short plasma half-life of approximately 24 hours, make it very attractive in terms of diagnosis and monitoring. Although low PCT concentrations make bacteremia less likely, it does not reliably rule out sepsis or infection, hence should not be used to support clinical decisions to withhold antibiotics and other interventions to a patient suspected of sepsis. On the other hand, an elevated PCT value especially in patients whom diagnosis is uncertain, supports initiation of sepsis management while further diagnostic evaluation is being pursued.

Consensus Panel Issues. 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.

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FLUID THERAPY

Sepsis and septic shock are life-threatening conditions which require emergent interventions. Among these interventions, fluid resuscitation is crucial to improve tissue perfusion and has been recommended as first line strategy in patients with sepsis and septic shock.[1]

In 2001, Rivers and colleagues introduced a protocolized resuscitation strategy for septic patients which we now know as the early goal-directed therapy (EGDT).[2] It included central venous pressure (CVP), mean arterial pressure (MAP), and central venous oxygen saturation (SCVO2) "goals" for the first six hours of therapy. Patients assigned to EGDT had significantly lower mortalities (30.5% vs 46.5%) compared to those assigned to standard care. They noted that the former group of patients received significantly more intravenous fluids (5L vs 3.5L), more frequent red-cell transfusion (64% vs 18.5%), and inotropic support (13.7% vs 0.8%) during the six-hour period. Their methodology was later adopted in the earlier recommendations of the Surviving Sepsis Campaign as a sepsis resuscitation "bundle" and influenced the widespread practice of administering large volume of fluids to patients with sepsis and septic shock.[3] However, recent observational studies have questioned the safety of the "liberal approach" with findings that large fluid volumes were associated with greater mortality compared to a more fluid-restrictive approach.[4,5] In the same way, other components of the sepsis bundle were questioned including the usefulness of targeting CVP of 8-12mmHg and obtaining SCVO2 measurements.[6]

In recent years, there has been rapid turnover of evidence related to various components of fluid therapy in sepsis including the type of fluid for resuscitation, the timing of fluid administration, the optimal amount of fluid to be used, as well as the assessment of fluid responsiveness. There is also an evolving concept in fluid therapy that recognizes four phases or stages of fluid resuscitation among patients with sepsis and septic shock.[7] These include: Rescue, Optimization, Stabilization, and De-escalation or De-resuscitation. The Rescue phase anticipates an immediate escalation of fluid therapy for resuscitation of patients, such as in cases of sepsis-induced hypoperfusion or shock. Optimization occurs when the patient is no longer at imminent risk of death, but at a state of compensated shock, such that additional fluids are titrated to optimize perfusion and mitigate organ dysfunction. Stabilization is a steady state where there is absence of shock or imminent risk of shock, and that fluids are only used for ongoing maintenance. And finally, de-escalation or de-resuscitation phase pertains to active removal of fluid in order to promote a negative fluid balance.

Taken altogether, the abundance of new data and the concept of resuscitation by different phases only show that fluid therapy in patients with sepsis and septic shock is not actually straightforward. There is a need to validate new data and assess its applicability in our setting.

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

Recommendations

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).*

Summary of Evidence

Current evidence show that crystalloids have the highest benefit-to-risk ratio among intravenous fluids for patients with sepsis or septic shock. Two meta-analyses by Rochwerg in 2014 and 2015 analyzed 18,916 (14 RCTs) and 6,664 (10 RCTs) patients with sepsis, respectively.[1,2] The first meta-analysis looked into mortality, while the second focused on renal replacement therapy. 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). This finding was also supported by a meta-analysis that focused on comparisons of crystalloids and HES. It included a total of 4,624 patients (10 RCTs), with results showing no differences in short- and long-term mortality but greater risk of acute kidney injury (RR 1.24, 95% CI 1.13 to 1.36) and renal replacement therapy (RRT) (Relative Risk [RR] 1.36, 95% CI 1.17 to 1.57) with the use of HES.[3] This effect was seen not only in patients with sepsis but critically-ill patients in general.[4,5]

Aside from the apparent advantage of using crystalloids as above, crystalloids are almost always available in health facilities and are economical compared to colloids, and hence are strongly recommended.

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

Recommendation

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).*

Summary of Evidence

There were two cluster-randomized crossover trials that included critically-ill patients randomized to either balanced crystalloid or normal saline solution. Both trials analyzed a subgroup of patients with sepsis.[1,2] The SMART trial included 1,641 sepsis patients from a total of 15,802 critically-ill patients enrolled in the study.[1] The SPLIT trial included 84 sepsis patients from a total of 2,093 critically-ill patients enrolled.[2] Data on mortality and renal replacement therapy were extracted. We performed a meta-analysis on the risk of acute kidney injury between balanced crystalloids and normal saline solution as initial fluid for resuscitation of patients with sepsis or septic shock.

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),[1] but no difference in the 90-day mortality (OR 0.98, 95%CI: 0.28, 3.42).[2] 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.

Consensus Panel Issues. The risk of bias related to secondary analysis of a subgroup of patients with sepsis, as well as imprecision, emphasizes the need for more studies to definitely assess whether one treatment has an advantage over the other. At this time, there are three ongoing randomized clinical trials comparing balanced crystalloids and normal saline solution.[3-5] As we wait for the results of these 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. We found no issues related to cost and resource availability for both fluids for resuscitation.

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

Recommendation

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)*.

Summary of Evidence

A meta-analysis by Xu and colleagues compared the effect of albumin supplementation versus crystalloids alone in the mortality of 3,658 patients with sepsis (former "severe sepsis") and 2,180 patients with septic shock.[1] An updated meta-analysis by Zou and colleagues in 2018 focused on the mortality of 3,088 patients with septic shock.[2] In both studies there was 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).[1] With regard to adverse events, a meta-analysis that included 2,771 patients who received either albumin or crystalloid solution found no increased risk for renal replacement therapy (RRT) with the use of albumin.[3]

Two registered trials on the use of albumin in septic shock patients already completed enrolment, and their results are awaited. One study, the Fluid Resuscitation in Early Septic Shock (PRECISE)[4] was funded by the Ottawa Hospital Research Institute and aimed to

compare 5% albumin with normal saline solution. The other study, the Early Albumin Resuscitation During Septic Shock[5] trial was funded by Laboratoire Français de Fractionnement et de Biotechnologies and compared 20% albumin with normal saline solution. The result of these trials will hopefully provide further guidance on the optimal resuscitation fluid for patients with sepsis and septic shock.   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.

   Consensus Panel Issues*.* It is important that fluid responsiveness be assessed prior to the infusion of additional intravenous fluids, including albumin. The use of albumin for patients with sepsis is to maintain intravascular oncotic pressure and maintain perfusion, which is a step forward towards resuscitation. Although beyond the scope of this guidelines, note that albumin may be given for other indications in patients with sepsis or septic shock.

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

Recommendation

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

Summary of Evidence

Review of literature revealed that most studies bundle the pre-specified timing of fluid administration together with other interventions (i.e. amount and type of fluid, timing of antibiotics, and lactate-guided resuscitation), such that available studies on single or component therapy were assessed to be of low to moderate quality.

Of the ten studies retrieved, the best evidence came from a large prospective cohort study that included 11,182 adult patients with sepsis and septic shock.[1] This study analyzed patients who received crystalloids within 30 minutes, 31-120 minutes, and more than 120 minutes from sepsis recognition. 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).[1] Further analysis showed that risk reduction was similar even when a cut-off of 120 minutes was used. 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. With these results, it may be difficult to ascertain whether the appropriate timing of fluid resuscitation is bound by a critical window period or a dose-response effect, and this limitation and other possible biases were cited in the article. "Sicker patients" may have received fluids earlier, as observed in the positive effect modification among hypotensive patients and those presenting at the emergency department. On the other hand, more patients with risk for fluid congestion (heart failure and renal failure) received fluids at a later time, though statistical analysis revealed no significant interaction effect in this subset of patients.

The Surviving Sepsis Campaign published in 2016 and updated in 2018 recommend immediate fluid resuscitation in patients with sepsis and septic shock. Like the SSC, the task force recognizes sepsis and septic shock as life-threatening conditions, hence the strength of our recommendation. Fluid resuscitation is crucial to improve tissue perfusion while pursuing source control and diagnostic evaluation. We make no recommendation regarding the timing of fluid resuscitation so as not to misconstrue that fluid loading may be delayed until a particular cut-off period. Doing so would impose serious risks especially among

patients with hypotension and signs of hypoperfusion. Until better evidence on a window period or threshold for fluid initiation is available, the dose-response effect will serve as the basis for recommending immediate fluid resuscitation in patients with sepsis and septic shock.

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

Recommendation

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.

Summary of Evidence

The 2016 Surviving Sepsis Campaign (SSC) Guidelines and its 2018 update continue to recommend administration of at least 30ml/kg of intravenous crystalloids to patients with sepsis-induced hypoperfusion despite absence of moderate to high quality evidence.[1,2] The SSC recommendation was based on a large prospective observational study (n= 29,470) showing lower mortality (OR 0.79, 95%CI 0.73, 0.85) with compliance to a sepsis resuscitation bundle that included the 30ml/kg intravenous fluid bolus.[3] Additional data from 17 observational studies (n=15,662) also revealed similar reductions in mortality (OR 0.78, 95%CI 0.71, 0.85) with compliance to a sepsis resuscitation bundle.[4] In these studies, however, several confounders were identified including early antibiotic administration and use of adjunctive aids in the intervention group. They were unable to adjust survival

estimates based on these factors; hence the overall quality of evidence was deemed to be low.

Apart from the evidence cited above, there are no studies that looked into the volume element of the sepsis resuscitation bundle. Furthermore, there is also limited evidence on the efficacy of giving intravenous fluid bolus to those who do not have sepsis-induced hypoperfusion. Patients with sepsis-induced hypoperfusion include those presenting with hypotension or lactate ≥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. 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.

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

Recommendation

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).

Summary of Evidence

Studies on fluid volumes are limited and often do not define a specific amount or cut-off of fluid for initial resuscitation. The best available evidence comes from a large retrospective study which included 23,513 patients. Results showed incremental increase in mortality of 2.3% per liter of fluid in excess of 5 liters given within the first day of admission even after adjusting for illness severity (Supplementary Material 2, Figure sQ12.1).[1]   On the other hand, low volume resuscitation (1 to 4.99L) exhibited small reduction in mortality of 0.7% per liter (-1.0 to -0.4).   Patients who were mechanically ventilated had over-resuscitation signal for harm, while those with shock but not mechanically ventilated had harm signals for both under- and over-resuscitation (Supplementary Material 2, Figure sQ12.2).

This recommendation is in consideration of the harm associated with overyhydration 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.

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

Recommendation

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.

Summary of Evidence

An international, multicenter, observational cohort that included 1,808 patients with sepsis demonstrated increased mortality with greater cumulative fluid balance at day 3 after adjustment for possible confounders (Supplementary Material 2, Figure sQ13.1).[2]   The investigators noted that the cumulative fluid intake was similar at 24 hours, 3 days, and 7 days, and that the lower cumulative fluid balance observed among survivors was due to greater fluid output. Given the retrospective nature of the analysis, they were not able to determine whether limiting fluids or enforcing diuresis would be the most appropriate approach to achieve a lower cumulative fluid balance.

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.[3] 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).

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

Recommendations

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).*

Summary of Evidence

For patients who remain hypotensive despite initial fluid resuscitation, the decision to give additional fluids is not always easy. Only about half of hemodynamically unstable patients respond to further fluid administration.[1] In some cases, overzealous hydration can lead to pulmonary edema, worsen heart failure and increase the risk of death. Thus, it is crucial to identify patients who will likely benefit from fluid administration.

For years, static measurements of preload have been relied on to predict fluid responsiveness. Static variables take "snapshot" estimations of preload, with measurements of central venous pressure (CVP) being the most common. A systematic review and meta-analysis that included 23 studies and 1148 patient data sets showed that the predictive value of CVP was similar across different cut-off values.[2] CVP is an invasive method of assessing preload and should not be used in predicting responsiveness to fluid loading when more accurate indices of fluid responsiveness are available.

Dynamic variables are proven to be accurate predictors of fluid responsiveness. In order to assess fluid responsiveness, maneuvers that increase preload are combined with measurements of variation in cardiac output. Commonly utilized indices of cardiac output are stroke volume and pulse pressure, and their variations with certain maneuvers and situations. Stroke volume variation (SVV) is the natural stroke volume increase during inspiration and decrease during expiration, induced by changes in the intrathoracic pressure resulting from mechanical ventilation. Pulse pressure is the difference between systolic and diastolic blood pressure. Pulse pressure variation (PPV) is the calculated difference between pulse pressures during the respiratory cycle. A systematic review of 29 diagnostic accuracy studies (n=685) show high diagnostic accuracies for both SVV (Sensitivity 0.82, 95% CI 0.75 to 0.98, Specificity 0.86, 95% CI: 0.77 to 0.92) and PPV (Sensitivity 0.89, 95%CI 0.82 to 0.94, Specificity 0.88, 95% CI 0.81 to 0.92). The diagnostic threshold for both SVV and PPV is ≥12%.[3] PPV values between 9% and 13% are considered by some to be "gray zone values" and may be less conclusive.[4] Beyond this range, PPV more accurately delineates between fluid responsiveness and unresponsiveness with an AUROC >0.90. PPV and SVV can be measured using peripheral arterial pressure waveforms or pulse contour analysis that are obtained through an arterial catheter or calibrated noninvasive cardiac output monitoring devices. Alternatively, SVV can be measured centrally by echocardiography.

Given the physiologic basis of SVV and PPV measurements, they are deemed unreliable in spontaneously breathing patients, ventilated patients with low tidal volume, and patients with cardiac arrhythmias. However, certain maneuvers that increase preload have been shown to override these limitations, allowing their use in conjunction with SVV, PPV, and other measures of cardiac output. These maneuvers include passive leg raise (PLR), mini- fluid challenge, end-expiratory occlusive test, and tidal volume challenge. The evidence is more extensive for PLR, while evidence for the rest came from small observational studies.

Passive leg raise coupled with monitoring of change in flow or pressure variables have high sensitivity and specificity for predicting fluid responsiveness. A meta-analysis that included 23 studies with 1,013 critically-ill patients demonstrated PLR sensitivity and specificity for predicting fluid responsiveness of 0.86 (95% CI 0.79, 0.92) and 0.92 (95% CI 0.88, 0.96), respectively.[5] Majority of the patients included were diagnosed with sepsis and septic shock. The heterogeneity (I^2=50.2%) observed was attributed to differences in the technique utilized for measuring cardiac output. PLR-induced changes in pulse pressure (Sn 0.58%, 95% CI, 0.44 to 0.71, Sp 0.83, 95% CI 0.68 to 0.92) exhibited lower diagnostic performance compared to PLR-induced changes in flow variables (Sn 0.85, 95% CI 0.78 to 0.90, Sp 0.92, 95% CI 0.87 to 0.94).[5] PPV is said to poorly reflect stroke volume during sepsis because of increased arterial compliance.[6] Stimulation of arterial baroreceptors - through pain, for instance - can also increase pulse pressure, thus inaccurately reflecting stroke volume. Different techniques used to measure flow variables exhibit comparable sensitivities and specificities, as shown in **Table Q12.1**. Subgroup analysis showed similar

diagnostic performance when PLR was used in both spontaneously- breathing and mechanically-ventilated patient scenarios (*p* 0.10), with starting position of supine versus semi-recumbent (*p* 0.33), and use of either crystalloid or colloid (*p* 0.36).

Table Q14.1. Diagnostic Accuracy of Passive Leg Raise combined with different Primary Measurement Techniques measuring Flow Variables.

Technique	No. of Studies	No. of Fluid Challenges in Combination With Passive Leg Raise	Sensitivity	Specificity	Area Under the Receiver Operating Characteristic Curve
Esophageal Doppler	3	130	96 (84–99)	92 (77–97)	0.96
Transthoracic echocardiography	7	272	79 (68–87)	91 (86–95)	0.88
Pulse contour analysis	10	423	84 (77–89)	92 (87–95)	0.92
Bioreactance	3	209	84 (67–93)	86 (68–94)	0.89

The 95% CI is given in parentheses. When calibrated pulse contour analysis was used as reference, applied in 10 studies and consequently the most frequent applied measurement technique, no significant differences were found compared with esophageal Doppler (*p* = 0.43), transthoracic echocardiography (*p* = 0.69), and bioreactance (*p* = 0.37).

From Cherpanath TG, Hirsch A, Geerts BF, Lagrand WK, Leeflang MM, Schultz MJ, Groeneveld AB. Predicting fluid responsiveness by passive leg raising: a systematic review and meta-analysis of 23 clinical trials. Critical care medicine. 2016 May 1;44(5):981-91.

PLR is performed by elevating the lower limbs to 45 degrees for two minutes, while placing the patient in the supine position to mobilize blood from the lower body and create sufficient venous return to increase preload. Measurements of cardiac output are taken at baseline and after PLR. The use of hospital beds equipped with the ability to raise the legs are preferred since manual stimulation may result to increased sympathetic tone and result to false readings. The thorax should be kept in the horizontal position, and not lower, to prevent gastric fluid aspiration. Of the primary measurement techniques used to measure cardiac output, ultrasound is a readily-accessible, and the least invasive, tool to the clinician in various settings (ED, ICU, ward). The limitation lies in that ultrasonography is operator-dependent, requires some level of technical training, and may be limited by poor acoustic window brought about by obesity, high positive end-expiratory pressure (PEEP), high tidal volume, and others. Nonetheless, technique is very important when using ultrasound, and pressure transducers should be kept at heart level during the PLR maneuver.

PLR has limitations and cannot be implemented in every clinical setting. It may be difficult, painful, dangerous or impossible in some situations such as in patients with hip or extensive lower leg surgery, amputated patients, patients in the prone position, some patients who underwent gynecologic or urologic operations, and patients with increased intracranial pressure.[7,8] In such instances, other maneuvers or techniques may be more applicable.

Small prospective observational studies have demonstrated the feasibility of mini-fluid challenge when assessing fluid responsiveness. Mini-fluid challenge involves rapid infusion of 100ml of fluid with estimation of cardiac output before and after. A study that included 49 patients with circulatory shock, mostly septic (94%), and on low tidal volume ventilation revealed sensitivity of 0.86 (95% CI: 0.65 to 0.97) and specificity of 0.89 (95% CI: 0.71 to 0.98) for SVV, and sensitivity 0.86 (95% CI: 0.64 to 0.96) and specificity of 0.85 (95% CI: 0.65 to 0.95) for PPV.[9] Accuracy was highest using a cutoff of 2% for both SVV and PPV. Another study which included 39 patients measured subaortic velocity time index (VTI) after mini-fluid challenge.[10] Transthoracic echocardiography (TTE) provided a noninvasive assessment of VTI by pulse-waved Doppler on a 5-chamber apical view. An increase of ≥10% in VTI has a sensitivity of 0.95 (95% CI: 0.87 to 0.99) and specificity of 0.78 (95% CI: 0.59 to 0.97) in predicting fluid responsiveness. The best cut off was 3% but was found to be inferior to 10% in terms of interobserver variability.

