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SEPSIS MANAGEMENT

National Clinical Guideline No. 6 (2020 Update)

National Clinical Effectiveness Committee

V3 July 2019

Notes:

CEU actions are marked in red.

GDG actions are highlighted in yellow and content write up is flagged in *blue italics*. Font style is Calibri 12 and justified

Version History

Date	Version	Details
November 2014	1	New
October 2018	2	Updated recommendations accommodating new sepsis definition and post discharge care.
July 2019	3	Maternity Section update

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This National Clinical Guideline has been developed by the Sepsis Guideline Development Group (GDG), within the HSE National Clinical Programme for Sepsis - (National Sepsis Programme). The NCEC was requested by the Minister for Health to commission the 2014 guideline arising from a significant patient safety/policy matter and this is the scheduled update.

Using this National Clinical Guideline

This National Clinical Guideline applies to all adult patients, including pregnant women and women 42 days post birth, in the acute hospital sector. **All maternity specific informtion is highlighted using purple text**. It does not apply to paediatric patients. This National Clinical Guideline is relevant to all healthcare professionals working in the acute hospital sector.

Disclaimer

NCEC National Clinical Guidelines do not replace professional judgment on particular cases, whereby the clinician or health professional decides that individual guideline recommendations are not appropriate in the circumstances presented by an individual patient, or whereby an individual patient declines a recommendation as a course of action in their care or treatment plan. In these circumstances the decision not to follow a recommendation should be appropriately recorded in the patient's healthcare record.

Users of NCEC National Clinical Guidelines must ensure they have the current version (hardcopy, softcopy or App) by checking the relevant section in the National Patient Safety Office on the Department of Health website: http://health.gov.ie/national-patient-safety-

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Membership of the Guideline Development Group (GDG)

The GDG was chaired by Dr Vida Hamilton BE, MB, BAO, LRCP & SI, FCARCSI, EDIC, FJFICMI, National Clinical Lead for Sepsis (2014 – 2018). This National Clinical Guideline is supported by HSE Clinical Strategy & Programmes Division.

Membership nominations were sought from a variety of clinical and non-clinical backgrounds so as to be representative of all key stakeholders within the acute sector. GDG members included those involved in clinical practice, education, administration, research methodology and 2 persons representing patients and the public.

TABLE 1. THE NATIONAL CLINICAL GUIDELINE DEVELOPMENT GROUP

Name	Job title and affiliation
Dr. Vida Hamilton (Chair)	National Clinical Advisor and Group Lead (Acute Hospitals) National Sepsis Clinical Lead (2013 – 2018)
Dr Martina Healy	National Sepsis Clinical Lead (2018 onwards)
Ciara Hughes Christina Doyle	Programme Manager National Sepsis (2019 onwards) Programme Manager National Sepsis (2013 – 2018)
Mary Bedding	Sepsis ADON RCSI Hospital Group
Dr Karn Cliffe	Sepsis ADON/M Dublin Midlands Hospital Group
Celine Conroy	Sepsis ADON Ireland East Hospital Group
Yvonne Young	Group ADON University Limerick Hospital Group
Ronan O'Cathasaigh Fidelma Gallagher	Group ADON Saolta Hospital Group (2016 – 2018) Group ADON Saolta Hospital Group (2019 onwards)
Sinead Horgan Kay O'Mahony	Group ADON Saolta Hospital Group (2015 – 2018) Group ADON South / South West Hospital Group (2019 onwards)
Dr Fidelma Fitzpatrick	Chair of Steering Group / Consultant Microbiologist
Dr Miriam Bell	Project Lead for National Early Warning System Guideline 2020 update
Dr Dorothy Breen	Consultant Anaesthetist, Cork University Hospital
Avilene Casey	Lead for the Deteriorating Patient Improvement Programme (Response and Recognition)
Dr Garry Courtney	Clinical Lead for the National Acute Medicine Programme
Linda Dillon	Patient Representative
Barbara Egan	Patient Representative
Dr Lynda Fenelon	Consultant Microbiologist
Julieann Kielly	Patient Representative
Jamie Logan	Nurse Lead for the National Clinical Programme for Surgery
Dr Anna Moore	Consultant in Emergency Medicine, Tullamore Hospital
Dr Gerry McCarthy	Clinical Lead for the Emergency Medicine Programmme
Fiona McDaid	Nurse Lead for the Emergency Medicine Programme
Dr Deborah McNamara	Clinical Lead for the National Clinical Programme for Surgery
Michelle O'Neill	HRB-CICER
Dr Michael Power	Clinical Lead for the Critical Care Programme
Dr Karen Power	Irish Maternity Early Warning System representative
Dr Geraldine Shaw	Acting Director, Office of Nursing & Midwifery Services Director