In patients who are mechanically ventilated, an end-expiratory occlusion (EEO) prevents the cyclic decrease in cardiac preload and acts as a fluid challenge. A study that included 34 patients, 32 of whom had sepsis, assessed the diagnostic accuracy of EEO combined with measurements of PPV and change in cardiac index.[11] Investigators employed a 15-second EEO using the automatic device of the ventilator for measuring positive end-expiratory pressure. Measurements of cardiac output were taken before and at the last five seconds of the EEO. Fluid responsiveness was predicted by a ≥5% increase in PPV, demonstrating a sensitivity of 0.87 (95% CI: 0.66 to 0.97) and specificity of 1.00 (95% CI: 0.71 to 1.00), and by a ≥5% increase in cardiac index with a sensitivity of 0.91 (95% CI: 0.72 to 0.99) and specificity of 1.00 (95% CI: 0.72 to 1.00). Another study which included 50 patients - 20 of them with septic shock - evaluated the diagnostic accuracy of EEO with the aid of echocardiography.[12] An increase of >9% in subaortic VTI induced by EEO showed a sensitivity of 0.93 (95% CI: 0.68 to 1.00), and specificity of 1.00 (95% CI: 0.78 to 1.00). An increase of >4% in continuous pulse contour cardiac index had a sensitivity of 0.93 (95% CI: 0.68 to 1.00) and specificity of 1.00 (95% CI: 0.78 to 1.00) in predicting fluid responsiveness.[12] In this study, a 12-second EEO was employed.

The evidence on tidal volume challenge was from a single study that included 20 mechanically-ventilated patients on low tidal volume ventilation. Increasing the tidal volume for one minute from 6 ml/kg to 8 ml/kg of predicted body weight demonstrated a sensitivity of 94% and specificity of 100% for PPV, and sensitivity of 88% and specificity of 100% for SVV. The best cut off values for PPV and SVV were 3.5% and 2.5%, respectively.[13]

In summary, 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.[14] We provided a clinical algorithm (**Figure 4**) to guide clinicians on the techniques, modalities and threshold used in assessing fluid responsiveness.[7,8,15]
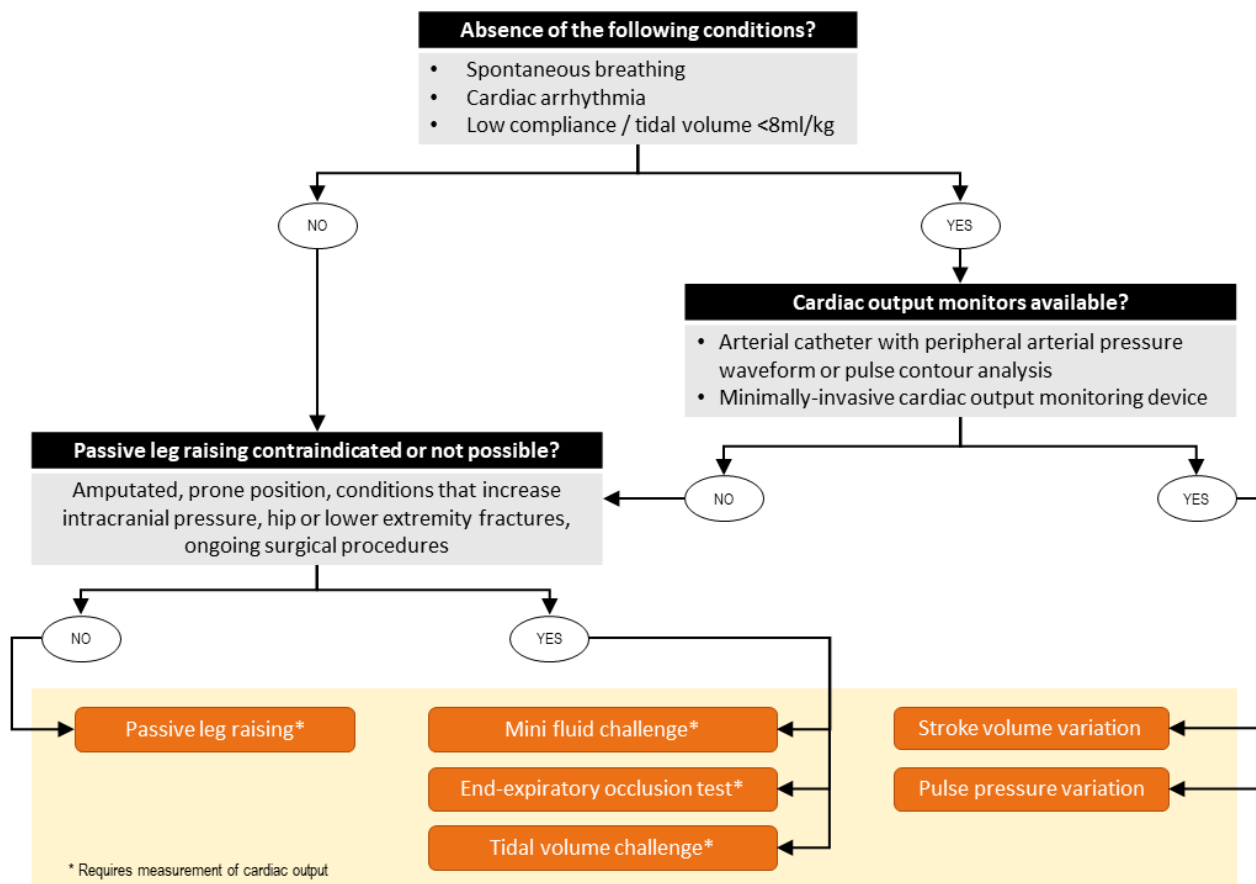

Figure 4. Clinical Algorithm for the Assessment of Fluid Responsiveness

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VASOACTIVE AGENTS

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

Recommendation

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

Summary of Evidence

In septic shock, when initial fluid resuscitation is insufficient to maintain a mean arterial pressure (MAP) ≥ 65mmHg, vasopressor therapy is indicated. Norepinephrine is recommended as the first-line vasopressor agent. 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.[1] 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.[2]

The use of epinephrine, vasopressin, or terlipressin in patients with septic shock did not show improvement in 28-day mortality. Meta-analysis of randomized controlled trials showed no significant mortality benefit with the use of epinephrine (RR 0.97, 95% CI 0.77-1.21, I2=0%), vasopressin (RR 1.04, 95% CI 0.70-1.53, I2 = 0%), or terlipressin (RR 0.98, 95% CI 0.83-1.15) compared to norepinephrine as first-line vasopressor agent.[3] In terms of major adverse events, epinephrine (RR 0.88, 95% CI 0.60-1.30, I2=38%) and vasopressin (RR 0.47, 95% CI 0.18-1.18) showed no significant difference with norepinephrine as well. Major adverse events for epinephrine and vasopressin included arrhythmias, acute coronary events, acute mesenteric and limb ischemia, and acute cerebrovascular events. Compared with terlipressin, norepinephrine showed significantly decreased adverse events (RR 0.43, 95% CI 0.31-0.60, I2 = 0%). Most commonly observed adverse events in the use of terlipressin when as a first-line vasopressor included acute mesenteric and digital ischemia.[4]

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

Recommendation

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).*

Summary of Evidence

Several studies have investigated the value of adding a second vasopressor to norepinephrine for patients with septic shock. Three options can be considered: vasopressin, terlipressin and dobutamine. Among these three vasopressors, we only found literature that studied vasopressin and terlipressin as add-on to norepinephrine.

Norepinephrine plus vasopressin

A recent meta-analysis of 23 trials investigating the benefit of a second vasopressor to norepinephrine failed to demonstrate the mortality benefit of vasopressin after filtering out studies with high risk of bias.[1] Despite an overall RR estimate of 0.89 (95% CI, 0.82 to 0.97; RD, -0.04 [95% CI, -0.07 to 0.00]), mortality benefit was not observed when limited to trials with low risk of bias, where the RR estimate was 0.96 (95% CI, 0.84 to 1.11). This analysis is consistent with other trials and meta-analyses that have demonstrated no mortality benefit from vasopressin in patients with septic shock.[2-5]

In terms of the prespecified primary outcome of atrial fibrillation, the addition of vasopressin resulted in lower rates of atrial fibrillation (RR 0.77, 95% CI 0.67-0.88).[1] However, the benefit was not observed for the secondary outcomes of requirement for renal replacement therapy, rate of myocardial injury, stroke, ventricular arrhythmias, or length of hospital stay.

Aside from mortality and arrhythmia mitigation, the reduction of pre-existing norepinephrine dose is another outcome worthy of consideration when contemplating a second vasopressor. The TERLIVAP trial in 2009 by Morelli and colleagues , however, failed to demonstrate a reduction in norepinephrine doses despite the addition of vasopressin.[6] They surmise that the lack of reduction in norepinephrine requirements may potentially be explained by the low dose infused in their present study (0.03 U/min). This theory seems to be corroborated by Luckner and colleagues who reported that 0.067 U/min is more effective in hemodynamic support and catecholamine reduction than 0.033 U/min.[7] And although previous studies suggest that AVP infusion in septic shock should not exceed 0.04 U/min because of the potential risk of adverse effects, the observations noted above raise the issue of effectiveness of 0.03 U/min vasopressin.[8,9]

Norepinephrine plus terlipressin

For patients with distributive shock from sepsis who are already on norepinephrine, there was only one study that compared stand-alone norepinephrine versus norepinephrine plus terlipressin.[10] In addition to the fact that the study had a very small sample size of 45, there was no benefit, but rather harm, seen with add-on terlipressin [RR of 2.83, CI 1.12 to 7.18], on the seven-day survival rates or mortality outcomes.

Norepinephrine plus dobutamine

There were no studies comparing stand-alone norepinephrine and norepinephrine plus dobutamine with respect to mortality benefit, as well as other clinical end points.

In essence, 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.

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

Recommendation

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).*

Summary 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.[1] 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 with a relative risk of 0.94 (95% CI 0.57-1.53). Complication rates were also comparable with a relative risk of 0.70 (95% CI 0.31-1.59). The adverse events included in the study were acute coronary syndrome, arrhythmia, cerebral stroke, and limb ischemia. In terms of physiologic and hemodynamic standpoints, dobutamine infusion also resulted in significantly better arterial pH and lower serum lactate compared to epinephrine.[2] To date, no randomized

controlled trials had investigated the effects of dobutamine versus placebo in this population.

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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?

Recommendations

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)*.

Summary of Evidence

Septic shock is often associated with multiple organ failure, mainly respiratory and renal in nature. Early and adequate hemodynamic support is crucial to prevent further worsening of organ dysfunction. As the severity of each of these disorders is variable from patient to patient, it is important to assess the degree of each component of the hemodynamic failure in order to select the appropriate therapeutic measures.[1]

The blood pressure level that should be targeted during the management of septic shock is an important clinical issue. The mean arterial pressure (MAP) is one of the first variables that is monitored in these patients. The Surviving Sepsis Guidelines recommend that vasopressor therapy initially target a MAP of 65 mmHg (grade 1C recommendation), but the actual value should be individualized.[2] The study of 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.[3]

However, targeting higher blood pressure may increase mortality in patients who have been treated with vasopressors for more than six hours.[4]

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.[5] A cohort study by Lee and colleagues in 2019 showed that in patients with previously known high blood pressure trends, targeting a MAP of 75-85mmHg improved survival, however, the mortality risk starts to increase at MAP >85mmHg.[6]

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

Recommendation

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)*

Summary of evidence

The Surviving Sepsis Campaign proposes to guide hemodynamic resuscitation by measuring blood lactate levels, considering the strong relationship between hyperlactatemia, lactate kinetics, and mortality.[1-3] However, persistent hyperlactatemia may be related to causes other than tissue hypoperfusion.[4] Moreover, lactate kinetics is relatively slow even in survivors,[3,5] 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.[2]

In a recent systematic review comprised of seven randomized controlled trials (n= 1,301 patients), the effects of LGT versus ScvO2-guided therapy on in-hospital mortality among septic patients was evaluated.[6] LGT was found to produce significantly better in-hospital survival rates (RR 0.68, 95% CI 0.56 to 0.82; P < .00001; fixed- effect model) with no significant heterogeneity between studies (x^2 = 2.87, degrees of freedom [df] = 7, P = .90, I2 = 0%). Lactate guidance also resulted to shorter ICU stay (mean difference [MD]-1.64 days, 95% CI -3.23 to -0.05), shorter mechanical ventilation time (MD -10.22 hours, 95% CI -15.94 to -4.5), and lower APACHE II scores (MD -4.47, 95% CI -7.25 to -1.69), but no difference in total length of hospital stay and SOFA scores. In another meta-analysis that included six randomized controlled trials (n=917 patients), the effectiveness of LGT was compared to early goal-directed therapy (EGDT).[7] In these RCTs there was no heterogeneity, and EGDT was shown to be associated with higher mortality (RR 1.42, 95%CI 1.19 to 1.70). Use of red-cell transfusion, vasopressor infusion, dobutamine infusion, and mechanical ventilation did not differ between LGT and EGDT. The optimal or desired rate of lactate clearance is still open to debate, with most studies aiming for normalization of lactate levels or a decline of at least 10% in six hours. To achieve this goal, hemodynamic resuscitation using intravenous fluids, vasopressors and inodilators were usually employed.

In a systematic review of eight observational studies (n= 3,063 patients), the effectiveness of point-of-care lactate (POCL) was investigated.[8] Six studies focused on patients with sepsis or septic shock. Four studies evaluated mortality, and found a pooled odds ratio of 0.419 (95 CI, 0.268-0.654).[9-12] Turn-around time was also shortened with the use of POCL compared to laboratory lactate testing, from a median of 122 minutes to 34 minutes.[11] Time to treatment was also reduced with POCL testing. Time to receive intravenous fluids was reduced from a median time of 71 minutes to 55 minutes.[13] More patients (25% versus 15%) also received antibiotics within an hour of admission.[14] As these studies were observational, the utility of POCL testing should be investigated further in controlled clinical trials.

In the Philippines, not all centers have access to lactate determination. Interestingly, a recently concluded multicenter randomized controlled trial (The ANDROMEDA-SHOCK trial) that included 424 patients compared resuscitation strategies targeting normalization of capillary refill time (CRT) versus normalization of serum lactate levels among patients with septic shock.[15] In the study, CRT was measured by applying firm pressure to the ventral surface of the right index finger distal phalanx with a glass microscope slide. The pressure was increased until the skin was blank, and then maintained for 10 seconds. The time for return of the normal skin color was registered with a chronometer, and a refill time greater than three (3) seconds was defined as abnormal. Mortality at 28 and 90 days did not differ between the two resuscitation strategies with hazard ratio of 0.75 (95% CI 0.55, 1.02) and 0.82 (95% CI 0.61, 1.09), respectively. There was a trend towards benefit with normalization of peripheral perfusion targets. At 72 hours, patients in the peripheral perfusion group had less organ dysfunction with mean difference in SOFA score of -1.00 (95%CI -1.97 to -0.02).

There were no differences in mechanical ventilator-free days, renal replacement-free days, vasopressor-free days, ICU length of stay, and hospital length of stay. This is the first study that looked into peripheral perfusion targets and further trials should be conducted to affirm the usefulness of CRT as a viable goal for hemodynamic monitoring. In centers without access to lactate tests, targeting normal CRT provides a feasible and inexpensive alternative to lactate monitoring.

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

Recommendation

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).*

Summary of Evidence

Lactate has been used a biomarker of the shock state, which entails immediate fluid resuscitation. Since serum lactate tests are not readily available in all centers in the Philippines, options to estimate lactate levels have been explored. According to Pogmanee and Vattanavanit, lactate and anion gap showed a strong correlation with each other.[1] Lactate and base excess showed a moderate correlation, and each may possibly be used interchangeably to help determine septic shock severity in patients. This is supported by a study by Montassier and colleagues, which showed that base excess levels may predict elevated lactate levels among septic patients in the emergency department.[2] This suggests the availability of a quick marker in assessing the severity of hypoperfusion.

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

Recommendation

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

Summary of Evidence

There is existing evidence - though from small studies - regarding the value of targeting improvement in base excess levels. These studies report a trend towards survival among patients with sepsis and septic shock. Single center studies by Palma and colleagues as well as Park and colleagues 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.[1,2] This same observation was noted by Smith and colleagues in another single center but with a larger sample size.[3] It was noted that 15 of 85 patients died after an increase in base excess levels from admission while 36 of 63 patients died after having lower base excess levels compared to baseline.

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

Recommendation

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.

Summary of Evidence

The central venous-to-arterial tension difference is the gradient between the PCO_2 in central venous blood and PCO_2 in arterial blood. It has been directly linked to CO_2 production and inversely linked to cardiac output.[1] In the study of Mallat et al., it was suggested that it can be used as a marker to identify under-resuscitated patients.[1] The results of the study by Vallee et al. suggest that a gap or difference of > 6 mmHg has been suggested to reflect insufficient blood flow to the tissues, even when the central venous oxygenation ($ScvO_2$) is greater than 70%.[2]

Multiple small studies, mostly from single centers, have consistently proposed that a low CO2 gap was associated with a higher cardiac index, and a lower lactate level.   These studies have noted that patients with lower CO_2 gap levels – less than or equal to 6 mmHg – from the consensus statement on circulatory shock and hemodynamic monitoring from the European Society of Intensive Care Medicine - had higher survival rates compared to those with higher CO_2 gap levels.[3]

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

Recommendation

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).*

Summary of Evidence

Sepsis is known to cause various presentations of mixed shock states that require targeted hemodynamic monitoring. Hemodynamic monitoring allows for assessment of important variables and the identification of the causes of hemodynamic instability - which can then be targeted, treated and tracked.[1]

Among different available tools and equipment, the pulmonary artery catheter has been used to manage patients with underlying cardiac conditions such as acute heart failure and cardiogenic shock, and for monitoring during major cardiac surgeries.[2] It has also been used for hemodynamic monitoring in the ICU especially for sepsis patients, who are at risk of developing myocardial dysfunction as one of its severe complications.[1]

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.[2] As a result, the general use of PA catheter declined. This was seen in the study of Koo and colleagues that included 15,006 patients, showing more than 50% decrease in the use of the PA catheter over a five-year period.[3] The extent and efficiency of PA catheter employment is affected by illness severity and greatly by the skill of the intensive care unit and attending physician utilizing it as a monitoring device.

It is worthy to note, however, that using the PA catheter with other tools or methods of hemodynamic monitoring may provide benefit in patients with high-severity illness, such as when blood volume analysis and PA catheter monitoring are performed together versus PA catheter monitoring alone.[4]

The 2016 Surviving Sepsis Campaign Guidelines have strongly recommended against the routine use of the pulmonary artery catheter for patients with sepsis-induced acute respiratory distress syndrome (ARDS).[5] There was no explicit recommendation on its use

as a means for hemodynamic monitoring, whether as a static or dynamic measure of response to therapy.

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ANTIMICROBIAL THERAPY

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

Recommendation:

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.

Summary of Evidence

On first recognition of sepsis or septic shock, a decision must be made regarding empiric antimicrobial therapy. Because of the pervasive problem of rising antimicrobial resistance, the need for empiric broad-spectrum antimicrobial therapy must always be balanced with the need for antimicrobial stewardship. The choice of what antimicrobial regimen to start on a septic patient has become increasingly difficult. In considering this question about empirical therapy, we included studies on appropriate versus inappropriate

empiric therapy as a surrogate to answer the question of how broad an antimicrobial regimen must be. There are two systematic reviews which synthesized the evidence and were considered by the Consensus Panel for this recommendation.