Dr Yvonne Smith	Clinical Lead for the National Acute Medicine Programme
Dr Omar Tujjar	Consultant Anaesthetist and Intensivist, Sligo University Hospital
Dr Michael Turner	Clinical Lead for the National Programme for Obstetrics and Gynae.
Geithin White	Clinical Librarian – Research, Information and Economic expert
Experts co-opted on to GDG	*Subgroup of: ICU Dietitians Group of INDI (Irish Nutrition and Dietetic Institute). Membership* (Appendix 18).

(CEU)Credits

The role of the NCEC is to prioritise, quality assure and recommend clinical guidelines to the Chief Medical Officer for endorsement by the Minister for Health. It is intended through Ministerial endorsement that full implementation of the guideline will occur through the relevant service plans.

The NCEC and the Department of Health acknowledge and recognise the Chair and members of the Guideline Development Group (GDG) for development of the guideline. The NCEC and Department of Health wish to express thanks and sincere gratitude to all persons contributing to this National Clinical Guideline; especially those that give of their time on a voluntary basis.

Acknowledgments

We wish to acknowledge all the members of the National Sepsis Steering Committee and the Guideline Development Group members (Table.1) who gave freely of their time and expertise. A special word of thanks to the external expert, Prof. Kevin Rooney, National Clinical Lead on Sepsis, Healthcare Improvement Scotland and Professor of Care Improvement, University of the West of Scotland and the validators Dr. John Bates from the Joint Faculty of Intensive Care Medicine in Ireland and Dr. Christian Subbe, Consultant in Acute, Respiratory and Critical Care Medicine and Senior Clinical Lecturer at the School of Medical Sciences, Bangor University, UK.

Many thanks go to Ms. Grainne Cosgrove, Health Information Unit, Department of Health for providing extensive support regarding HIPE data analysis and Ms. Deirdre Murphy, Ms. Jacqui Murphy and Ms. Marie Glynn from the Health Pricing Office for their contribution to the audit subcommittee. We also wish to acknowledge the contribution of the National Cancer Control programme (NCCP) in support of this guideline.

Dr. Fidelma Fitzpatrick, Chair, National Sepsis Steering Committee, November 2014

Dr. Vida Hamilton, National Sepsis Lead,Chair, Guideline Development Group November 2014

A full list of members of the Guideline Development Group is available in the previous page/s.

Signed by the Chair(s):  Date: _____

Fidelma Fitzpatrick

National Clinical Guidelines

Providing standardised clinical care to patients in healthcare is challenging. This is due to a number of factors, among them diversity in environments of care and complex patient presentations. It is self-evident that safe, effective care and treatment are important in ensuring that patients get the best outcomes from their care.

The Department of Health is of the view that supporting evidence-based practice, through the clinical effectiveness framework, is a critical element of the health service to deliver safe and high quality care. The National Clinical Effectiveness Committee (NCEC) is a Ministerial committee set up in 2010 as a key recommendation of the report of the Commission on Patient Safety and Quality Assurance (2008). The establishment of the Commission was prompted by an increasing awareness of patient safety issues in general and high profile health service system failures at home and abroad.