The systematic review and meta-analysis of Paul et al.[1] provides the most robust evidence in favor of giving broad-spectrum antimicrobials at the onset of treatment for sepsis or septic shock. The review included 69 prospective cohort studies from 1965 to 2008, providing data from 21,338 adult patients with various infections. It is important to note that not all patients in the individual studies have actual sepsis or septic shock and it was not possible to extract data specific only to the septic patients. Despite this heterogeneity in the pooled study population (I^2 = 79.7%), the adjusted multivariable analysis of risk factors 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). In maneuvers to explain the heterogeneity, the authors further showed that none of the other clinical variables affected the results of the study (study year and setting, patient's age, bacteremia, source of infection, neutropenia, and causative bacteria) except for septic shock, which resulted in higher ORs.

The systematic review and meta-analysis of Marquet et al.[2] investigated the outcomes of inappropriate empiric antibiotics on hospital mortality, reviewing studies published between 2004 to 2014. The review included data from 27 studies, covering 15,306 patients with "severe infections." The meta-analysis showed that risk ratios for 30-day mortality and in-hospital mortality were 0.71 (95% confidence interval 0.62 to 0.82) and 0.67 (95% confidence interval 0.56 to 0.80), respectively. Heterogeneity was high in this review as well (I^2 = 86.6% for in-hospital mortality). Notably, the Marquet review included the study by Kumar et al.,[3] perhaps the largest single study on outcomes of inappropriate empiric antibiotics in septic shock patients. The study was a multicenter, multi-country, retrospective review of 5715 patients with septic shock from 1996-2005. It demonstrated a 5-fold reduction in survival of patients who received inappropriate empiric antibiotics (Survival$_{appropriate}$ = 52%, Survival$_{inappropriate}$ = 10.3%; adjusted OR 8.99, 95% CI 6.6-12.23, p<0.0001).

A question that arises from the data presented above is how "broad" broad-spectrum regimens should be. The answer to this has important implications for antimicrobial stewardship and the development of antimicrobial resistance. Certainly, a knowledge of the most common pathogens associated with the suspected infection site plays the greatest role in determining the best empiric regimen. Other factors to consider include whether the infection is community-acquired or nosocomial in origin, the presence of shock, the presence of devices, as well as patient age and other patient-related factors. Knowledge of local antimicrobial susceptibility rates and whether multidrug-resistant organisms must be considered are also important. If in doubt, an infectious disease specialist, in localities and situations when one is available, should be consulted. In some centers where algorithms are employed for managing patients with sepsis, an infectious disease consultation is mandatory.

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

Recommendation

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).*

Summary of Evidence

The prompt use of empiric antimicrobial therapy in patients with sepsis and septic shock is a critical determinant of survival in this type of population.[1] The 2016 Surviving Sepsis Campaign (SSC) guidelines on the management of sepsis and septic shock recommended the use of empiric broad-spectrum therapy with one or more antimicrobials (combination therapy) of different classes and mechanisms of action.[2] Multidrug therapy tends to broaden the spectrum of therapy or potentially accelerate pathogen clearance.[2] Combination therapy, which is a form of multidrug therapy, tends to accelerate pathogen clearance rather than broaden the antimicrobial coverage. Combination therapy also inhibits bacterial toxin production and conveys assurance that the pathogen is sensitive to at least one of the antibiotics given, in the face of the prevalent problem of microbial resistance.[2,3] The initiation of appropriate antimicrobial therapy - defined as having in-vitro activity appropriate to the isolated pathogenic organisms or, if a pathogen was not isolated, appropriate for the underlying clinical syndrome - has been associated with increased survival in patients with septic shock.[4] This has been the primary cornerstone of recommending initial empiric combination therapy in serious life-threating infections.[5] However, several studies showed conflicting results regarding the use of empiric combination therapy over monotherapy in septic patients. This unresolved issue is one of the top six identified research priorities by the Surviving Sepsis Research Committee.[3]

A retrospective, propensity-matched, multi-center, cohort study was done by Kumar et al., which involved 4,662 adult ICU patients with culture-positive bacterial septic shock.[6] Combination therapy was associated with decreased 28-day mortality and significant reductions in mortality in the ICU and in the hospital, compared to patients on monotherapy. The authors also noted more ventilator-free days, more pressor-free days and shorter length of hospital stay among patients given early empiric combination therapy.

In contrast, other reports have shown no benefits in the use of combination therapy. Paul et al. did a systematic review of 69 randomized and quasi-RCTs on β-lactam antibiotic monotherapy vs β-lactam–aminoglycoside antibiotic combination therapy for sepsis.[7] All-cause mortality was similar among both monotherapy and combination therapy groups. A subgroup analyses showed no difference in all-cause mortality. There was also no difference in the treatment failure and adverse events, except for nephrotoxicity, between both groups. Nephrotoxicity was found to be more common in the combination arm in nearly all studies, with a highly significant combined risk ratio in favor of monotherapy (RR 0.30, 95% CI 0.23-0.29). It is important to note that this study used β-lactam–aminoglycoside combination and this adverse effect cannot be generalized in other combination antimicrobials with less nephrotoxic risks. Hence a recommendation on the adverse events cannot be derived.

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.[5] More prospective, randomized studies are needed to evaluate the benefits of empiric combination therapy in sepsis as suggested by the Surviving Sepsis Research Committee.

In general, 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.[8,9] Current local and international guidelines provide the recommended empiric combination therapy for a specific given focus of infection (**Table Q25.1**).

Table Q25.1. Recommended initial empiric antibiotic therapy for patients with sepsis and/or septic shock.

Site of infection	Guideline	Recommendation

Community-acquired pneumonia, severe	(ATS/IDSA 2019) Diagnosis and Treatment of Adults with Community-Acquired Pneumonia[10]	**Without risk for MRSA or *Pseudomonas aeruginosa*:**
		    Ampicillin + Sulbactam 1.5g-3g IV q6 **OR** Cefotaxime 1-2g IV q8
		    OR Ceftriaxone 1-2g IV q24
		
		    PLUS
		    Azithromycin dihydrate 500mg IV q24 **OR** Clarithromycin 500mg PO bid
		    OR Levofloxacin 750mg IV q24 **OR** Moxifloxacin 400mg IV q24
		
		With risk for *Pseudomonas aeruginosa*:
		    Piperacillin-Tazobactam 4.5g IV q6 **OR** Cefepime 2g IV q8
		    OR Ceftazidime 2g IV q8 **OR** Aztreonam 2g IV q8
		    OR Meropenem 1g IV q8 **OR** Imipenem 500mg IV q6
		
		    PLUS
		    Azithromycin dihydrate 500mg IV q24 **OR** Clarithromycin 500mg PO bid
		    OR Levofloxacin 750mg IV q24 **OR** Moxifloxacin 400mg IV q24
		
		With risk for MRSA, add:
		    Vancomycin 15mg/kg IV q12 **OR** Linezolid 600mg IV q12
		
		All doses should be adjusted based on the patient's renal function.
		
		Risk factor for Pseudomonas infection: [11]
		    1. History of chronic or prolonged (>7 days within the past month) use of broad-spectrum antibiotic therapy
		    2. With severe underlying bronchopulmonary disease
		    3. Malnutrition
		    4. Chronic use of steroid therapy >7.5mg/day

Hospital-acquired pneumonia	(ATS/IDSA 2016) Management of Adults with Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guideline by the Infectious Disease Society of America and the American Thoracic Society[12]	**Not at high risk of mortality but with factors increasing the likelihood of MRSA:**
		    Ceftazidime or Cefepime 2g IV q8 **OR** Piperacillin-Tazobactam 4.5g IV q6
		    OR Levofloxacin 750mg IV q24 **OR** Ciprofloxacin 400mg IV q8
		    OR Aztreonam 2g IV q8 **OR** Imipenem 500mg IV q6 **OR** Meropenem 1g IV q8
		
		    PLUS
		    Vancomycin 15mg/kg IV q8-12 (consider a loading dose of 25-30mg/kg for severe illness) **OR** Linezolid 600mg IV q12
		
		High risk of mortality or receipt of IV antibiotics during the prior 90 days:
		    Two of the following but avoid 2 β-lactams:
		    Ceftazidime or Cefepime 2g IV q8 **OR** Piperacillin-Tazobactam 4.5g IV q6
		    OR Levofloxacin 750mg IV q24 **OR** Ciprofloxacin 400mg IV q8
		    OR Aztreonam 2g IV q8 **OR** Imipenem 500mg IV q6
		    OR Meropenem 1g IV q8 **OR** Amikacin 15-20mg/kg IV q24
		    OR Gentamicin 5-7mg/kg IV q24 **OR** Tobramycin 5-7mg/kg IV q24
		
		    PLUS
		    Vancomycin 15mg/kg IV q8-12 (consider a loading dose of 25-30mg/kg for severe illness) **OR** Linezolid 600mg IV q12
		
		All doses should be adjusted based on the patient's renal function.

		High risk for mortality include need for ventilatory support due to pneumonia and septic shock.

Ventilator-associated pneumonia	(IDSA/ATS 2016) Management of Adults with Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guideline by the Infectious Disease Society of America and the American Thoracic Society[12]	**VAP in units where empiric MRSA coverage and double antipseudomonal/ gram-negative coverage are appropriate:**
		    Vancomycin 15mg/kg IV q8-12 (consider a loading dose of 25-30mg/kg for severe illness) **OR** Linezolid 600mg IV q12
		
		    PLUS
		    Piperacillin-Tazobactam 4.5g IV q6 **OR** Cefepime or Ceftazidime 2g IV q8-12 **OR** Imipenem 500mg IV q6 **OR** Meropenem 1g IV q8 **OR** Aztreonam 2g IV q8
		
		    PLUS
		    Levofloxacin 750mg IV q24 **OR** Ciprofloxacin 400mg IV q8 **OR** Amikacin 15-20mg/kg IV q24 **OR** Gentamicin 5-7mg/kg IV q24 **OR** Tobramycin 5-7mg/kg IV q24 (**OR** Colistin 5mg/kg IV loading dose followed by 2.5mg x (1.5 x CrCl + 30) IV q12 **OR** Polymyxin B 2.5-3mg/kg/day divided in 2 daily doses, after consulting an ID specialist)
		
		All doses should be adjusted based on the patient's renal function.

Intraabdominal infections	Asian Consensus Taskforce on Complicated Intra-Abdominal Infections (ACT-cIAI) 2014[13]	**Severe community-acquired complicated intraabdominal infection:**
		    (Cefazolin **OR** Cefuroxime **OR** Ceftriaxone **OR** Ceftazidime **OR** Cefepime **OR** Cefotaxime) **PLUS** Metronidazole
		
		    OR
		    Piperacillin-Tazobactam 4.5g IV q6
		
		    OR
		    (Levofloxacin **OR** Ciprofloxacin) **PLUS** Metronidazole
		
		Severe healthcare-associated complicated intraabdominal infection:
		    (Meropenem **OR** Imipenem/Cilastatin **OR** Doripenem) **with or without** Vancomycin **OR** Linezolid
		
		    OR
		    Tigecycline **PLUS** (Aztreonam **OR** Ciprofloxacin **OR** Levofloxacin)
		
		    OR
		    Carbapenem **PLUS** (Tigecycline **OR** Polymyxin B **OR** Colistin, after consulting an ID specialist)
		
		All doses should be adjusted based on the patient's renal function.

Severe skin and soft tissue infection	(IDSA 2014) Practice Guidelines for the Diagnosis and Management of Skin and Soft Tissue Infections: 2014 Update by the Infectious Diseases Society of America[14]	**Severe Purulent SSTI**
		    Vancomycin **OR** Linezolid
		
		Severe Nonpurulent SSTI (Necrotizing Infection/Cellulitis/Erysipelas)
		    Vancomycin **OR** Linezolid
		
		    PLUS
		    (Ceftriaxone **PLUS** Metronidazole) **OR** Piperacillin-Tazobactam **OR** Meropenem **OR** Imipenem
		
		Severe purulent SSTI: patients who have failed incision and drainage plus oral antibiotics with signs of SIRS or those who are immunocompromised.

		Severe nonpurulent SSTI: patients who have failed oral antibiotic treatment or those with signs of SIRS, or those who are immunocompromised, or those with clinical signs of deeper infection such as bullae, skin sloughing, hypotension, or evidence of organ dysfunction. Clindamycin should be administered as soon as possible to patients with necrotizing fasciitis. [15] All doses should be adjusted based on the patient's renal function.
Sepsis/Septic shock, source is unclear	National Antibiotic Guidelines 2017[16]	Piperacillin-Tazobactam 4.5g IV q 6 **OR** Meropenem 1g IV q8 **PLUS** Vancomycin 25-30mg/kg IV loading dose then 1g IV q8, if with substantial risk for MRSA infection (The reader is directed to Question 23 on when to add MRSA coverage). All doses should be adjusted based on the patient's renal function.

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

Recommendations

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).*

Summary of Evidence

The Philippine Antimicrobial Resistance Surveillance Program of 2018 reported that the local cumulative rate of MRSA is 53% (n= 3,794).[1] Many of these isolates were from cutaneous (43%) and blood (21%) culture isolates. Majority (63%) were presumptively community-acquired. Invasive MRSA infections are associated with mortality that is as high as 30-40%. Compared to methicillin-sensitive strains, bacteremia caused by MRSA is associated with a worse prognosis such as increased hospital stay, morbidity, and mortality. After thorough search, no studies were found directly answering when empiric MRSA coverage is indicated for septic patients. Search terms used include methicillin-resistant *Staphylococcus aureus*, MRSA, sepsis, septic shock, and empiric antibiotic. In lieu of this, there are several published observational reports which identified the risk factors predisposing patients to have MRSA infections. Based on the presence of identified risk factors and high clinical suspicion that MRSA is the possible cause of the sepsis, prompt empiric antibiotics to cover for MRSA must be given to optimize patient outcome.

A retrospective paired case-control study was conducted in 41 intensive care units in Colombia with the aim of determining risk factors associated with the emergence of MRSA bacteremia.[2]   It included 372 subjects, of which 186 cases had MRSA bacteremia and 186 had methicillin-sensitive *Staphylococcus aureus* (MSSA) bacteremia. The multivariate analysis demonstrated an association between the presence of MRSA and history of use of vascular catheters (OR=1.986; 95% CI: 1.038-3.801) and of urinary catheters prior to hospitalization (OR=2.559; 95% CI: 1.170-5.596). The increased risk of MRSA infection can be explained by factors such as bacterial colonization of devices, greater exposure to manipulation and therefore to cross-transmission, and increased exposure to the use of prophylactic antimicrobials which could have a selective effect on the microorganism. The previous use of intravenous antibiotics emerged as the main risk factor for the presence of MRSA as a causal agent of bacteremia. A gradient related to the number of antibiotic families used was found in the study population: one family (OR=4.565, 95% CI: 2.541-8.203), two families (OR=12.405, 95% CI: 5.286-29.111) and three or more families (OR=31.742, 95% CI: 8.967-112.367). The effect of carbapenems on the emergence of MRSA was greater than that of quinolone, beta-lactams, aminoglycosides and vancomycin.[2]   The presence of these histories should serve as an alert to identify at-risk populations so as to anticipate and prevent the negative consequences of MRSA infection.

Another case control study by Carnicer-Pont in Wales, United Kingdom included 132 patients for whom risk factors for hospital-acquired MRSA bacteremia were identified.[3] Forty two cases had MRSA bacteremia and 90 patients who stayed in the hospital for more than two days were selected as controls. After adjusting for all factors, having a central line [adjusted OR (aOR) 35.3, 95% CI 3.8–325.5] or a urinary catheter (aOR 37.1, 95% CI 7.1–193.2) inserted during the stay, and suffering from a surgical site infection (aOR 4.3, 95% CI 1.2–14.6) remained independent risk factors for hospital-acquired MRSA bacteraemia.

Patients with end-stage renal disease have a 100-fold higher risk of MRSA infection compared to the general population. To estimate the prevalence of MRSA colonization in dialysis patients and long-term risk of subsequent infections, a meta-analysis of 38 studies including 5596 patients was published by Zacharioudakis. It revealed that 6.2% of dialysis patients are MRSA-colonized, and that patients on hemodialysis were more frequently colonized than those who are on peritoneal dialysis (p=0.01).[4]   The risk of developing MRSA infections increased among colonized hemodialysis patients compared to noncolonized patients (RR, 11.5 [95%CI, 4.7 to 28.0]).

In a case control study by Torre-Cisneros, clinical predictors of MRSA nosocomial or healthcare-associated pneumonia were identified to define a high-risk population in whom coverage against MRSA may be needed. The variables associated with the risk of MRSA pneumonia were respiratory infection/colonization caused by MRSA in the previous year, hospitalization in the previous 90 days and age (sensitivity 74.5%, specificity 63.3, positive predictive value 52.5%, and a negative predictive value 82.0%).[5]

Several studies have been done to identify factors associated with mortality among patients with MRSA bacteremia. Previous hospitalization in the past three months, residence in a long-term care facility, previous admission in the ICU, and complicated, severe or critical

initial presentation (endocarditis, septic shock, altered mental status) may be used as a guide for empirical MRSA therapy and application of infection control measures in older adults with suspected *S. aureus* bacteremia.[6]

Table Q26.1 Risk Factors Associated with MRSA Infection

Study	Design	Risk Factor	Odds Ratio	95% Confidence Interval
Zacharioudakis, 2014	Meta-analysis (n=5596)	MRSA colonization	11.5	4.7-28.0
Arias-Ortiz, 2016	Retrospective paired case-control study (n=372)	Intravascular device	1.986	1.038-3.801
		Urinary device	2.559	1.170-5.596

		Number of antibiotic families
		   One
		   Two
		   Three or more
			
			4.565
			12.405
			31.742
				
				2.541-8.203
				5.286-29.11
				8.967-112.367

Carnicer-Pont, 2006	Case control (n=132)	Intravascular line	35.3	3.8-325.5
		Urinary catheter	37.1	7.1-193.2
		Surgical Site Infection	4.3	1.2-14.6
Torres-Cisneros, 2017	Case-control (n=320)	Respiratory infection or colonization with MRSA in the previous year	14.81	4.13-53.13
		Hospitalization in the previous 90 days	2.41	1.21-4.81
		Age	1.02	1.001-1.05
Bader, 2006	Retrospective cohort (n=209)	Previous hospitalization in the past 3 months	2.6	1.1-5.9
		Residence in a long-term care facility	4.5	1.7-12.3
		Altered mental status at the onset of S. aureus	2.5	1.5-5.16

In summary, 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. 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.

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

Recommendation

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

Summary of Evidence

The Surviving Sepsis Campaign Bundle: 2018 Update recommends the administration of antibiotics within the first hour of recognition of sepsis, as initial studies showed mortality benefit on patients who received the antibiotics within the first hour.[1] 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.[2] The latter focused on the timely administration of appropriate antibiotics, based on antibiogram and culture sensitivity results. With a total of 2,154 septic shock patients (78.9% total) who received effective antimicrobial therapy after the onset of hypotension, delay in effective antimicrobial initiation was shown to be associated with in-hospital mortality (adjusted odds ratio 1.119 [per hour delay], 95% CI, 1.103 to 1.136, p <.0001).   Furthermore, a survival rate of 79.9% was seen with administration of effective antimicrobial for isolated or suspected pathogens within the first hour of hypotension.