The NCEC on behalf of the Department of Health has embarked on a quality assured National Clinical Guideline development process linked to service delivery priorities. Furthermore, implementing National Clinical Guidelines sets a standard nationally, to enable healthcare professionals to deliver safe and effective care and treatment while monitoring their individual, team and organisation's performance.

The aim of these National Clinical Guidelines is to reduce unnecessary variations in practice and provide an evidence base for the most appropriate healthcare in particular circumstances. As a consequence of Ministerial mandate, it is expected that NCEC National Clinical Guidelines are implemented across all relevant services in the Irish healthcare setting.

The NCEC is a partnership between key stakeholders in patient safety. NCEC's mission is to provide a framework for national endorsement of clinical guidelines and clinical audit to optimise patient and service user care. The NCEC has a remit to establish and implement processes for the prioritisation and quality assurance of clinical guidelines and clinical audit so as to recommend them to the Minister for Health to become part of a suite of National Clinical Guidelines and National Clinical Audit. The aim of the suite of National Clinical Guidelines is to provide guidance and standards for improving the quality, safety and cost-effectiveness of healthcare in Ireland. The implementation of these National Clinical Guidelines will support the provision of evidence-based and consistent care across Irish healthcare services.

NCEC Terms of Reference

1. Provide strategic leadership for the national clinical effectiveness agenda.
2. Contribute to national patient safety and quality improvement agendas.
3. Publish standards for clinical practice guidance.
4. Publish guidance for National Clinical Guidelines and National Clinical Audit.
5. Prioritise and quality assure National Clinical Guidelines and National Clinical Audit.
6. Commission National Clinical Guidelines and National Clinical Audit.
7. Align National Clinical Guidelines and National Clinical Audit with implementation levers.
8. Report periodically on the implementation and impact of National Clinical Guidelines and the performance of National Clinical Audit.
9. Establish sub-committees for NCEC workstreams.
10. Publish an annual report.

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Section 1. National Clinical Guideline recommendations

1.1 Summary of recommendations

TABLE 2. THE SURVIVING SEPSIS CAMPAIGN (SSC) RECOMMENDATIONS ARE ADOPTED IN TOTAL FOR THIS GUIDELINE.

Section	Recommendation	Grade/Level
SCREENING FOR SEPSIS AND PERFORMANCE IMPROVEMENT	1. We recommend that hospitals and hospital systems have a performance improvement program for sepsis, including sepsis screening for acutely ill, high-risk patients (SSCG Section B, Recommendation1)	Best Practice Statement (BPS).
INITIAL RESUSCITATION	2. **Sepsis** and **septic shock** are medical emergencies, and we recommend that treatment and resuscitation begin immediately (SSCG Section A, Recommendation 1)	(BPS).
	3. We recommend that, in the resuscitation from sepsis-induced hypoperfusion, at least 30 mL/kg of IV crystalloid fluid be given within the first 3 hours (SSCG Section A, Recommendation 2)	(strong recommendation, low quality of evidence).
	4. We recommend that, following initial fluid resuscitation, additional fluids be guided by frequent reassessment of hemodynamic status (SSCG Section A, Recommendation 3)	(BPS).
	5. We recommend further hemodynamic assessment (such as assessing cardiac function) to determine the type of shock if the clinical examination does not lead to a clear diagnosis (SSCG Section A, Recommendation 4)	(BPS).
	6. We suggest that dynamic over static variables be used to predict fluid responsiveness, where available (SSCG Section A, Recommendation 5)	(weak recommendation, low quality of evidence).
	7. We recommend an initial target mean arterial pressure (MAP) of 65 mm Hg in patients with septic shock requiring vasopressors (SSCG Section A, Recommendation 6)	(strong recommendation, moderate quality of evidence).
	8. We suggest guiding resuscitation to normalize lactate in patients with elevated lactate levels as a marker of tissue hypoperfusion (SSCG Section A, Recommendation 7)	(weak recommendation, low quality of evidence).
	9. We recommend that a fluid challenge technique be applied where fluid administration is continued as long as hemodynamic factors continue to improve (SSCG Section F, Recommendation 1)	(BPS).
	10. We recommend crystalloids as the fluid of choice for initial resuscitation and subsequent intravascular volume replacement in patients with sepsis and septic shock (SSCG Section F, Recommendation 2)	(strong recommendation, moderate quality of evidence).
	11. We suggest using either balanced crystalloids or saline for fluid resuscitation of patients with sepsis or septic shock (SSCG Section F, Recommendation 3)	(weak recommendation, low quality of evidence).
	12. We suggest using albumin in addition to crystalloids for initial resuscitation and subsequent intravascular volume replacement in patients with sepsis and septic shock when patients require substantial amounts of crystalloids (SSCG Section F, Recommendation 4)	(weak recommendation, low quality of evidence).