In a systematic review done by Sterling et al., the association between the timing of antibiotics and mortality in septic and septic shock patients was assessed. In 11 studies that included a total of 11,017 patients from the emergency department and ICU, patients were divided into two groups: those who received antibiotics more than three hours after triage, and those who received the antibiotics at least one hour after recognition of severe sepsis and septic shock. In the first group, the pooled OR for mortality was 1.16 (0.92 to 1.46, p=0.21), in the second group the pooled OR was 1.46 (0.89 to 2.40, p=0.13).[3] The study showed no significant difference in mortality whether antibiotics were started at least an hour, or after three hours.   We performed a meta-analysis on the subgroup of patients with septic shock patients. **Figure sQ27.1** showed a trend favoring the administration of

antibiotics within one hour of septic shock recognition, with an OR for mortality of 0.49 (0.13 to 1.83). However, majority of the studies used in this meta-analysis only focused on the timeliness of the administration of antibiotics rather than the appropriateness of the antibiotics used.

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.

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

Recommendations

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.

Summary of Evidence

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.[2] Utilizing knowledge on altered drug pharmacokinetics during sepsis in order to optimize antimicrobial administration may improve outcomes in critically-ill patients.

Beta-lactams

Beta-lactams are commonly used in the intensive care unit (ICU) for critically-ill patients, including those with sepsis or septic shock. They are time-dependent antibiotics and exhibit maximum bactericidal activity when unbound concentrations of the drug exceed the minimum inhibitory concentration of the bacterial pathogen (f_T>$_{MIC}$).

To overcome the problem of possible reduction of the f_T>$_{MIC}$ in patients with sepsis, prolonging the infusion time is considered a strategy in optimizing beta-lactam therapy. Prolonged infusion may be administered either continuous (constant throughout a 24-hour period) or extended (≥3 hours). Intermittent infusion is administered over a period of ≤60 minutes.

A meta-analysis conducted by Roberts in 2009 did not report any benefit of the continuous infusion of beta-lactam antibiotic,[3] but more recent meta-analyses by several authors showed benefit in terms of mortality and clinical cure. [4-11] The populations in these studies, however, included critically-ill patients, not specified if diagnosed with sepsis or not.

Prolonged infusion of piperacillin-tazobactam was associated with 1.46-fold lower odds of mortality, 1.77-fold higher odds of clinical cure and 1.22-fold higher odds of microbiological cure in a study done by Rhodes et al.[7]

In a meta-analysis done by Yu et al., prolonged infusion of meropenem in severe infection, either extended or continuous, also had a significantly lower mortality compared to intermittent bolus. The bacterial eradication rate was significantly higher in extended or continuous group compared to the intermittent infusion group. [8]

Prolonging or extending cephalosporin infusion did not show significant benefit in terms of mortality and clinical cure compared to short-term infusions based on the meta-analysis conducted by Korbila and colleagues. In eight of the 11 studies included in the analysis, patients in the extended or continuous group received a lower total daily dosage of the antibiotic compared with patients in the short-term infusion group. Only three out of the six randomized controlled trials that provided data for mortality had the same total daily dosage of the antibiotic administered in both groups.[9] The quality of evidence was downgraded because of this inconsistency.

Similar findings were found in a meta-analysis done by Vardakas et al. in 2017. Prolonged infusion of antipseudomonal β-lactams (carbapenems, penicillins, cephalosporins) was associated with lower all-cause mortality compared to short-term infusion. Subgroup analysis of studies on cephalosporins did not show significant results. Among the carbapenems, only meropenem administered via prolonged infusion showed a significant reduction in mortality. Two studies on imipenem-cilastatin did not show significant result for all-cause mortality.[10]

Vancomycin

Vancomycin is a widely-used glycopeptide for the treatment of gram-positive infections, especially community- and hospital-acquired MRSA in patients with sepsis and septic shock. It exhibits a time-dependent bactericidal activity and its administration by continuous intravenous infusion (CIV) maintains a constant plasma concentration at a steady state as compared with intermittent intravenous (IIV).[11]

In the revised consensus guidelines on therapeutic monitoring of vancomycin (2019), trough-only monitoring is no longer recommended for patients with MRSA infection, and in turn advocates Bayesian- derived AUC/MIC$_{BMD}$ ratio of 400-600, as this targets to achieve clinical efficacy while improving patient safety. CIV offers ease of drug level monitoring (i.e. steady- state concentration is taken at any time during the CIV) and is able to provide a

convenient way of achieving the desired therapeutic range of 20-25 mg/L (i.e. by multiplying steady state concentration by 24, a target steady state concentration of 20-25 mg/L would equate to AUC_{24}/MIC of 480 to 600 assuming MIC of 1ug/ml). It likewise provides less variability in serum concentrations and has lower risk of nephrotoxicity.[1,12] It is recommended to give a loading dose of 25-35mg/kg total body weight (TBW),[1,13] based on actual body weight not exceeding 3000mg, to be infused over a period of not less than 60 minutes followed by daily maintenance continuous infusion based on creatinine clearance.

CIV is comparable in efficacy and tolerance and is more cost effective than IIV[14] but it failed to show clinical superiority to IIV in terms of mortality.[15,16] In a meta-analysis done by Cataldo et al. in 2012, it was suggested that CIV is associated with a significantly lower risk of nephrotoxicity (RR 0.6, 95% CI 0.4–0.9, P= 0.02; I2=0%) and mortality in comparison to IIV (RR 1.03, 95% CI 0.7–1.6, P=0.9; I2=0%). This was comparable to the meta-analysis by Hao et al. in 2015, which showed a lower incidence of nephrotoxicity (RR = 0.61, 95% CI 0.47–0.80; P < 0.001), similar clinical efficacy, and no significant difference in treatment failure nor mortality (RR = 1.15, 95% CI 0.85–1.54; P=0.365) in CIV as compared with IIV. The meta analysis by Chu et al. in 2019 showed that with CIV, it was significantly easier to reach the effective concentration of the drug; CIV was superior to IIV in preventing the incidence of nephrotoxicity (RR= 1.70, CI 1.34-2.14; I2=0%). The body of evidence had limitations in that there were very few RCTs for CIV, and only one RCT with septic patients.

Overall, there is no difference in mortality between CIV and IIV vancomycin infusions; but CIV mitigates the risk of nephrotoxicity that is inherently increased in patients with sepsis and septic shock. **Table Q28.1** shows the dose adjustment of vancomycin and specific instructions for continuous IV infusion.

Table Q28.1. Continuous Infusion Maintenance Dosing[18] of Vancomycin after loading dose of 25-35 mg/kg

Estimated Creatinine Clearance	Continuous Infusion (added to a 500mL or 1000ml normal saline infused in 24 hours)
>90 mL/min	45 mg/kg/24 hours
75-89 mL/min	35 mg/kg/24 hours
60-74 mL/min	30 mg/kg/ 24 hours
45- 59 mL/min	25 mg/kg/24 hours
<45 mL/min	Intermittent traditional dosing is preferred
* Dose adjustments should be made in 250mg/day intervals	

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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?

Recommendation

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

Summary of Evidence

De-escalation refers to the discontinuation of an antimicrobial agent or the narrowing of antimicrobial coverage on the basis of the susceptibility pattern of the isolated pathogen, which is generally available at 48-72 hours.[1] Once the patient is hemodynamically stable and clinically improved, de-escalation can be done to help decrease antimicrobial resistance, avoid superinfection with resistant organisms, and prevent unnecessary costs and side effects.[1]

In search for robust evidence for de-escalation for adults with sepsis and septic shock, Silva et al. (2013) did a systematic review on 493 studies.[2] Their search revealed that there were no published RCTs testing this treatment approach and they concluded that there is no adequate direct evidence on the effectiveness and safety of de-escalation. However, they found one ongoing RCT by Leone et al., which was published the following year.[3] The multi-center, non-blinded, randomized, noninferiority trial was done in nine ICUs in France and is thought to be the first RCT on de-escalation. A total of 116 adult ICU patients with sepsis were randomized into the de-escalation arm (n=59) or continuation of empirical therapy group (n=57), tested for the primary outcome of length of ICU stay and defined a noninferiority margin of ≤2 days. Per-protocol analysis showed that patients whose antibiotics were de-escalated stayed longer in the ICU than the continuation group (3.4 days; 95% CI -1.7.8.5; p=0.71; considered inferior). There was also a higher number of superinfections and antibiotic days in the ICU among the de-escalation group (27% vs 11%; p=0.03; and 9 days vs 7.5 days; p=0.03, respectively). The occurrence of more superinfections justified the longer duration of antibiotic days and stay in the ICU. In contrast, there was no significant difference in the 90-day mortality, occurrence of organ failure, ventilator-free days, pressor-free days, and rate of readmission after discharge (31% vs 23%; p=0.35; HR = 1.31, 95% CI 0.64–2.67; p=0.49; ΔSOFA score 3 [0; 4] vs 2 [-1; 3]; p=0.63; 18.9 ± 11.6 vs 19.3 ± 11.8; p=0.55; 22.3 ± 10.3 vs 21.6 ± 11.2; p=0.93; 36% vs 32%; p=0.64, respectively) comparing the two strategies.   It is important to note that the study had a relatively small population and the randomization resulted in imbalances between the groups (in terms of age) and this could have influenced the findings.

A systematic review and meta-analysis by Guo et al. on the de-escalation of empiric antibiotics in patients with sepsis was published last 2016.[4]   Out of 285 studies initially considered, only nine were included in the meta-analysis, including the abovementioned

study. There was a total of 1,873 adult patients with sepsis or septic shock in six Western and three Asian studies. Four out of nine studies were rated having good methodological quality with a Newcastle-Ottawa scale (NOS) of 7-9 points [Leone, 2014 (8 points)]. The mortality trend was lower in the de-escalation group when compared with the continuation group, but did not reach statistical significance (RR=0.74; 95% CI 0.54-1.03; p=0.005; I^2=63.8%). Sensitivity analysis of the four studies with good methodological quality also showed no significant difference in mortality between the two groups (RR=0.85; 95% CI 0.67-1.08; p=0.373, I^2=3.9%). Another subgroup analysis of the five prospective studies showed a similar result (RR=0.91; 95% CI 0.75-1.12; p=0.651; I^2=0.0%). The authors concluded that de-escalation therapy has no detrimental influence on the mortality of patients having sepsis or septic shock.

De-escalation should be encouraged, whenever possible, in the context of a dedicated antibiotic stewardship program.[5] It is emphasized that the patient trajectory should be monitored closely; deterioration should prompt investigation for a recurrent or potential new source of infection, but not an automatic conclusion that de-escalation has failed.[1]

Consensus Panel Issues. Some of the panel members believe that 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.

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

Recommendations

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).*

Summary of Evidence

Different studies have confirmed that in patients with sepsis and septic shock, inadequate empirical antibiotic therapy is associated with higher mortality rates and increased the length of ICU and hospital stay. On the other hand, overuse and prolonged use of antimicrobial medications is directly related to untoward consequences in terms of toxicity, selection of resistant bacteria, patient compliance, and indirectly to financial costs. There is no one study that dealt with antibiotic duration for septic patients, aside from a post-hoc study among patients with complicated intraabdominal infection by Rattan, et.al. In general, most studies on antibiotic duration depend on the focus of infection and studies did not specifically analyze patients with sepsis. In critically-ill patients, clinicians are frequently reluctant to shorten duration of antimicrobial therapy. While patient factors direct and influence the length of antibiotic therapy, a treatment duration of 7-10 days (in the absence of source control issues) is generally adequate for most serious infections.

Ventilator-associated pneumonia (VAP) is the paradigm of severe infection in the critical care setting accounting for a high number of antibiotic prescriptions in the intensive care unit (ICU). Several studies on antibiotic duration for hospital-acquired pneumonia (HAP) and VAP were done; however, only one study specifically discussed the critically-ill. 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.[1] 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.

Despite diversity of specific processes in different complicated intra-abdominal infections, the basic tenets of management are similar: resuscitate patients who have the systemic inflammatory response syndrome (SIRS), control the source of contamination, remove most of the infected or necrotic material, and administer antimicrobial agents to eradicate residual pathogens. Antimicrobial therapy for the management of intra-abdominal infections continues to evolve. The appropriate duration of therapy, however, remains unclear. 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. Currently-used guidelines, including those published jointly by the Surgical Infection Society (SIS) and the Infectious Diseases Society of America (IDSA), recommend a treatment course of four to seven days, depending on the clinical response.

The STOP-IT trial was a prospective, randomized, investigator-initiated, open-label multicenter trial conducted at 23 US and Canadian academic medical centers.[2,3] Patients were eligible for enrollment in the study if they were 16 years of age or older, if they presented with a complicated intra-abdominal infection with either fever (temperature ≥38.0°C), leukocytosis (≥11,000 peripheral white cells per cubic millimeter), or gastrointestinal dysfunction due to peritonitis precluding intake of more than half their normal diet, and if they had undergone an intervention to achieve source control. Source control - defined as procedures that eliminate infectious foci, address factors that promote ongoing infection, and correct or manage anatomical derangements to restore normal physiological function - is critical to the management of any infection. The adequacy of source control was confirmed by the local investigator and the principal investigator of the overall study. The trial showed that for patients with intra-abdominal infections who had undergone an adequate source control procedure, the outcomes after fixed-duration antibiotic therapy (approximately four days) were similar to those who had a longer course of antibiotics (approximately eight days) that extended until after the resolution of physiological abnormalities.

The post-hoc study by Rattan which included septic patients (112/518) from the STOP-IT trial revealed that surgical site infection, recurrent intra-abdominal infection, extra-abdominal infection, hospital days, days to recurrent intra-abdominal infection, days to extra-abdominal infection, and mortality were similar between the short- versus long-course therapy. Days to surgical site infection was lower in the four-day therapy group (6.9±3.5 vs 21.3±6.1, p<0.001). Principles of treatment for complicated intra-abdominal infection remain constant: resuscitation of those with sepsis, removal of source of infection, and prompt initiation of systemic antimicrobial therapy.

In 2013, a systematic review and meta-analysis of randomized controlled trials on acute pyelonephritis and septic urinary tract infection was done.[4] Based on the study, seven

days of treatment for acute pyelonephritis is equivalent to longer treatment in terms of clinical failure and microbiological failure, and this was seen to be true even with the inclusion of bacteremic patients. However, in patients with urogenital abnormalities, longer treatment is required.[5]

The optimal duration of therapy for primary bloodstream infection and blood stream infection secondary to major organ system infections has been poorly defined. With the objective of determining whether the therapeutic equivalence of shorter- and longer- course antibiotic therapy extends to patients with bacteremia, a systematic review and meta-analysis of RCTs was done by Havey and colleagues. Low quality of evidence 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*.[5]

A systematic review by Garnacho-Montero described optimal duration of antimicrobial therapy in most infections affecting critically-ill patients. The review also included all the above-mentioned studies. It concluded that unjustified long antibiotic regimen may be associated with serious untoward effects. Short-course treatment of seven to eight days in VAP is not associated with higher mortality or relapses than prolonged courses (14 days).[6] Critically-ill patients with bacteremia are often treated with long courses of antibiotics. A seven- to ten-day course is possible in a great number of patients, excluding those with *Candida spp* or *S. aureus*. Measurement of procalcitonin (PCT) level could lend valuable information that, interpreted within the patient's clinical context, may be of help in deciding to stop antimicrobial therapy in doubtful situations.

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

Recommendation

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.

Summary of Evidence

The patient-level meta-analysis of 11 randomized controlled trials by Wirz et al. investigated the impact of procalcitonin-guided antibiotic therapy on mortality and other clinical outcomes among patients with sepsis.[1]   Of 4,482 patients included in the analysis, only 3,235 (72%) fulfilled the Sepsis-3 definition.   In this specific group of patients, 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). There was no effect on the duration of ICU and hospital stay.   Although no statistically significant differences in mortality were observed across different illness severities, organ dysfunction and infection types, the confidence intervals were towards benefit.

Examination of the outcomes based on infection types showed that patients with respiratory infections were the ones who benefited from reduced antibiotic exposure with PCT guidance (MD -1.36 days, 95%CI -1.99, -0.73).   This effect could have influenced the overall data of the study, given that nearly half (49%) of patients included in the analysis had respiratory infections.   This finding is 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.[2]   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.   The quality of evidence was low due to potential selection bias, performance bias, and indirectness; adherence to the PCT protocol ranging from 44% to 97% was the main variable involved. Sensitivity analysis was not carried out. Another meta-analysis of PCT-guided therapy which included critically-ill patients, regardless of diagnosis, did not show mortality benefit with higher compliance to PCT-guided therapy.[3]

It is important to note that BioMérieux Inc provided unrestricted grant to the analysis by Wirz and colleagues.[1]   Some of the authors also received support, attended meetings, and fulfilled speaking engagements with both BioMérieux and ThermoFisher, the companies that manufacture and distribute PCT assays.

Areas for Research. Future studies should look into the cost-effectiveness of PCT-guided therapy by considering the local cost of PCT measurements and potential savings in antibiotic consumption. Likewise, the effect of this strategy in terms of recurrence of infection and reduction in antibiotic resistance should be further investigated.

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SOURCE CONTROL

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

Recommendations

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.

Summary of Findings

The term "*source control*" encompasses a spectrum of interventions whose objective is the physical control of foci of infection and the restoration of optimal function and quality of life. Adequate source control – in conjunction with antibiotics, resuscitation and support of vital organ function – is a cornerstone of the successful management of the septic patient[1,2]. Early source control is defined as intervention within 6-12 hours of identification of the source of infection.

In the last decade an increased interest on fluids, vasopressors, antibiotics, and organ support techniques has been described. The importance of source control has also been highlighted in the Surviving Sepsis Campaign but it only makes limited statements on this matter,[3] likely a result of the following: there is paucity of high-level published evidence, with few rigorous large clinical series, and even fewer clinical trials. Second, the decision-making process in the individual patient is complex, and often not amenable to study using the design of a randomized controlled trial. Decisions involve consideration not only of the

underlying disease but of the stability of the patient, the presence of comorbidities, and the prior surgical history, factors that can each heavily influence the decision to choose one therapeutic option rather than another[2,4].

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[5]. Often it involves early diagnosis, drainage of infected fluids, debridement of infected soft tissues, removal of infected devices or foreign bodies. It eventually leads to definite measures that can be summed up in two ways: to correct anatomic derangements that result in ongoing microbial contamination, and to restore optimal function[6].

A large, prospective, multicenter observational analysis of the Antibiotic Intervention in Severe Sepsis study in Spain[7] evaluated the impact of source control on patients with septic shock. It was comprised of a total of 3,663 patients, of whom 1,173 (32%) underwent source control for abdominal (n=788, 67.2%), urinary (n=147, 12.5%), and soft-tissue infections (n=118, 10.1%). 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 [8-11] which showed that early intervention improved outcome. The largest study of Bloos et al.[9] was a prospective observational multi-center cohort study involving 44 German ICUs and 1,011 patients with severe sepsis or septic shock, with 424 patients (41.94%) who received interventional or surgical source control. Those who received source control later than six (6) hours after onset of organ dysfunction had a significantly higher 28-day mortality than patients with earlier source control (42.9% versus 26.7%, P <0.001). In contrast, in the study by Martinez et al.[7], time to source control of >12 hours was not associated with increased mortality.

There is insufficient evidence[12] to recommend a specific method of source control – whether minimally invasive, or open surgery.