	13. We recommend against using hydroxyethyl starches (HESs) for intravascular volume replacement in patients with sepsis or septic shock (SSCG Section F, Recommendation 5)	(strong recommendation, high quality of evidence).
	14. We suggest using crystalloids over gelatins when resuscitating patients with sepsis or septic shock (SSCG Section F, Recommendation 6)	(weak recommendation, low quality of evidence).
ANTI MICROBIAL THERAPY	15. We recommend that appropriate routine microbiologic cultures (including blood) be obtained before starting antimicrobial therapy in patients with suspected **sepsis** or **septic shock** if doing so results in no substantial delay in the start of antimicrobials (SSCG Section C, Recommendation 1)	(BPS).
START SMART	16. We recommend that administration of IV antimicrobials be initiated as soon as possible after recognition and within one hour for both sepsis and septic shock. (SSCG Section D, Recommendation 1)	(Strong recommendation, moderate quality of evidence).
	17.We recommend empiric broad-spectrum therapy with one or more antimicrobials for patients presenting with sepsis or septic shock to cover all likely pathogens (including bacterial and potentially fungal or viral coverage) (SSCG Section D, Recommendation 2)	(strong recommendation, moderate quality of evidence).
	18. We recommend that dosing strategies of antimicrobials be optimized based on accepted pharmacokinetic/pharmacodynamic principles and specific drug properties in patients with **sepsis** or **septic shock** (SSCG Section D, Recommendation 5)	(BPS).
	19. We suggest empiric combination therapy (using at least two antibiotics of different antimicrobial classes) aimed at the most likely bacterial pathogen(s) for the initial management of **septic shock** (SSCG Section D, Recommendation 6)	(weak recommendation, low quality of evidence).
	20. We suggest that combination therapy not be routinely used for ongoing treatment of most other serious infections, including bacteraemia and sepsis without shock (SSCG Section D, Recommendation 7)	(weak recommendation, low quality of evidence).
	21. We recommend against combination therapy for the routine treatment of neutropenic sepsis/bacteraemia (SSCG Section D, Recommendation 8)	(strong recommendation, moderate quality of evidence).
Then Focus	22. We recommend that empiric antimicrobial therapy be narrowed once pathogen identification and sensitivities are established and/or adequate clinical improvement is noted (SSCG Section D, Recommendation 3)	(BPS).
	23. If combination therapy is initially used for septic shock, we recommend de-escalation with discontinuation of combination therapy within the first few days in response to clinical improvement and/or evidence of infection resolution. This applies to both targeted (for culture-positive infections) and empiric (for culture-negative infections) combination therapy (SSCG Section D, Recommendation 9)	(BPS).
	24. We recommend daily assessment for de-escalation of antimicrobial therapy in patients with sepsis and septic shock (SSCG Section D, Recommendation 13)	(BPS).
	25. We recommend against sustained systemic antimicrobial prophylaxis in patients with severe inflammatory states of non-infectious origin (e.g., severe	(BPS).