The immediate removal of central venous catheters (CVC) remains controversial. To date, evidence from randomized controlled trials is lacking[13]. On one hand, catheter-related bloodstream infection (CRBSI) has been associated with increased mortality and delayed CVC removal could lead to worse prognosis if the focus of infection is the CVC itself [14,15]. On the other hand, immediate CVC removal may be unwarranted when catheter-related infection CRI is suspected but not confirmed, particularly when vascular access is problematic. Clinical practice guidelines for the management of CRI by the Infectious Diseases Society of America (IDSA) are unclear on what strategy to adopt in patients with CVC and suspected CRI[16]. Data from the two observational studies of Deliberato et al. and Lorente et al. [17,18] showed no mortality benefit of early catheter removal.

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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?

Recommendation

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*).

Summary of Evidence

Critical illness-related corticosteroid insufficiency (CIRCI) is characterized by dysregulated systemic inflammation resulting from inadequate intracellular glucocorticoid-mediated anti-inflammatory activity for the severity of the patient's critical illness (i.e. sepsis and septic shock, ARDS, severe CAP, burn, trauma etc.).[1,2] It results from dysregulation of the hypothalamus-pituitary-adrenal (HPA) axis, inadequate circulating levels of free cortisol and corticosteroid tissue resistance.[1,3]

Traditionally, the diagnosis of adrenal insufficiency is based on a random total serum cortisol level or changes in the serum cortisol level in response to a stimulation by 250 µg of adrenocorticotropic hormone (ACTH), the so-called Δcortisol.[4,5] Most recent guideline from the Endocrine Society confirmed that the high-dose (250-µg) ACTH stimulation test is superior to other existing diagnostic tests to establish the diagnosis of primary adrenal insufficiency, where peak cortisol levels below 18 µg/dl (assay dependent) at 30 or 60 min are interpreted as indicative of adrenal insufficiency.[6] A random cortisol of < 10 mg/dL also appears to be a strong predictor for the diagnosis of adrenal insufficiency in the critically-ill.[2]

The overall incidence of adrenal insufficiency in critically-ill patients is approximately 20%, with an incidence as high as 60% in patients with sepsis and septic shock.[2] It may affect several organ systems, and hypotension refractory to fluids and requirement of vasopressors is a common manifestation of CIRCI.[2,5] In these populations, it is emphasized that doing ACTH stimulation test or determining random cortisol is not required to diagnose the adrenal insufficiency. Nevertheless, identifying patients with existing or absolute adrenal insufficiency is extremely crucial, as they will be requiring longer or chronic corticosteroid coverage after the existing illness is resolved.

The response of septic shock patients to fluid and vasopressor therapy remains to be an important factor in identifying patients for optional corticosteroid therapy. Since the publication of the updated Surviving Sepsis guidelines, two large, multicenter RCT investigated the effect of low dose corticosteroids in septic shock patients. The Adjunctive Corticosteroid Treatment in Critically Ill Patients with Septic Shock (ADRENAL) Trial included patients with septic shock (defined as fulfilled two or more criteria of the systemic inflammatory response syndrome, and who had been treated with vasopressors or inotropic agents for a minimum of four hours up to and at the time of randomization) on mechanical ventilation in the ICU.[7] Continuous intravenous infusion of hydrocortisone at 200 mg per day did not result in significant reduction in mortality at day 90. However, the administration of hydrocortisone led to faster resolution of shock (HR 1.32; 95% CI, 1.23 to 1.41; P<0.001), shorter time to ICU discharge (HR 1.14; 95% CI, 1.06 to 1.23; P<0.001), and earlier cessation of the initial episode of MV (HR1.13; 95% CI, 1.05 to 1.22; P<0.001). Fewer patients in the hydrocortisone group compared to placebo group received a blood transfusion (OR 0.82; 95% CI, 0.72 to 0.94; P = 0.004).

On the other hand, the Activated Protein C and Corticosteroids for Human Septic Shock (APROCCHSS) Trial, reported a lower 90-day mortality in the hydrocortisone-fludrocortisone group (hydrocortisone 50 mg IV bolus every 6 hours, and fludrocortisone 50 µg tablet/NGT OD, administered for 7 days) compared with the placebo group. There was absolute difference of 6% (P=.03).[8] The trial involved ICU patients who had indisputable or probable septic shock for less than 24 hours; septic shock was defined as presence of a clinically or microbiologically documented infection, a SOFA score of 3 or 4 for at least two organs and at least six hours, and receipt of vasopressor therapy for at least six hours to maintain a systolic blood pressure of at least 90 mm Hg or a mean blood pressure of at least 65 mm Hg. All-cause mortality was also lower at discharge from the ICU and hospital, and at day 180. The time to weaning from vasopressors, to weaning from mechanical ventilation, and to reaching a SOFA score below 6 was shorter with hydrocortisone-fludrocortisone than with placebo. The trial was conducted in multiple centers in Europe where both medications are accessible. In the Philippines, however, fludrocortisone is not readily available.

Lv et al.[9] conducted a single-center RCT in China involving patients with onset of septic shock, which they defined as sepsis-induced hypotension where the systolic blood pressure was < 90 mmHg, or decreased by more than 40 mmHg or less than 2 standard deviations below normal for age in the absence of other causes of hypotension, within six hours despite adequate volume resuscitation. They found that low-dose hydrocortisone, given in a dose of 200mg/day as continuous IV for six days with tapering, did not provide benefit with regard to mortality, reversal of shock, in-hospital mortality and the duration of ICU and hospital stay. A similar outcome was observed by Tongyoo et al,[10] in a single-center RCT in Bangkok that involved adult patients with severe sepsis or septic shock within 12 h of their meeting ARDS criteria. The administration of hydrocortisone 50 mg IV every 6 h did not result in significant survival benefit.

The survival benefit of corticosteroids to treat sepsis and septic shock continues to be controversial. A meta-analysis by Rochwerg et al.[11] included 42 trials, involving critically ill children and adults diagnosed with sepsis, severe sepsis and septic shock. Half of the trials

have low risk of bias (RoB), and 30 of them were already included in the 2015 Cochrane review[12]. Majority used low-dose hydrocortisone (< 400 mg/d or equivalent) over a short course of therapy (< 3 d). This review revealed a small absolute reduction (2%) in mortality based on low-to-moderate certainty evidence. Likewise, corticosteroids resulted in higher rates of shock reversal at day 7 (RR 1.26; 95% CI, 1.12–1.42) and lower SOFA scores at day 7 (mean difference, −1.39; 95% CI, −1.88 to −0.89).

The most recent meta-analysis by Fang et al.[13] analyzed the results of 37 trials, eighteen of which involved septic shock patients. Eleven studies were appraised to have low risk of bias, but overall the meta-analysis had issues of significant publication bias and clinical heterogeneity. Majority used low-dose IV hydrocortisone (<400mg/d). Corticosteroid use was associated with reduced 28-day mortality (RR 0.90; 95% CI, 0.82-0.98; I^2 = 27%). Subgroup analysis revealed that 28-day mortality was significantly lower in patients taking corticosteroids among the long-course treatment trials (≥4 days, RR 0.92; 95% CI 0.85 to 0.98) and low-dose corticosteroids trials (hydrocortisone <400mg/d, RR 0.91; 95% CI 0.85 to 0.98). Similarly, corticosteroids were significantly associated with reduced ICU mortality (RR 0.85; 95% CI, 0.77-0.94; I^2 = 0%) and in-hospital mortality (RR 0.88; 95% CI, 0.79-0.99; I^2 = 38%). The review also showed increased shock reversal at day 7 (MD, 1.95; 95% CI, 0.80-3.11), and vasopressor-free days (MD, 1.95; 95% CI, 0.80-3.11) and with ICU length of stay (MD, −1.16; 95% CI, −2.12 to −0.20), SOFA score at day 7 (MD, −1.38; 95% CI, −1.87 to −0.89), and time to resolution of shock (MD, −1.35; 95% CI, −1.78 to −0.91).

Increased risk of hyperglycemia and hypernatremia was observed in the corticosteroid group compared to the control. On the other hand, rates of any severe adverse events or superinfections were not statistically significant.[13]

A smaller network meta-analysis by Gibbison[14] included 22 trials that did not show benefit in reducing mortality or reducing incidence of gastrointestinal bleeding or superinfection in septic shock. However, it did show that hydrocortisone boluses (OR 2.34, 95% CI 0.99–5.50) and infusions (OR 3.68, 95% CI 1.52–8.93) were more likely than methylprednisolone boluses and placebo to result in shock reversal.

Based on this recent evidence, we thus recommend giving low-dose intravenous corticosteroids (<400mg/d), either as boluses of continuous drip, and for a minimum of 4 days. We recommend giving the corticosteroids within 6 hours, following the evidence of the latest 2 large RCTs.[7,8]

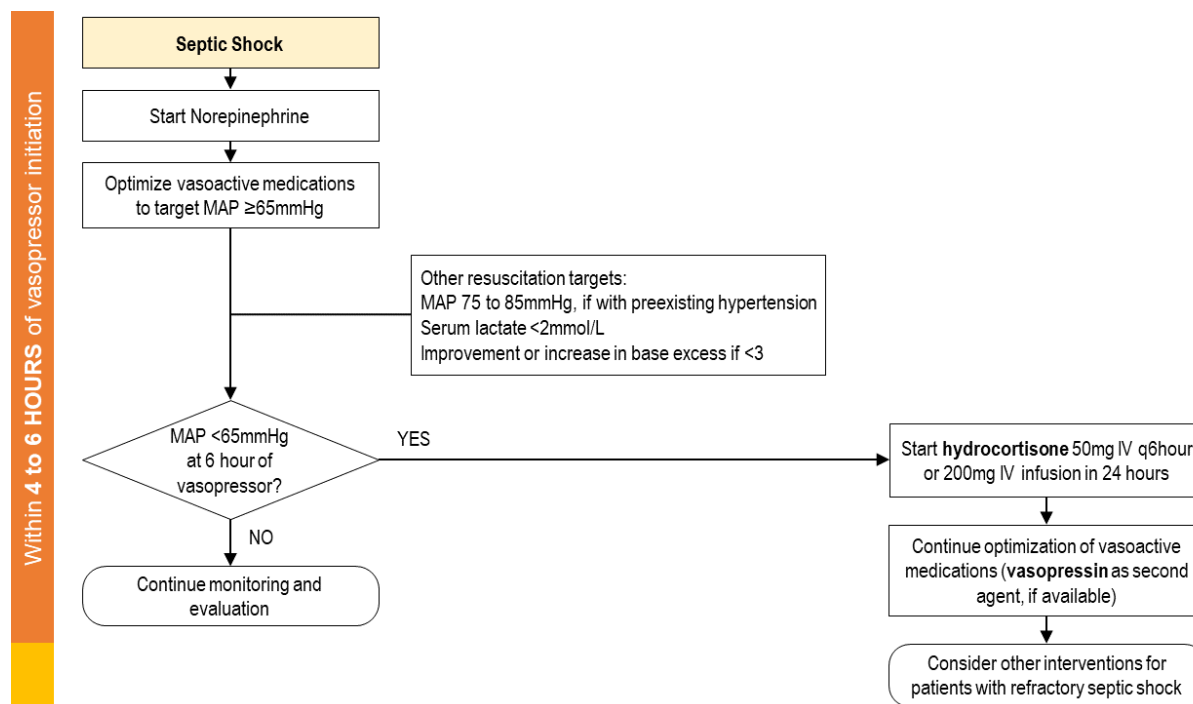**Figure 5.** Management of Patients with Septic shock

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GLYCEMIC CONTROL

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

Recommendation

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).*

Summary of Evidence

Based on moderate quality of evidence, there was no significant decrease in mortality and severity of illness with the use of intensive insulin therapy over conventional glucose control. With respect to adverse events, there was greater incidence of significant hypoglycemia with the use of intensive insulin therapy.

Most clinical trials comparing outcomes of intensive insulin therapy versus conventional sugar control among critically ill patients generally define "intensive insulin therapy" as targeting a blood glucose range of around 80 – 110 mg/dl (4.4 – 6.1 mmol/L), as opposed to "conventional sugar control" which targets a blood glucose range of 180-200mg/dl.[1-6] These trials enrolled either medical or surgical ICU patients or a mix of both, inclusive of patients with sepsis.

The largest clinical trial to date comparing intensive insulin treatment with conventional sugar targets was the multicenter Normoglycemia in Intensive Care Evaluation Survival Using Glucose Algorithm Regulation (NICE-SUGAR) trial[3] which randomly assigned 6,104 medical and surgical ICU patients to either intensive insulin treatment (target blood glucose level of 81 to 108 mg/dL [4.5 to 6 mmol/L]) or conventional glucose control (target blood glucose of <180 mg/dL [<10 mmol/L]). Patients on the conventional glucose control arm had their insulin infusion discontinued when they achieved a blood glucose level of 8mmol/L (144mg/dl). Thus, even though the conventional blood glucose arm was defined only in terms of its upper limit of 180mg/dl, since insulin infusion was essentially discontinued at 144mg/dl, the blood glucose range targeted by patients in this arm was in

effect 144-180mg/dl. In the NICE-SUGAR trial, there was no significant difference in the mortality rates of the group with intensive insulin treatment and conventional insulin treatment. Moreover, there was a significant increase in mortality among patients assigned to intensive insulin treatment (OR for intensive control, 1.14; 95% CI 1.02 to 1.28; P=0.02). Incidence of severe hypoglycemia (blood glucose level, ≤40 mg per deciliter [2.2 mmol per liter]) was also increased in the intensive-control group as opposed to the conventional-control group (P<0.001). With respect to 90-day mortality, the treatment effect did not differ significantly between patients with severe sepsis (OR 1.13, 95% CI 0.89-1.44) and patients without severe sepsis (OR 1.15, 95% CI 1.01-1.31) at randomization (P=0.93).

Meta-analyses which included the NICE-SUGAR trial[7,8] 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. 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.[8] 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).

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ACUTE RESPIRATORY FAILURE

Acute Respiratory Distress Syndrome (ARDS) is a type of acute, diffuse, inflammatory lung injury leading to increased vascular permeability, increased lung weight and loss of aerated lung tissue. This condition is characterized by hypoxemia, bilateral lung opacities on radiography, increased venous admixture, increased physiologic dead space and decreased lung compliance. Histologically, ARDS manifests as acute diffuse alveolar damage. The ARDS Berlin Definition[1] further categorizes severity of ARDS into mild, moderate and severe.

Table Q34.1 Acute Respiratory Distress Syndrome Definition

Acute Respiratory Distress Syndrome	
Timing	Within 1 week of a known clinical insult or new or worsening respiratory symptoms
Chest imaging[a]	Bilateral opacities—not fully explained by effusions, lobar/lung collapse, or nodules
Origin of edema	Respiratory failure not fully explained by cardiac failure or fluid overload. Need objective assessment (eg, echocardiography) to exclude hydrostatic edema if no risk factor present
Oxygenation[b]	
Mild	200 mm Hg < PaO_2/FiO_2 ≤ 300 mm Hg with PEEP or CPAP ≥5 cm H_2O[c]
Moderate	100 mm Hg < PaO_2/FiO_2 ≤ 200 mm Hg with PEEP ≥5 cm H_2O
Severe	PaO_2/FiO_2 ≤ 100 mm Hg with PEEP ≥5 cm H_2O

Abbreviations: CPAP, continuous positive airway pressure; FiO₂, fraction of inspired oxygen; PaO₂ partial pressure of arterial oxygen; PEEP, positive end-expiratory pressure.
[a] Chest radiograph or computed tomography scan.
[b] If altitude is higher than 1000 m, the correction factor should be calculated as follows: [PaO_2/FiO_2 × (barometric pressure/760)].
[c] This may be delivered noninvasively in the mild acute respiratory distress syndrome group.

From Ranieri, VM, Rubenfield, G., Thompson B. T., Ferguson, N. D., Caldwell, E., Fan, E., Camprota, L., Stutsky, A. S., (2012) Acute Respiratory Distress Syndrome The Berlin Definition. JAMA. 307(23):2526-2533.

On review of current evidence, the latest recommendations on Acute Respiratory Distress Syndrome Ventilatory Management came from the official joint statement of the American Thoracic Society, European Society of Intensive Care Medicine and the Society of Critical Care Medicine in 2017.[2] There are likewise recommendations on ARDS management from the Surviving Sepsis Guidelines 2016[3] and the Japanese Guidelines for the Management of Sepsis and Septic Shock.[4] It should be noted that most trials on ARDS involved a heterogenous population with varying underlying cause, although, majority of patients were with sepsis, septic shock and pneumonia.

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.

Consensus Panel Issues. As questions on ARDS were tackled during the meeting, several panel members raised issues concerning experience and expertise in terms of performing the interventions and maneuvers recommended for patients with this condition. Monitoring response and need for further intervention may also seem complicated for some generalists and internists, thus necessitating referral to trained or specialized physicians. For these reasons, majority of the panel member included the following recommendation:

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

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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?*

Recommendations

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 and 45.5 + 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).*

Remark: The reader is directed to Tables Q36.1 and Q36.2 for the ARDSNET PEEP / FiO2 tables

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.

Summary of Evidence

There are no large RCT's that specifically investigate the effects of mechanical ventilation on sepsis-induced ARDS. As shown in **Tables sQ36.1, sQ36.2, and sQ36.3 (Supplementary Material 2)**, 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.[1] Following the ARDSNET trial, studies[2-10] 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. 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.

The rationale for low tidal volume and limiting plateau pressures is directed towards preventing Ventilator-Induced Lung Injury (VILI). The application of PEEP is beneficial in providing lung recruitment for gas exchange.

The initial tidal volume should be set at 6 ml/kg PBW and can be increased to 8 ml/kg PBW if the patient is double triggering, or if the inspiratory airway pressure falls below the assigned PEEP. Double triggering occurs when the ventilator's inspiratory time is shorter than that of the patient's, such that a second ventilator breath is drawn because of the patient's incomplete respiration. More RCTs are needed to determine whether further reductions in tidal volume (< 6 ml/kg PBW, ie. <4ml/ kg PBW) are associated with greater improvements in patient outcomes.

Physiologically, application of PEEP leads to lung recruitment of the collapsed alveoli in ARDS. This leads to improved oxygenation but carries a risk of inducing barotrauma on already distended alveoli leading to VILI. It is recommended that application of high PEEP during ARDS Mechanical Ventilation be tempered not only with low tidal volumes but also by limiting plateau pressures. The optimum plateau pressure for obtaining treatment benefits without causing VILI is currently uncertain. Validation of the target plateau pressure is necessary. There is also recent observational data from patients pooled from multiple RCTS which demonstrate that driving pressure (deltaP = plateau pressure – PEEP) is a better predictor of outcome in ARDS rather than plateau pressure.[15] RCTs are needed to further evaluate such potential strategy.

Table Q36.1. Lower PEEP / higher FIO2 table. Adapted from the ARDS NET Protocol 2000.

FiO2	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

FiO2	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

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

Recommendation

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

Summary of Evidence

Only three studies exploring the use of low tidal volume in ventilating patients without ARDS were reviewed.[1-3]   None of these was an RCT; study designs were quasi-experimental[1] as well as prospective[2] and secondary retrospective cohorts.[3] Unlike the RCTs employing lung protective ventilation strategies in patients with ARDS, no study prespecified patients with sepsis - although in majority of the patients in these studies, the cause of the need for mechanical ventilation was attributed to sepsis. The quasi-experimental before-and-after study of Fuller (n=920) employed low TV (<6ml/kg PBW) and high PEEP for those with respiratory failure not meeting the criteria for ARDS. In this study, a third of each intervention group was composed of septic patients; results showed that those who received the low TV/ high PEEP intervention had an adjusted mortality OR of 0.47 (0.35 – 0.63). More studies, however, are needed to provide better quality evidence of benefit in using lung protective strategies in patients with sepsis who do not have ARDS.