	pancreatitis, burn injury) (SSCG Section D, Recommendation 4)	
	26. We suggest that measurement of procalcitonin levels can be used to support shortening the duration of antimicrobial therapy in sepsis patients (SSCG Section D, Recommendation 14)	(weak recommendation, low quality of evidence).
	27. We suggest that procalcitonin levels can be used to support the discontinuation of empiric antibiotics in patients who initially appeared to have **sepsis**, but subsequently have limited clinical evidence of **infection** (SSCG Section D, Recommendation 15)	(weak recommendation, low quality of evidence)
	28. We suggest that an antimicrobial treatment duration of 7 to 10 days is adequate for most serious infections associated with sepsis and septic shock (SSCG Section D, Recommendation 10)	(weak recommendation, low quality of evidence).
	29. We suggest that longer courses are appropriate in patients who have a slow clinical response, undrainable foci of *infection*, bacteraemia with S aureus, some fungal and viral infections, or immunologic deficiencies, including neutropenia. (SSCG Section D, Recommendation 11)	(weak recommendation, low quality of evidence).
	30. We suggest that shorter courses are appropriate in some patients, particularly those with rapid clinical resolution following effective source control of intra-abdominal or urinary sepsis and those with anatomically uncomplicated pyelonephritis (SSCG Section D, Recommendation 12)	(weak recommendation, low quality of evidence).
	31. We recommend that a specific anatomic diagnosis of **infection** requiring emergent source control be identified or excluded as rapidly as possible in patients with **sepsis** or **septic shock**, and that any required source control intervention be implemented as soon as medically and logistically practical after the diagnosis is made (SSCG Section E, Recommendation 1)	(BPS).
	32. We recommend prompt removal of intravascular access devices that are a possible source of **sepsis** or **septic shock** after other vascular access has been established (SSCG Section E, Recommendation 2)	(BPS).
	33. We recommend norepinephrine as the first-choice vasopressor (SSCG Section G, Recommendation 1)	(strong recommendation, moderate quality of evidence).
SOURCE CONTROL	34. We suggest adding either vasopressin (up to 0.03 U/min) (weak recommendation, moderate quality of evidence) or epinephrine (weak recommendation, low quality of evidence) to norepinephrine with the intent of raising MAP to target, or adding vasopressin (up to 0.03 U/min) to decrease norepinephrine dosage. (SSCG Section G, Recommendation 2)	(weak recommendation, Low/moderate quality of evidence)
	35. We suggest using dopamine as an alternative vasopressor agent to norepinephrine only in highly selected patients (e.g., patients with low risk of tachyarrhythmias and absolute or relative bradycardia) (SSCG Section G, Recommendation 3)	(weak recommendation, low quality of evidence).
VASOACTIVE MEDICATIONS	36. We recommend against using low-dose dopamine for renal protection (SSCG Section G, Recommendation 4)	(strong recommendation, high quality of evidence).

	37. We suggest using dobutamine in patients who show evidence of persistent hypoperfusion despite adequate fluid loading and the use of vasopressor agents (SSCG Section G, Recommendation 5)	(weak recommendation, low quality of evidence).
	38. We suggest that all patients requiring vasopressors have an arterial catheter placed as soon as practical if resources are available (SSCG Section G, Recommendation 6)	(weak recommendation, very low quality of evidence).
	39. We suggest against using IV hydrocortisone to treat **septic shock** patients if adequate fluid resuscitation and vasopressor therapy are able to restore hemodynamic stability. If this is not achievable, we suggest IV hydrocortisone at a dose of 200 mg per day (SSCG Section H, Recommendation 1)	(weak recommendation, low quality of evidence).
	40. We recommend that RBC transfusion occur only when hemoglobin concentration decreases to < 7.0 g/dL in adults in the absence of extenuating circumstances, such as myocardial ischemia, severe hypoxemia, or acute haemorrhage. (SSCG Section I, Recommendation 1)	(strong recommendation, high quality of evidence).
	41. We recommend against the use of erythropoietin for treatment of anaemia associated with **sepsis** (SSCG Section I, Recommendation 2)	(strong recommendation, moderate quality of evidence).
CORTICOSTEROIDS	42. We suggest against the use of fresh frozen plasma to correct clotting abnormalities in the absence of bleeding or planned invasive procedures (SSCG Section I, Recommendation 3)	(weak recommendation, very low quality of evidence).
BLOOD PRODUCTS	43. We suggest prophylactic platelet transfusion when counts are < 10,000/mm^3 (10×10^9/L) in the absence of apparent bleeding and when counts are < 20,000/mm^3 (20×10^9/L) if the patient has a significant risk of bleeding. Higher platelet counts (≥ 50,000/mm^3 [50×10^9/L]) are advised for active bleeding, surgery, or invasive procedures (SSCG Section I, Recommendation 4)	(weak recommendation, very low quality of evidence).
IMMUNOGLOBULINS	44. We suggest against the use of IV immunoglobulins in patients with **sepsis** or **septic shock** (SSCG Section J, Recommendation 1)	(weak recommendation, low quality of evidence).
BLOOD PURIFICATION	45. We make no recommendation regarding the use of blood purification techniques. (SSCG Section K, Recommendation 1)	N/A
ANTICOAGULANTS	46. We recommend against the use of antithrombin for the treatment of **sepsis** and **septic shock** (SSCG Section L, Recommendation 1)	(strong recommendation, moderate quality of evidence).
	47. We make no recommendation regarding the use of thrombomodulin or heparin for the treatment of **sepsis** or **septic shock**. (SSCG Section L, Recommendation 2)	N/A
MECHANICAL VENTILATION	48. We recommend using a target tidal volume of 6 mL/kg predicted body weight (PBW) compared with 12 mL/kg in adult patients with **sepsis** induced ARDS (SSCG Section M, Recommendation 1)	(strong recommendation, high quality of evidence).
	49. We recommend using an upper limit goal for plateau pressures of 30 cm H_2O over higher plateau pressures in adult patients with **sepsis** induced severe ARDS (SSCG Section M, Recommendation 2)	(strong recommendation, moderate quality of evidence).
	50. We suggest using higher PEEP over lower PEEP in adult patients with **sepsis** induced moderate to severe ARDS	(weak recommendation, moderate quality of evidence).

	(SSCG Section M, Recommendation 3)	
	51. We suggest using recruitment manoeuvres in adult patients with **sepsis** induced, severe ARDS (SSCG Section M, Recommendation 4)	(weak recommendation, moderate quality of evidence).
	52. We recommend using prone over supine position in adult patients with **sepsis** induced ARDS and a Pa$\mathbf{O}_2$/F $\mathbf{IO}_2$ratio < 150(SSCG Section M, Recommendation 5)	(strong recommendation, moderate quality of evidence).
	53. We recommend against using high-frequency oscillatory ventilation (HFOV) in adult patients with **sepsis**-induced ARDS (SSCG Section M, Recommendation 6)	(strong recommendation, moderate quality of evidence).
	54. We make no recommendation regarding the use of non-invasive ventilation (NIV) for patients with **sepsis** induced ARDS. (SSCG Section M, Recommendation 7)	N/A
	55. We suggest using neuromuscular blocking agents (NMBAs) for ≤ 48 hours in adult patients with **sepsis** induced ARDS and a Pa$\mathbf{O}_2$/F $\mathbf{IO}_2$ratio < 150 mm Hg (SSCG Section M, Recommendation 8)	(weak recommendation, moderate quality of evidence).
	56. We recommend a conservative fluid strategy for patients with established **sepsis** induced ARDS who do not have evidence of tissue hypoperfusion (SSCG Section M, Recommendation 9)	(strong recommendation, moderate quality of evidence)
	57. We recommend against the use of β-2 agonists for the treatment of patients with **sepsis** induced ARDS without bronchospasm (SSCG Section M, Recommendation 10)	(strong recommendation, moderate quality of evidence).
	58. We recommend against the routine use of the PA catheter for patients with **sepsis** induced ARDS (SSCG Section M, Recommendation 11)	(strong recommendation, high quality of evidence).
	59. We suggest using lower tidal volumes over higher tidal volumes in adult patients with **sepsis** induced respiratory failure without ARDS (SSCG Section M, Recommendation 12)	(weak recommendation, low quality of evidence).
	60. We recommend that mechanically ventilated **sepsis** patients be maintained with the head of the bed elevated between 30 and 45 degrees to limit aspiration risk and to prevent the development of VAP (SSCG Section M, Recommendation 13)	(strong recommendation, low quality of evidence).
	61. We recommend using spontaneous breathing trials in mechanically ventilated patients with **sepsis** who are ready for weaning (SSCG Section M, Recommendation 14)	(strong recommendation, high quality of evidence).
	62. We recommend using a weaning protocol in mechanically ventilated patients with **sepsis** induced respiratory failure who can tolerate weaning (SSCG Section M, Recommendation 15)	(strong recommendation, moderate quality of evidence).
SEDATION AND ANALGESIA	63. We recommend that continuous or intermittent sedation be minimized in mechanically ventilated **sepsis** patients, targeting specific titration end points (SSCG Section N, Recommendation 1)	(BPS).
GLUCOSE CONTROL	64. We recommend a protocolized approach to blood glucose management in ICU patients with **sepsis**, commencing insulin dosing when two consecutive blood glucose levels are > 180 mg/dL (10mmol/L). This approach should target an upper blood glucose level ≤ 180 mg/dL (10mmol/L) rather than an upper target blood glucose level ≤ 110 mg/dL (6.1mmol/L) (SSCG Section O, Recommendation 1)	(strong recommendation, high quality of evidence).
	65. We recommend that blood glucose values be	(BPS).