Areas of research. Lung protection in non-ARDS patients needs to be defined. It would seem that in the available observational studies reviewed, low tidal ventilation carries no harm and can potentially improve mortality. The effect of modest to high PEEP needs to be further explored in non-ARDS patients who likely do not have collapsed lung zones needing recruitment. Recommendations for PEEP setting in non-ARDS patients are lacking.

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

Recommendation

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

Summary of Evidence

Recent meta-analysis by Silversides et al. (2016) including 49 studies and was designed to exclude observational studies with high risk of bias, concluded that conservative fluid management with or without deresuscitation during the post-resuscitation phase of sepsis only decreased ventilator dependency and ICU stay but not overall mortality.[1] It must be noted that the effects of active deresuscitation - actively giving diuretics in the post-resuscitative phase - cannot be distinguished from conservative fluid management alone, as studies are heterogenous and commonly employ both fluid strategies. Moreover, the start of the "post-resuscitation" phase in the studies is not adequately defined, making it difficult to recommend when to start deresuscitation. Fluid restriction and deresuscitation are only given to patients who are hemodynamically stable and with no evidence of tissue hypoperfusion. Even without a mortality benefit, the strong evidence suggesting decrease in ventilator dependency[1] and ICU stay[1,2] as well as a good safety profile[1] of a fluid conservative strategy mandate a recommendation. Thus, we recommend conservative fluid management and deresuscitation in sepsis-induced ARDS, in patients past the fluid resuscitation phase of sepsis and to those who are hemodynamically stable and show no evidence of tissue hypoperfusion.

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

Recommendation

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*).

Summary 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. RMs involve transient increase in the transpulmonary airway pressure with the intention of opening or recruiting atelectatic lung segments and increasing the number of alveolar units capable of receiving tidal ventilation. Various strategies have been utilized, including sigh maneuvers, decremental PEEP, incremental PEEP, sustained inflation maneuvers, to name a few.   Initial studies have shown conflicting results. The latest meta-analysis, in 2017[1], of six trials with varied RMs showed that RMs are associated with reduced mortality, improved oxygenation, and lesser need for rescue therapy. 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[2]. 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.

Due to the lack of consistent evidence on the proper recruitment maneuver strategy as well as the contemplated level of PEEP needed after a RM, plus issues of indirectness (since the population involved in the trials in the systematic review included non-sepsis ARDS patients), we have decided to give a conditional recommendation for the use of recruitment maneuvers under the care of a pulmonary specialist or intensivist for patients with sepsis-induced ARDS who are hemodynamically stable, with baseline plateau pressure of <30 cmH_2O and who present with refractory hypoxemia after initial lung protection strategy (low TV/ high PEEP).

Area of Research. Recruitment maneuvers employed in various studies are variable. The optimum way of conducting a recruitment maneuver with attention to safety (barotrauma, hemodynamic effects) needs to be elucidated. The guide to determining optimum PEEP after a recruitment maneuver is still an area that needs to be explored. The optimum PEEP after a maneuver should be able to maintain maximum recruitment while preventing VILI.

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

Recommendation

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

Summary of Evidence

Proning is a recruitment maneuver that allows increase in the amount of aerated lung tissue during ARDS management. The landmark trial of PROSEVA 2013 highlighted the importance of early proning in ARDS, provided over a longer period of time, in reducing short-term and long-term mortality. Unlike previous proning studies which only included a minor population of septic patients (<5%) [2-4], the PROSEVA trial enrolled a significant number – up to 85% - of patients with ARDS who had accompanying sepsis.   It supported earlier studies that showed improved oxygenation[5]. A recent meta-analysis by Munshi et al.[6] further illustrated in a subgroup analysis that studies which placed patients longer on prone position (minimum of 12 hours) showed mortality reduction (RR, 0.74; 95% CI, 0.56–0.99) overall while those positioned over shorter durations did not (RR, 1.03; 95% CI, 0.88–1.20). There is, however, an increased risk for unplanned extubation, with an RR 1.15 (0.89 to 1.50). Hence, we recommend early proning of patients with sepsis who have severe ARDS, for longer periods of time > 12 hours/day.

Area of Research. The PROSEVA landmark trial as well as all the other prone positioning studies on ARDS involved centers with high experience in conducting the maneuver. The effect of prone positioning on patient outcomes in centers with minimal to low experience, or to those new to the maneuver, needs to be determined.

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

Recommendation

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).*

Summary of Evidence

It must be noted that the three pioneer RCTs in the use of NM Blockade did not distinguish sepsis in its study population and all used cisatracurium as the NM blocker.[1-3]   A meta-analysis by Alhazzani et al.[4] showed that if used early in ARDS, it can decrease ICU mortality (RR 0.70, CI, 0.55 to 0.89, p = 0.004) and mortality at 28 days (RR, 0.66, CI 0.50 to 0.87, p = 0.003). It can also increase ventilator-free days (mean difference 1.91, CI 0.28 to 3.55, p= 0.02); however, there was a high risk of bias in this study. Meanwhile, a large retrospective cohort study[5] investigated NM blocker use specifically in severe sepsis with ARDS. This study observed an in-hospital mortality risk ratio of 0.88, (CI 0.8 to 0.96; 95%)[5] in favor of NM blockade use in sepsis-induced ARDS.

The latest ROSE study[6], was the largest RCT to date that investigated early neuromuscular blockade in ARDS. The trial was prematurely stopped for futility and showed

no significant difference in terms of mortality even at 90 days between those that used NM blockade and those that did not with RR 0.99 (CI 0.84 – 1.17). 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 (**Figure sQ41.1, Supplementary Material 2**). 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) (**Figure sQ41.2, Supplementary Material 2**).

While the technical group's meta-analysis showed the potential benefit of NM blockade in patients with severe ARDS in terms of reducing mortality, the potential high risk of bias and a lack of specificity addressing sepsis-induced ARDS pose limitations. We therefore provide a weak recommendation on the use of early neuromuscular blockade in moderate-severe ARDS. We acknowledge, however, the need for further studies exploring NM blockade, as well as other NM -blocking agents, in sepsis-induced ARDS.

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

Recommendation

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

Summary of Evidence

Extracorporeal life support (ECLS) has been in use since the 1970s as salvage therapy for various illnesses. ECLS is the use of an external device that provides gas exchange in an extracorporeal circulation. Therefore, it can provide oxygenation (Extracorporeal Membrane Oxygenation, ECMO) and removal of accumulated carbon dioxide (Extracorporeal Removal of Carbon Dioxide, $ECCO_2R$) in respiratory failure refractory to conventional mechanical ventilation. The technology behind ECLS has changed significantly from its infancy in the 1970s to the current times. Much interest on the use of ECMO in recent years came from the experience of managing ARDS that developed among patients afflicted with the pandemic AH1N1 strain in the late 2000s.[1]

Performing ECMO has associated higher costs, increased expertise needs and technology requirements. ECMO is used in refractory ARDS and common indications include 1) refractory hypoxemia with PF ratio <80, 2) hypercapnia with acidemia pH<7.15, and 3) a persistently high end-inspiratory plateau pressures ≥35cm H_2O, despite receiving optimal mechanical ventilation and recruitment maneuvers.

Most of studies that looked into the use of ECMO in ARDS are low-powered prospective studies, reports of experiences or review of case cohorts or databases. To date, there are only two big RCTs[2-3], three systematic reviews,[4-6] and multiple reported experience and review of case cohorts in the literature. Because most studies on ECMO involved patients who developed ARDS from pneumonia, the proportion of subjects presenting with sepsis from other sources of infections cannot be determined.

The systematic reviews [3-6] involved trials that utilized various ECLS technologies, and even studies that took place before the current standard lung protection strategies were put in practice. These factors, along with the heterogeneity of the included populations, presented difficulty in combining the results. A 2017 meta-analysis[6] concluded that there is still limited evidence on the use of ECMO in ARDS patients.

The CESAR study[2] in the UK was the first RCT in the current intensive care management era which strengthened the recommendation of early ECMO in ARDS. It suggested that referral to an ECMO-capable center within 3-6 hours of failed recruitment maneuvers may be beneficial. It should be noted, however, that there was lack of standardization in the way conventional mechanical ventilation was provided in the non-ECMO group.

The recent ten-year RCT of EOLIA[3] enrolled the largest population of ARDS patients undergoing ECMO, most of whom had pneumonia as the primary cause of ARDS. It failed to show mortality benefit at day 60 (primary outcome) when compared with a strategy that used conventional mechanical ventilation. For ethical reasons, 28% of the patients in the control group were allowed to cross over to the ECMO group. The authors did recognize that this methodology may have influenced the results of the primary outcome. Inspite of this, the EOLIA trial strengthened the recommendation that the early use of ECMO, rather than late, in the course of the illness attains success rates similar to other therapies for ARDS such as proning maneuvers and neuromuscular blockade.

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. Further research is needed to strongly recommend by-protocol use of ECMO in ARDS, and to determine target populations for its use and the influence of new advances in equipment for ECMO on patient outcomes.

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.

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

Recommendation

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

Summary of Evidence

This recommendation echoes the 2016 Surviving Sepsis Campaign guidelines on ventilation in sepsis-induced ARDS. The latest meta-analysis[1] published in the ATS involving six trials supports the premise that HFOV does not reduce 30-day hospital mortality due to ARDS. As shown in Table sQ43.1, we only considered studies that mentioned sepsis, septic shock and non-pulmonary sepsis in their study population.

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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)?

Recommendations

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).*

Summary of Evidence

NPPV has been an established intervention for patients with exacerbation of COPD, acute cardiogenic pulmonary edema, obstructive sleep apnea and as a bridge to successful weaning from mechanical ventilation..

In treating severe ARDS, it is worthy to call upon the results of the first RCT which dealt with treating severe ARDS with noninvasive ventilation[1]. The later LUNG SAFE study[2] demonstrated that NIV is used in about 15% of patients with ARDS, irrespective of the severity of hypoxemia; patient selection then becomes a factor in determining NIV failure and, consequently, mortality and morbidity. Helmets[3], exclusive bilevel positive airway pressure (BiPAP) machines[4] and ventilators with NIV employing vented and non-vented face-mask[5] were used in different studies that investigated the use of NIV in ARDS. These

were prospective and retrospective cohort studies in design, but 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. 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

Similar to the experience of the Japanese 2017 ARDS guidelines[6], the group anticipated difficulty in retrieving studies that employed NIV in ARDS. Hence, a more useful clinical question was explored, and this is regarding the use of NIV in patients with sepsis who also have non-cardiogenic hypoxic respiratory failure. The evidence tables compare NIV with oxygen therapy and NIV with outright ventilation. It is interesting to note that although this does not directly address sepsis-induced ARDS, more than 80% of the pooled study population were identified as having pneumonia even if not all studies explicitly stated the presence of sepsis.

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ACUTE KIDNEY INJURY

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

Recommendation

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.

Summary of Evidence

Acute kidney injury remains a common complication among critically ill septic patients. There has been an increase in the use of various extracorporeal blood purification techniques such as intermittent hemodialysis (IHD) and continuous renal replacement therapy (CRRT) [1].   The use of peritoneal dialysis (PD) was once a widely accepted and favored modality of renal replacement therapy in acute kidney injury in the 1970s. No extracorporeal machine is required in the conduct of the process and so it is postulated to have good hemodynamic tolerance, more physiologic tolerability and less inflammatory response compared to the extracorporeal therapies such as continuous or intermittent hemodialysis[2].   Yet there are concerns that PD may not be adequate for acutely ill patients, particularly those patients who are hypercatabolic[3].   Its use remains to be more widespread in the low resource setting because of its lower cost and minimal infrastructure equipment requirements[4].

There is paucity of good quality evidence on the use of peritoneal dialysis in acute kidney injury. A systematic review was published by Chionh et al. in 2013, and it described the outcomes of patients with acute kidney injury who were treated with peritoneal dialysis compared with other extracorporeal blood purification techniques. Twenty-four studies with a total of 1,556 patients were included in the review. Thirteen studies were descriptive in nature, in which PD was discussed as a modality in AKI. The pooled mortality was 39.3%, whereas mortality in the individual studies ranged from 1.1% to 100%. Six of the thirteen studies reported the proportion of septic patients involved, and this ranged from 38.6-40%. In the studies that included only 0%–10% septic patients, there was found to be lower mortality rates ranging from 1.1% to 26%. Majority of the studies came from low-resource settings in Asia, Africa, and South America. Eleven studies compared PD with any extracorporeal blood purification technique, majority of which were intermittent hemodialysis.   Sample sizes of these studies were fairly small (median size= 60). Seven studies were observational cohorts while four were randomized controlled trials. Pooled mortality was 58% in PD and 56% in extracorporeal blood purification techniques. Among

the observational studies, there was no significant difference in mortality between the two groups (odds ratio, 0.96; 95% CI 0.51-1.71). Pooled results from the randomized controlled trials showed a tendency to harm when peritoneal dialysis was compared to other extracorporeal blood purification techniques, but this was not significant (OR 1.50, 95% CI 0.46-4.86). However, significant heterogeneity was noted (I^2= 73%, p=0.03) among the four studies which may have been due to the varied etiologies of acute kidney injury among the included populations (sepsis, hemodynamic alterations, prerenal causes and malaria).

Current literature shows that either modality may be used in the setting of acute kidney injury in sepsis. 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.

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

Recommendations

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.

Summary of Evidence

Acute renal injury that is severe enough to need renal replacement therapy remains a critical problem in patients with sepsis. Several modalities for extracorporeal replacement of renal function have become available although none proven to be superior over the other. 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]. However, disadvantages include high cost, the need for specialized machinery, lines, replacement fluid, experienced nephrologists and nurses, and increased workload among the staff. Furthermore, there is a definite need for continuous anticoagulation during CRRT to prevent clotting. Several studies [2–5]have shown an association with improved survival but the evidence is not robust and lacks statistical significance.

A meta-analysis of 13 studies examining the use of CRRT versus IRRT in critically ill patients showed no overall difference in mortality between the two groups (RR 0.93 CI 0.79-1.09 p=0.29).[6] Only three of the 13 studies were RCTs, and even when randomized, equal allocation to treatment arms based on severity of illness was not ensured. Moreover, study population was not primarily composed of septic patients, thus the strength of evidence was further downgraded. Another meta-analyses of six RCTs did not show any significant difference between intermittent and continuous RRT (0.96 95%CI 0.85-1.08, P=0.50).[7] There was no significance difference seen in mean arterial pressure or change in systolic blood pressure between the two modalities. [4,8,9] The recommendation remains unchanged and stays consistent with the 2016 Surviving Sepsis guidelines.

An alternative to CRRT in hemodynamically unstable patients is prolonged intermittent renal replacement therapy (IRRT) which is a special form of intermittent dialysis that uses low blood and dialysate flow rates, translating to slower rate of solute and fluid removal, and more stable blood pressures. Metabolic control is noted to be comparable to CRRT.[10] A meta-analysis including six randomized trials and ten observational trials evaluated prolonged IRRT and CRRT in the treatment of AKI in critical illness. Among the randomized controlled trials, there was no significant difference in the risk for mortality between the two modalities (RR 1.06, 95% CI 0.92-1.22, P=0.42). There was also no significant difference in rate of recovery of kidney function with prolonged IRRT compared to CRRT (RR, 1.2; 95% CI, 0.94-1.53; P =0.14), but the studies included in this analysis showed moderate heterogeneity (I^2= 67%). Secondary outcomes such as difference in fluid removal also showed no significant difference between the two.[11] 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.

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

Recommendation

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.

Summary of Evidence

Sepsis-induced acute kidney injury has been associated with increased mortality of up to 75%.[1,2] It has been shown to have greater hemodynamic alterations and increased severity of illness. However, there is still a lack of consensus regarding the implementation of renal replacement therapy (RRT) in critically-ill septic patients with acute kidney injury. Currently, there is a lack of high-quality evidence to guide doctors on the optimal time to start RRT.

A systematic review and meta-analysis of 15 studies published in 2011 suggests an association of early RRT with reduced mortality (OR 0.45; 95% CI 0.28-0.72, P<0.001 for mortality at 28 days) among critically ill patients. However, significant heterogeneity was demonstrated in the pooled studies (I^2= 78%).[3] Another meta-analysis of nine randomized controlled trails published later in 2017 reported no significant difference in mortality in early and late renal replacement therapy (RR 0.91; 95% CI 0.72-1.16 P= 0.46).[4] In these studies, moderate heterogeneity was seen (I^2= 49%, p=0.05). This was attributed to marked variability in study population, design and quality, and lack of consensus regarding the operational definition of "early" and "late" RRT. Criteria ranging from clinical factors (i.e. volume overload, symptoms of uremia) and biochemical cutoffs (blood urea nitrogen level, urine output, serum creatinine, and number of hours from diagnosis of AKI) were used. Majority of the studies[5–8] used blood urea nitrogen cutoffs to define early (< 21.4-28.6 mmol/L) and late RRT. The timing of measurement of these values varied between study designs. The quality of the included studies were judged to be low due to indirectness (different patient populations with acute kidney injury) and inconsistency (heterogenous trials).

There were seven studies that studied renal recovery with RRT. Among those who survived, recovery of renal function, enough to be off RRT, was similar between the early RRT and late RRT groups (RR 1.02, 95% CI 0.99–1.06, p = 0.16). No significant heterogeneity was detected (I^2 = 0%, p = 0.87). Meanwhile, among the fifteen studies included in this meta-analysis, four studies [9–12] reported catheter-related infections. In these studies, it was found that early RRT was associated with a higher incidence of catheter-related infections compared with late RRT (RR 1.82, 95% CI 1.03–3.21, p = 0.04). Thus, 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. The conventional indications for commencing RRT in patients with acute kidney injury, namely, refractory acidosis, severe hyperkalemia, uremia, oliguria/anuria, and volume overload unresponsive to diuretic therapy remain to be recognized and universally accepted.

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

Recommendation

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

Summary of Evidence

Severe acidemia in sepsis contributes to hemodynamic instability because of arterial vasodilation, reduced myocardial contractility, and reduced responsiveness to catecholamies[1].   A systematic review by Ghauri et al. in 2019 reviewed the evidence on the administration of bicarbonate therapy in critically-ill patients with metabolic acidosis. The main reason for starting bicarbonate therapy was to prevent or reverse the effects of metabolic acidemia, especially in the cardiovascular system.[2]   In the said review, twelve articles were included and results suggested limited benefit from the administration of bicarbonate in critically-ill patients with metabolic acidosis. Three recent studies explored its use in patients specifically with sepsis or septic shock[3–5], but these failed to prove that sodium bicarbonate therapy offered any significant benefit in mortality or time to reversal of shock.   A large retrospective observational study done by Zhang et al. in 2018 included 1,718 septic patients with metabolic acidosis all enrolled in the US-based critical care database, the Medical Information Mart for Intensive Care (MIMIC-III). Propensity score analysis showed that serum bicarbonate infusion was not associated with improved mortality in the overall population (HR 1.04, 95% CI 0.86- 1.26, p =0.673).   The evidence leads to the recommendation that remains consistent with the 2016 Surviving Sepsis guidelines.

In 2010 and 2018, two studies were conducted which explored the benefit of serum bicarbonate therapy in a subset of critically-ill patients with severe sepsis, and acute kidney injury. The BICAR-ICU trial, a phase III multicenter, randomized controlled trial, conducted an *a priori* analysis among septic patients diagnosed with acute kidney injury network (AKIN) criteria stage 2 or 3.   They found that infusion of sodium bicarbonate resulted in fewer deaths by day 28 compared to no infusion (63% [95% CI 52–72] *vs* 46% [35–55]; RR= 0.72, 95% CI 0.55-0.95, p=0.0283).[4]   A similar benefit was demonstrated among septic patients with acute kidney injury stage 2 or 3 in the observational study done by Zhang et al. (HR 0.74, 95% CI 0.51- 0.86, p=0.021).[5]   This data suggests that compared to other patients with metabolic acidosis, the administration of bicarbonate therapy among those with concomitant acute kidney injury (KDIGO or AKIN Stage 2 or 3), and severe metabolic acidosis of pH<7.2 may be considered as recent data show it may result in improved outcomes and a lower rate of mortality; however the current evidence remains of low quality since larger, randomized controlled studies are still needed.

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BLOOD PURIFICATION

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

Recommendation

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

Summary of Evidence

Sepsis remains to be one of the main causes of morbidity and mortality despite recent advances in critical care and sepsis management. The dysregulated immune response results to life-threatening organ dysfunction. There are pathogen-associated molecular patterns, and damage-associated molecular patterns involved with subsequent release of inflammatory cytokines.[1] Extracorporeal blood purification techniques have been proposed as adjunctive care. The principle lies in the removal and modulation of inflammatory mediators or bacterial toxins.[2]

A majority of studies were conducted in China, Japan, Europe and North America, among critically-ill patients admitted for intraabdominal, respiratory and genitourinary infections. Trials from Asia have released promising results; however, the recently published study conducted in 55 tertiary hospitals in United States and Canada called the EUPHRATES trial yielded inconclusive results.[3]

There are several different techniques being studied. Hemoperfusion involves the placement of a sorbent cartridge in direct contact with blood. Sorbents used include a polymyxin B-immobilized fiber column that captures circulating bacterial endotoxin, and CytoSorb, a novel filter that potentially removes both pro- and anti-inflammatory cytokines. Renal replacement devices such as hemofiltration remove part of the inflammatory mediators and toxins. Plasmapheresis, with use of fresh frozen plasma or albumin, has the potential to remove inflammatory cytokines and restore deficient plasma proteins. Coupled plasma filtration removes mediator molecules through initial plasma filtration followed by hemofiltration.[2]

A systematic review and meta-analysis by Putzu et al. reviewed the various blood purification modalities being used in sepsis and septic shock. The studies had unclear methods of randomization, allocation concealment and blinding, but since the outcome studied in most was mortality, the risk of bias from non-blinding and allocation concealment was judged to be low. There was a significant reduction in mortality among patients treated with hemoperfusion with polymyxin-B-immobilized fiber compared to patients given conventional therapy alone (RR 0.87, 95% CI, 0.77 to 0.98).[2] However, the sensitivity analysis which included only studies with low risk of bias showed no benefit; rather a trend towards harm (RR 1.10, 95% CI, 0.91 to 1.32).

The following modalities of blood purification - hemofiltration, hemoperfusion with other devices, combined hemofiltration and hemoperfusion - showed a trend towards benefit, but again results were inconclusive. Interestingly, a subgoup analysis of hemoperfusion studies done in Asia showed clear benefit in terms of mortality (RR 0.58, CI 0.40 to 0.82).[2]

There were two RCTs on plasmapheresis that looked at the outcome of mortality. Relevant methodologic issues included risk of bias (from unclear allocation concealment and randomization) and imprecision. The results showed that plasmapheresis is beneficial in terms of improving mortality outcomes (RR 0.63, CI 0.42 to 0.96).

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.

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BLOOD TRANSFUSION

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

Recommendation

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).*

Summary of Evidence

The study of Dupuis aimed to compare the benefit and harm of restrictive versus liberal transfusion strategies among patients in severe sepsis or septic shock. One randomized control trial and 12 cohort studies were included in this study. Restrictive transfusion strategy was not associated with increased mortality rate (overall pooled OR was 1.10 [0.75, 1.60]; $I2$ = 57%, p = 0.03). However, it was associated with the occurrence of nosocomial infection (OR 1.25 [1.04–1.50]; $I2$ = 0%, p = 0.97), acute lung injury (OR 2.75 [1.22–6.37]; p = 0.016), and acute kidney injury (OR 5.22 [2.1–15.8]; p = 0.001).[1] This association has limited external applicability due to several reasons, including differences in the outcome definitions (in-hospital mortality, crude mortality rate, etc) and modeling statistics between studies. Specifically, for acute lung injury and acute kidney injury, there was only one study each that cited these as the outcome of interest when transfusion (versus no transfusion) was added in the multivariate logistic regression as a possible outcome predictor. Furthermore, patients had different co-morbidities and were admitted at different intensive care units which could further influence the outcomes of the studies.

The TRISS trial by Rygard et al. was a randomized, multicenter clinical trial involving a total of 1,005 patients that specifically included those with septic shock. The results showed no difference in one-year mortality rate among patients who were transfused at a liberal versus restrictive transfusion threshold (RR 0.97; 95 % CI 0.85–1.09; P = 0.62).[2]

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.[3] Current evidence shows that a restrictive transfusion strategy is 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.

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

Recommendation

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

Summary 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. Studies also differ on what type of ESA is used, with most of the studies using erythropoietin alpha or erythropoietin beta.

A meta-analysis that included 3326 critically-ill patients (9 RCT) did not show mortality benefit with the use of erythropoietin compared to placebo (OR 0.86, 95% CI 0.71-1.05). They noted reduction in the proportion of patients who required blood transfusion (OR 0.73, 95% CI 0.64-0.84),[1] however this reduction disappeared in the latest trial which adopted a restrictive transfusion strategy (OR 0.91, 95% CI 0.74-1.12).[2] A trial by Corwin and colleagues enrolled a total of 1460 medical, surgical, and trauma patients. This study showed a decrease in number of packed red cell units transfused among critically-ill patients given erythropoietin.   However, subgroup analysis that included patients with infection and/or sepsis (OR 0.67, 95% CI 0.44-1.03) did not exhibit such benefit.[3]

Mesgarpour and colleagues did a systematic review on the harms of off-label ESA for critically-ill patients.   There were 53 studies included in the trial: seven involved patients with sepsis, six focused on the effects of ESA on increase in hemoglobin levels and decrease in packed red cell transfusion requirements among septic patients with anemia. The study showed no difference in hematopoietic effect (RR 1.01, 95% CI 0.78-1.32, I2 = 0%), and

adverse events (RR 1.05, 0.93-1.21) with use of ESA among septic patients with anemia.[4] However, the studies had issues in terms of allocation concealment, selective outcome reporting, blinding and source of funding.

A single observational study by Loftus, which involved 42 adult patients with sepsis, serially measured erythropoietin levels along with levels of plasma IL-6, IL-8, G-CSF, SDF-1, TNF-α, hemoglobin and MCV. There was a lack of correlation between anemia and erythropoietin levels.[5] This suggests that erythropoietin may not play a significant role in the pathophysiology of anemia among critically-ill septic patients, hence the lack of effect of ESA use on the hemoglobin levels and transfusion requirements as seen in other studies.

Currently there is 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.

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

Recommendation

We cannot recommend the use of prophylactic fresh frozen plasma transfusion in adult patients with sepsis and coagulation abnormalities due to insufficient evidence *(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).*

Summary 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. A retrospective study by Mica included a total of 2,033 patients with multiple injuries, none of whom had infection on admission. These patients were either transfused or not transfused with fresh frozen plasma. It was noted that there was a higher rate of development of infection (48% versus 28%; P <0.001) and sepsis (29% versus 13%; P<0.001) among patients who were transfused with fresh frozen plasma. The mortality rate and bleeding rate were not investigated in the study.[1]

A prospective observational cohort study done by Reiter et al. showed that for ICU-admitted septic patients ICU mortality (32 versus 38%, p = 0.80), 30-day mortality (35 versus 46%, p = 0.56), 90-day mortality (50 versus 54%, p = 0.97) and 365-day mortality (59 versus 62%, p = 0.79) were comparable between FFP transfused and non-transfused patients. On days of FFP transfusion, international normalized ratio levels (1.8 (1.4-2.3) versus 1.3 (1.2-1.6), p < 0.0001) were higher, and invasive procedures (p < 0.0001), episodes of bleeding (p < 0.0001), transfusion of red blood cells (p < 0.0001) and platelets (p < 0.0001) more frequent than on days without transfusion. However, two thirds of FFP transfusions were given to patients either 1) with clinical evidence of bleeding or 2) as prophylaxis before invasive procedures.[2]

A multicenter randomized open-label trial with blinded endpoint evaluation on the use of prophylactic FFP transfusion among critically-ill patients with a prolonged international normalized ratio (INR; 1.5-3.0) was done in 2013. This study was stopped before the predefined target enrollment was reached due to slow inclusion. Factors that added non-achievement of target enrollment include small window of opportunity for recruitment (pre-procedure), low consent rates among patients/relatives, and reluctance of attending physicians to include patients. The study was able to randomize 81 patients; however, there was an imbalance in the randomization with a higher proportion of patients with liver disease in the no FFP group. FFP transfusion resulted in a reduction of INR to less than 1.5 in 54% of transfused patients but incidence of bleeding did not differ between groups, with a total of one major and 13 minor bleedings (p = 0.08 for noninferiority).[3]

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

Recommendation

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).*

Summary 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.

An observational study by Schmidt and colleagues included 376 thrombocytopenic patients who received platelet transfusion prior to an invasive procedure. They noted 19 thrombotic events and 60 deaths within 30 days of prophylactic platelet transfusion. Most deaths that occurred in the study were due to infection, sepsis, or organ failure; none was due to bleeding or thrombosis.[1] Given that only 7% of the study participants (n=26) had an infection (not specifically sepsis), serious indirectness led to very low assessment of the quality of evidence.

The Surviving Sepsis Guidelines suggest transfusing platelets prophylactically only when platelets fall to 10,000 per cubic millimeter, assuming no bleeding is present. In patients considered at significant risk for bleeding, a threshold of 20,000 per cubic millimeter is suggested. For those with active bleeding or who are undergoing surgery or invasive procedures, transfusing platelets to 50,000 per cubic millimeter is suggested. These

recommendations are largely based on managing non-septic patients whose thrombocytopenia was due to production suppression, for instance, in chemotherapy-induced thrombocytopenia. [3]

Currently, the INFUSE trial - Intervening with Platelet Transfusion in Sepsis - is ongoing.[4] The main limitation of this study is that its primary outcome measure consists of biomarkers, with only some clinical outcomes as secondary outcomes.   Nonetheless, the study will still be able to add to the limited data that is available for prophylactic platelet transfusion among patients with sepsis.

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IMMUNOGLOBULINS

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

Recommendations

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*).

Summary 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.[1] Immunoglobulins have been proposed to have both inflammatory and immune properties that target the host response to infection.[2]

There has been increasing interest in the effect of immunoglobulins, initially in pediatric patients, then including adults in recent years. Formulations of immunoglobulins include polyclonal and monoclonal, low-dose versus high-dose, and those enriched with IgM. As an adjunctive treatment to source control and antibiotics, initial studies have shown no benefit to their use. Additional studies with enriched immunoglobulins have some promising data.

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.[1] 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.[2]

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.

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ANTICOAGULANT THERAPY

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

Recommendation

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

Summary of Evidence

The pathogenesis of sepsis involves systemic inflammation, endothelial injury, and upregulation of coagulation. Heparin potentiates the activity of antithrombin thereby inhibiting blood coagulation and thrombin formation. Thrombin inhibition serves to limit inflammation. The anti-inflammatory properties of heparin appear to be independent of its role as an anticoagulant.[1]

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.[1] 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.[2]

Currently, for recommendations concerning anticoagulation there is a discrepancy between the International Surviving Sepsis Campaign Guidelines 2016 and the regional clinical practice guidelines such as those seen in Japan. Such discordance may be explained by several factors including interpretation of sub-group analysis, availability of diagnostic

tests and inclusion of several types of anticoagulants.[3]   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.[4]

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VENOUS THROMBOPROPHYLAXIS

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

Recommendation

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.

Summary of Evidence

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.

Most studies focused on pharmacologic thromboprophylaxis and compared low molecular heparin and unfractionated heparin. 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.[1] 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 comparing UFH, LMWH, and IPC in both medical and surgical critically-ill patients showed lower risks for DVT in LMWH and UFH than IPC but the differences were not statistically significant (LMWH: OR, 0.76; 95% CrI (Credible intervals), 0.28-1.92; UFH: OR, 0.89; 95% CrI, 0.31-2.41).[2] IPC was associated with a reduced incidence of DVT compared to the control group, but the effect was not statistically significant (OR, 0.50; 95% CrI, 0.20-1.23). There was also a trend of increased major bleeding among LMWH and UFH groups compared to the IPC and control group (i.e. no thromboprophylaxis) though not statistically significant. Based on this analysis, pharmacological thromboprophylaxis seems more efficacious than mechanical thromboprophylaxis in critically-ill patients with a potential risk of bleeding.

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

Recommendation

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

Summary of Evidence

Sepsis involves systemic inflammation and a procoagulant response to infection. Given the relationship between coagulation and inflammation, anticoagulants have been evaluated in sepsis as prophylaxis for VTE.

In a meta-analysis by Wang et al. in 2014,[1] heparin therapy was found to reduce 28-day mortality in adult patients with severe sepsis, with no increased risk of bleeding.

Similarly, the efficacy and safety of LMWH treatment in sepsis was evaluated in another meta-analysis by Fan et al.[2] It showed that LMWH significantly reduced 28-day mortality and APACHE II score among septic patients. However, LMWH also significantly increased the bleeding events.[2]

Few studies compared LMWH with UFH as thrombophylaxis in critically-ill patients,[3-6] but data on patients with sepsis remain limited.

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.[3] Results were consistent with another meta-analysis which showed that LWMH, compared with UFH, reduced the risk of any DVT.[4] Safety of LMWH was equal to UFH with no significant difference in the occurrence of major bleeding.[3-6] 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.[6]

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STRESS ULCER PROPHYLAXIS

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

Recommendation

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

Summary of Evidence

The terms "stress ulcer," "stress-induced mucosal injury," "stress-related mucosal disease" or "stress gastritis" have been used to describe gastrointestinal (GI) bleeding among critically-ill patients.   It was first described in 1970 as acute gastroduodenal stress ulceration that typically occurs in the gastric body, esophagus and duodenum that could result to bleeding.[1]

Overt GI bleeding is defined as "bleeding that is visible to the patient or clinician." It may manifest as hematemesis, melena, or hematochezia.[2] The incidence of overt GI bleeding has been earlier reported to be 5 to 25% among critically-ill patients.[3]

Clinically-important GI bleeding is defined as "overt bleeding in association with hemodynamic compromise (drop in blood pressure of more than 20mmHg, an increase in pulse rate of more than 20 beats per min, or a drop in systolic blood pressure of more than 10mmHg measured on sitting up), or decrease in the hemoglobin level of more than 20 g/l with no increase in hemoglobin levels after subsequent transfusion by the number of units transfused minus 20 g/l."[4] The incidence of clinically-important GI bleeding ranges from 1-4%.[4-7]

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).[8] Mortality attributable to GI bleeding among critically-ill patients was found to be 3.54%.[9]

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%).[10] 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.[11]

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

Recommendation

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

Summary of Evidence

There were five meta-analyses published that compared proton pump inhibitors PPIs) to histamine 2 receptor antagonists (H2Ras) in stress ulcer prophylaxis. Four meta-analyses[1-4] concluded that PPIs are more efficacious than H2RAs in reducing GI bleeding in critically-ill patients. The most recent meta-analysis in 2017 included 14 trials and concluded that PPIs lowered the risk of clinically important GI bleeding compared to H2RAs (OR 0.38, 95% CI: 0.20, 0.73, p= 0.002, i2= 0%).[4] It was also found that PPIs probably increase pneumonia compared with H2RAs (OR 1.27; 95% CI 0.96, 1.68).[4] There was no significant difference in terms of mortality (OR 0.83, 95% CI: 0.63, 1.10).[4]

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.[5]

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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)?

Recommendation

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).*

Summary of Evidence

Malnutrition is defined as a "state resulting from lack of intake or uptake of nutrition that leads to altered body composition (decreased fat free mass) and body cell mass leading to diminished physical and mental function and impaired clinical outcome from disease."[1] Malnutrition can alter a patient's clinical course and lead to significant morbidity and mortality. Due to increased metabolic needs in septic patients, addressing nutrition has the potential to improve survival. Enteral nutrition (EN) refers to nutrition therapy given via an enteral tube or stoma. Parenteral nutrition (PN) is a type of nutrition provided through intravenous administration of nutrients such as amino acids, glucose, lipids, electrolytes, vitamins and trace elements through a central venous line, or a peripheral intravenous line.[1] The use of EN and PN alone or in combination has been studied extensively.

Overall, earlier studies did not show a clear benefit for EN over PN.[2,3] A large multicenter study done in 34 critical care units in the United Kingdom by Harvey et al. (CALORIES trial, 2016) showed that there was no difference in all-cause 30-day mortality between the two groups, and that PN equated to higher mean cost.[4] The second largest trial was done in France (NUTRIREA-2 study, 2018) and focused on mechanically ventilated patients requiring vasopressor support. Results showed that there was no significant difference in 28-day mortality (37% EN vs 35% PN), frequency of infectious complications (14% EN vs 16% PN), duration of mechanical ventilation, ICU length of stay or 90-day mortality.[5]

Two early systematic reviews, showed no difference in mortality and that EN was associated with less infectious complications.[6,7] The most comprehensive review was done by Lewis et al., which included 25 RCTs and showed no difference in in-hospital mortality (RR 1.19, 95% CI 0.80 to 1.77) or 30-day mortality (RR 1.02, 95% CI 0.92 to 1.13).   There was also no evidence that use of EN will increase or decrease risk of aspiration (RR 1.53, 95% CI 0.46 to 5.03) or pneumonia (RR 1.10, 95% CI 0.82 to 1.48). 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).[8] 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).[8]

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.[9,10] 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 include the potential risk of infection, and extra cost for PN in the absence of clinical benefit.[10] 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.[11] 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.

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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)?

Recommendation

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)*.

Summary 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 of six trials 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).[1]

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) to determine whether early enteral feeding among septic sarcopenic and non-sarcopenic patients is associated with mortality. The study 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).[2]

Liu et al. in 2018 also investigated in a retrospective cohort the effects of early enteral feeding on immune modulation and survival among septic patients needing mechanical ventilation. The study 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).[3]

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.[4,5]

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.[6] 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.[7] Lastly, the Surviving Sepsis Campaign (2016) also suggests starting early enteral feeding in patients with sepsis or septic shock.[8]

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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?

Recommendations

We suggest against routine supplemental parenteral nutrition on top of 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).*

Summary of Evidence

Studies on nutrition have shown that negative energy balance can have deleterious effects. However, enteral feeding has limitations in terms of patient tolerance and risk for aspiration. Hence, we explore the evidence for combination enteral and parenteral nutrition or supplemental parenteral nutrition in septic patients.

The Cochrane review by Lewis in 2018 showed that EN or combined EN and PN may make little or no difference on mortality in-hospital (RR 0.99, 95% CI 0.84 to 1.16; 5111 participants in five studies, with low-certainty evidence), and at 90 days (RR 1.00, 95% CI 0.86 to 1.18; 4760 participants in two studies, with low-certainty evidence).[1] It is uncertain whether combined EN and PN reduced mortality at 30 days because the certainty of the evidence was very low (RR 1.64, 95% CI 1.06 to 2.54; n=409; I^2 = 0%). Rates of feeding, tube obstruction and diarrhea did not differ with the addition of PN to EN. However, combining PN with EN showed greater risk for the development of bloodstream infection (RR 1.24, 95%CI 1.00, 1.53), wound infection (RR1.49, 95%CI 1.09, 2.02), and airway infection (e.g. bronchitis, pneumonia) (RR 1.54, 95%CI 1.38, 1.72).   Data for pneumonia and urinary tract infection did not show any difference, but a trend towards harm was observed with the addition of PN. 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.[3] A high-calorie deficit was also shown to have increased incidence of ARDS, sepsis and pressure sores in the 2006 study by Dvir.[4]   The study by Faisy in 2011 showed that a greater calorie deficit was related to staphylococcal ventilator-acquired pneumonia.[5]

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).[5] 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 $1,600) (P=0.04). Mortality rates were similar with both early and late initiation of PN.

The American Society for Parenteral and Enteral Nurition (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 adults patients who do not tolerate full dose EN during the first week in the ICU.

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

Recommendation

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).*

Summary 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%.[1] Often, FI is due to delayed gastric emptying but pathophysiology may be multifactorial. Contributory factors include pre-existing diabetes, hyperglycemia, electrolyte abnormalities, medications, mechanical ventilation, and presence of shock.[2,3] Once present, FI may potentially increase the risk for regurgitation, vomiting, and aspiration.[4,5] The gold standard for the diagnosis of gastric emptying is scintigraphy;[4] however, the test is costly, unavailable in many places, and impractical for clinical use. Measurement of gastric residual volume (GRV) is more feasible and has become a surrogate marker for the presence of delayed gastric emptying.[2] The definition of FI remain to be variable and inconsistent.[1] Studies to date use GRV ranging from 150 to 250 mL as the threshold for FI.[4,5,6] The most recent definition 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.[7]

Erythromycin, a macrolide antibiotic, works as a motilin receptor agonist to stimulate gastric smooth muscle contraction and augment gastric emptying.[2,3,5]Metoclopramide, a dopamine-receptor antagonist, is another prokinetic that has both central and peripheral effects.[2,3] 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.[9] 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.[9]

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.[10] Adverse effects of metoclopramide use include extrapyramidal symptoms, nausea and cardiac arrythmia.[3,10]

No statement was made in the European nutrition (ESPEN) guidelines and Surviving Sepsis Campaign on the use of prokinetics to prevent feeding intolerance.[7,11] The American guidelines (ASPEN) suggest the use of prokinetics, either metoclopramide or erythromycin in patients with high risk of aspiration when clinically feasible, but this is judged as low quality of evidence. Though no difference was found in mortality, the reduction in GRV's was taken into consideration. The authors also emphasized that use of these agents is associated with some undesirable effects.[12] To reiterate, a major limitation of current studies is the variable definition for feeding intolerance. Present studies are also on critically-ill and not specific for septic patients. In addition, intravenous erythromycin is not locally available. Oral erythromycin, which is locally available, has not been studied in feeding intolerance.

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

Recommendation

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).*

Summary 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).[1] 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.[1]

The Surviving Sepsis Campaign recommends the use of both prokinetic agents (metoclopramide or erythromycin) in critically-ill patients with sepsis or septic shock and concomitant feeding intolerance, with a weak recommendation and low quality of evidence.[2] The European guidelines (ESPEN) recommend erythromycin as first line, and alternatively

metoclopramide, or a combination, as prokinetic treatment in patients with feeding intolerance.[3] No recommendation is made on treatment of FI in the American nutrition guidelines (ASPEN). In addition, intravenous erythromycin is not locally available. Oral erythromycin has not been studied in feeding intolerance.

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

Recommendation

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).*

Summary of Evidence

Feeding intolerance due to delayed gastric emptying has been shown to occur in critically-ill patients. This may lead to reflux and put a patient at risk for aspiration pneumonia.[1] Other conditions, such as history of previous aspiration or presence of anatomic abnormalities of the GI tract, may also increase the risk for aspiration.[2] For patients with delayed gastric emptying, post-pyloric feeding may be beneficial due to its obvious advantage of bypassing the stomach to deliver nutrition to the small bowel which has better

absorptive capacity and motility. Several studies have focused on the role of post-pyloric feeding in the critically-ill.

Two earlier meta-analysis showed no clinical benefit of post-pyloric feeding over the gastric route.[2,3] A more recent systematic review by Alkhawaja et al. (Cochrane database 2015) showed moderate quality evidence that post-pyloric feeding is associated with lower rates of pneumonia (RR 0.65, 95% CI 0.51 to 0.84).[4] In six of the nine trials that reported pneumonia in the meta-analysis, all participants were on mechanical ventilation. The remaining trials did not specify if patients were mechanically ventilated. In addition to lower rates of pneumonia, there was a higher percentage of nutrient delivery in the post-pyloric group (MD 7.80, 95% CI 1.43 to 14.18). No statistically significant differences in mortality (RR 1.03, 95% CI 0.83 to 1.29; I2 = 0%), length of ICU stay (MD -0.70 day, 95% CI -2.31 to 0.91; I2 =40%), duration of mechanical ventilation (MD -0.92 day, 95% CI -2.11 to 0.28; I2 = 10%), vomiting (RR 1.01, 95% CI 0.54 to 1.89; I2 = 21%) or diarrhea (RR 0.96, 95% CI 0.74 0 to 1.25; I2 = 0%) were observed.[4] However, the authors stated that there were differences in the location or placement of post-pyloric tubes.

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.[5,6] 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.[5,6] 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.[7]

In general, mechanically-ventilated patients may benefit from early post-pyloric feeding due to evidence of lower risk of developing ventilator-associated pneumonia. However, routine placement of small bowel feeding may not be recommended at this time due to lack of standardized technique placement, and technique may be challenging and require technical skill, on top of additional cost as compared to the gastric route. Further studies in specific populations may help identify patients who will clearly benefit from post-pyloric feeding. Nevertheless, post-pyloric feeding in patients with a high risk for aspiration, or those with documented aspiration, as well as in the presence of gastric intolerance not improved with prokinetics, is recommended due to its potential in reducing pneumonia.

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

Recommendation

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).*

Summary 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.[1] 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[2] employed multiple evidence-based components (**Figure 6**) 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. [2]

Majority of the studies found were performed in medical-surgical ICUs. There were no studies for septic patients exclusively. There were differences among the studies with respect to the type of feeding protocol implemented. Volume-based feeding was employed in most protocols. In the retrospective study of Wang, those who were enrolled in a standard feeding protocol showed higher energy and achievement rates.[3] The achievement rate of less than 65% adequacy was associated with increased mortality rate. A prospective study by Yeh showed that the intervention group also achieved more calorie and protein intake, and outcome showed fewer late infections.[4] In contrast, the cohort study by Haskins showed longer ICU length of stay and duration of mechanical ventilation despite similar increase in caloric provision.[5]

Computerized nutrition protocols were also used to assist in nutrition prescription. In one study by Bousie, done on critically-ill mechanically-ventilated patients, there were more patients fed on target in the computerization group.[6] There was less hypokalemia, hypo- or hypernatremia upon implementation, but more hypomagnesemia. Nonetheless, these were found not to be statistically significant. In another study done by Conseil, utilizing computer help achieved more calorie and protein goals, and resulted in significant decrease in nosocomial infection. Mortality did not differ between groups.[7]

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). [8] Based on expert consensus, it is suggested that use of a volume-based feeding protocol or a top-down multistrategy protocol be considered (Quality of evidence: Moderate). This question was not addressed in the Surviving Sepsis Campaign[9] or in the latest European Society of Clinical Nutrition and Metabolism (ESPEN) Guideline for Critically-ill Patients. [10]
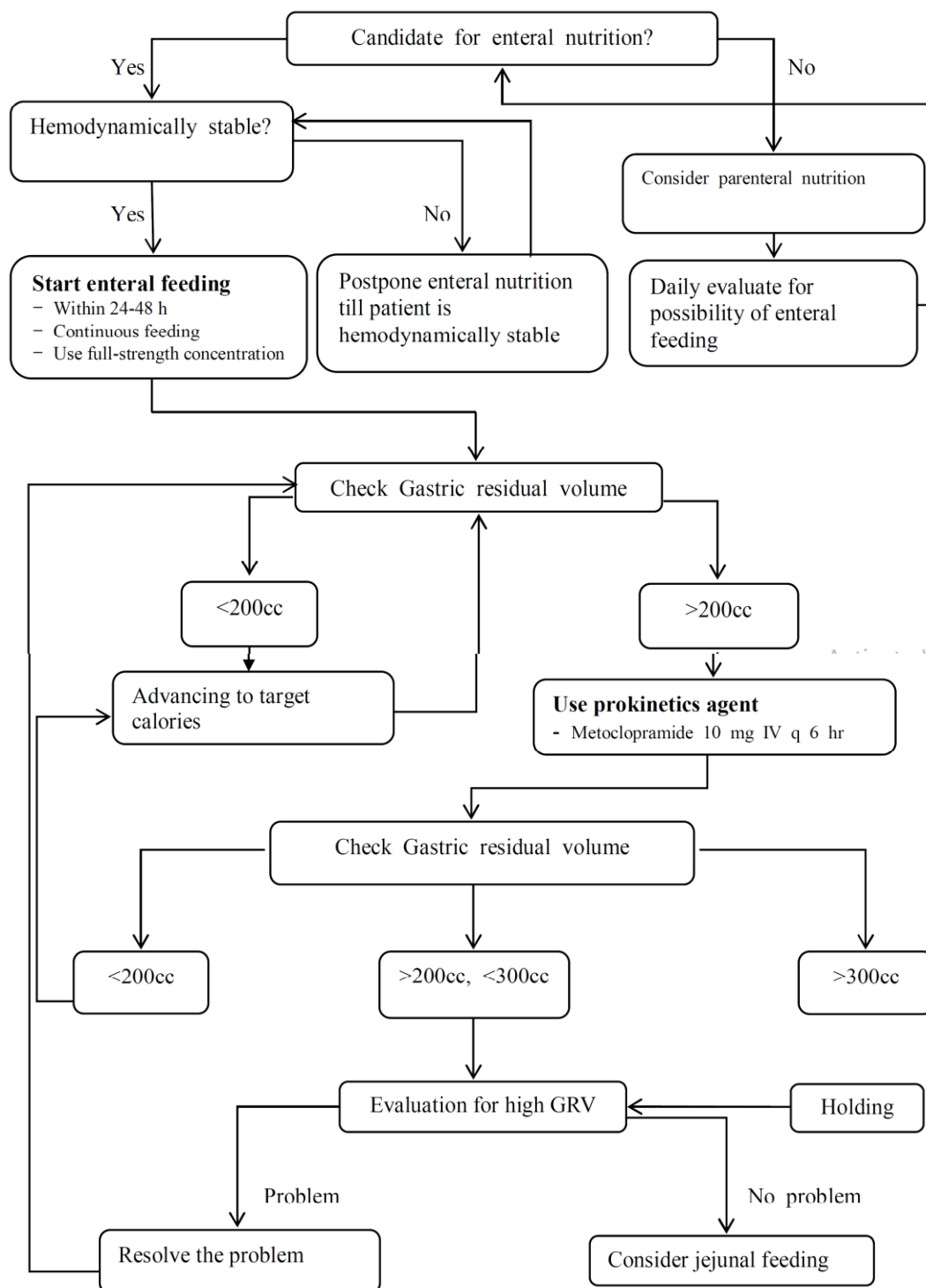
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Figure 6. Sample Standard Feeding Protocol. Adapted from: The impact of implementation of an enteral feeding protocol on the improvement of enteral nutrition in critically ill adults (Kim, 2017)

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SEDATION AND ANALGESIA

Adult patients in the intensive care unit (ICU) frequently experience pain, resulting from acute and chronic illness as well as the positioning and interventions that are standard to ICU care.[1,2] The adequate management of pain prevents agitation and delirium in mechanically-ventilated patients. There are also many physiologic responses to acute pain that can impact patient care in the ICU, including tachycardia, hypertension, increased work of breathing, increased cortisol release, and increased risk of infection.[2] Oftentimes, effective critical care strategies - like mechanical ventilation, targeted temperature management, intracranial hypertension management among others - require recognition and control of pain and agitation. Sufficient sedation and analgesia may address problems like ventilator dysynchrony, ineffective ventilation, shivering, increased oxygen consumption, etc. The incidence of pain is thought to be 50% or greater in ICU patients, and the inability to communicate due to mechanical ventilation does not negate the possibility that the patient is experiencing pain.[1]

Acute brain dysfunction, such as delirium and coma, is common in patients with sepsis, potentially worsening their clinical outcomes. The mechanisms by which such brain dysfunction occur are not fully understood, but disturbances in inflammation and coagulation pathways leading to microvascular thrombosis are thought to be partly responsible.[3-7]

Conversely, murine studies[8-13] have suggested that certain sedatives may potentially have an immunomodulating effect in sepsis such as the suppression of cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS), TNF-α, IL-1β, IL-6, and interferon-gamma (IFN-γ)[10-13]. The common practice of administering sedatives during the process of mechanical ventilation of septic patients adds an additional layer of complexity to understanding acute brain dysfunction in these patients.

The utility of adequate sedation and analgesia in the general ICU has been emphasized in the 2018 published ICU guidelines on pain, agitation/sedation, delirium, immobility, and sleep disruption.[14] However, these guidelines did not provide recommendations for the septic subpopulation. In the absence of evidence against the use of sedation and analgesia, we can consider these clinical guidelines applicable to the septic patient since translation of their recommendations in clinical practice may encompass all critically-ill subpopulations.

The latest Surviving Sepsis Campaign[15] highlighted the advantage of providing adequate sedation and analgesia in septic patients who are on mechanical ventilatory support. However, limited statements were made, owing perhaps to the following factors: a scarcity of high-level published evidence, few rigorous large clinical series, and even fewer clinical trials in humans.

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

Recommendation

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).*

Summary of Evidence

Recent guidelines on pain, agitation, and delirium in the general ICU population provide additional detail on the implementation of sedation management, including nonpharmacologic approaches for the management of pain, agitation, and delirium as well as immobility and sleep disruption.[1, 14] The 2018 Clinical Practice Guidelines[14] 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.[16] 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.

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.[17]

There are numerous tools or scoring systems that may be used in the critical care setting to measure the adequacy of sedation. Among these, the Riker Sedation-Agitation Scale (SAS)[18] and Richmond Agitation-Sedation Scale (RASS)[19] have the highest inter-rater reliability in the general ICU population and have been validated to allow the provider to effectively measure the depth of sedation and thus titrate medications accordingly. Utilization of these assessment tools and setting individualized end-goals will facilitate the minimal use of sedatives.

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

Recommendation

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).*

Summary of Evidence

The recent 2018 Clinical Practice Guidelines[14] for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU (PADIS) provides invaluable recommendations on the management of sedation in the general ICU population.

Fraser et al. compared the use of different benzodiazepines and non-benzodiazepines of ICU patients in a meta-analysis[20] 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.

When dexmedetomidine and propofol were compared in a single-center RCT,[21] Sigler et al. found that there was no statistical difference in number of ventilator days, length of ICU stay and 28-day mortality. In another RCT where standard sedation (propofol, fentanyl and/or midazolam) was used in combination with or without dexmedetomidine, Kawazoe et al.[22] reported that in mechanically-ventilated septic patients, the frequency and dose of propofol and midazolam were lower in the dexmedetomidine group than in the control group, but the frequency and dose of fentanyl were not significantly different. In the subgroup with APACHE II scores of 23 or higher, the dexmedetomidine group had lower hospital mortality outcomes. Investigators found that there was an 8% reduction in 28-day mortality in the dexmedetomidine group but the results did not show statistical significance, possibly due to the small study population.

Multiple studies[20-23] support the recommendation for the use of short-acting non-benzodiazepines like dexmedetomidine and propofol for sedation.

Use of sedation assessment tools like the Riker Sedation-Agitation Scale (SAS) and Richmond Agitation-Sedation Scale (RASS) while targeting individualized end-goals will help the clinician titrate these medications.[18,19] For the majority of patients undergoing mechanical ventilation in an ICU, an appropriate target is a score of 3 to 4 on the Riker

Sedation–Agitation Scale. Scores on the SAS range from 1 to 7, with scores of <4 indicating deeper sedation, a score of 4 indicating an appearance of calm and cooperativeness, and scores of ≥5 indicating increasing agitation. Using the RASS, an appropriate score is −2 to 0; the range of scores on the Richmond Agitation–Sedation Scale are −5 to +4, with more negative scores indicating deeper sedation and more positive scores indicating increasing agitation, with 0 representing the appearance of calm and normal alertness.

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

Recommendations

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).*

Summary of Evidence

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[14], 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. Issues include the potential for abuse or misuse once the patient is discharged. 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%).[24] 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.

Multimodal analgesia is based on the premise that the concurrent use of primarily non-opioid analgesics may have additive, if not synergistic, effects that produce superior analgesia while minimizing opioid use and opioid-related side effects, and keeping in mind that the endgoal is to ensure that the patient is pain-free. A combination of opioid and non-

opioid analgesics (such as acetaminophen, paracetamol) is recommended. A randomized contorl trial by Cattabriga et al. in 2007 showed that patients who received paracetamol postoperatively reported less pain at rest and required less cumulative doses of morphine as compared to placebo.[25] Memis et al.[26] in 2010 reported that intravenous infusion of paracetamol to a maximum dose of 4 grams per day, in combination with meperidine, reduced the use of opioids, extubation time, and opioid-related adverse effects after major surgery in the ICU when compared to meperidine alone. However, there have been reports of acetaminophen (paracetamol) infusion-related hypotension[27] but further studies are warranted.

Neuropathic pain medications such as gabapentin, carbamazepine and pregabalin may be used in combination with opioids for patients with pain in the ICU. Pesonen et al. reported that pregabalin may spare the need for opioid use in elderly post-cardiac surgery patients, but there was a delay in time to extubation in these patients compared to placebo.[28] Joshi et al. investigated the efficacy of pregabalin in acute and chronic post-operative pain and found that pain scores at rest were less in pregabalin-treated patients (P < 0.05).[29] Pain scores at deep breath were less in the pregabalin group than in control, and results were statistically significant up to 36 hours after extubation (P < 0.05). Tramadol consumption was reduced by 60% in the pregabalin group compared to the control group (P < 0.001). However, there have been no direct studies using pregabalin and other neuropathic pain medications in patients with sepsis.

The use of various pain assessment tools like the Visual Analog Scale (VAS),[30] Numerical Rating Scales (NRS),[30] Critical Care Pain Observation Tool (CPOT),[31-34] or the Behavioral Pain Scale (BPS)[31-34] may assist the clinician in individualizing effective analgesia. Among these tools, the Critical Care Pain Observation Tool (CPOT) and the Behavioral Pain Scale (BPS) have been validated in unconscious and sedated patients as well as in mechanically-ventilated, critically-ill patients.[31-35] For the majority of patients, an appropriate target is a BPS score of less than 3 or a CPOT score of less than 2.

Optimal pain control may require a referral to a pain management specialist if available.

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