	monitored every 1 to 2 hours until glucose values and insulin infusion rates are stable, then every 4 hours thereafter in patients receiving insulin infusions (SSCG Section O, Recommendation 2)	
	66. We recommend that glucose levels obtained with point-of-care testing of capillary blood be interpreted with caution because such measurements may not accurately estimate arterial blood or plasma glucose values (SSCG Section O, Recommendation 3)	(BPS).
	67. We suggest the use of arterial blood rather than capillary blood for point-of-care testing using glucose meters if patients have arterial catheters (SSCG Section O, Recommendation 4)	(weak recommendation, low quality of evidence).
RENAL REPLACEMENT THERAPY	68. We suggest that either continuous RRT (CRRT) or intermittent RRT be used in patients with **sepsis** and acute kidney injury (SSCG Section P, Recommendation 1)	(weak recommendation, moderate quality of evidence).
	69. We suggest using CRRT to facilitate management of fluid balance in hemodynamically unstable septic patients (SSCG Section P, Recommendation 2)	(weak recommendation, very low quality of evidence).
	70. We suggest against the use of RRT in patients with **sepsis** and acute kidney injury for increase in creatinine or oliguria without other definitive indications for dialysis (SSCG Section P, Recommendation 3)	(weak recommendation, low quality of evidence).
BICARBONATE THERAPY	71. We suggest against the use of sodium bicarbonate therapy to improve hemodynamics or to reduce vasopressor requirements in patients with hypoperfusion-induced lactic acidaemia with pH ≥ 7.15 (SSCG Section Q, Recommendation 1)	(weak recommendation, moderate quality of evidence).
VENOUS THROMBOEMBOLISM PROPHYLAXIS	72. We recommend pharmacologic prophylaxis (unfractionated heparin [UFH] or low-molecular-weight heparin [LMWH]) against venous thromboembolism (VTE) in the absence of contraindications to the use of these agents (SSCG Section R, Recommendation 1)	(strong recommendation, moderate quality of evidence).
	73. We recommend LMWH rather than UFH for VTE prophylaxis in the absence of contraindications to the use of LMWH (SSCG Section R, Recommendation 2)	(strong recommendation, moderate quality of evidence).
	74. We suggest combination pharmacologic VTE prophylaxis and mechanical prophylaxis, whenever possible (SSCG Section R, Recommendation 3)	(weak recommendation, low quality of evidence).
	75. We suggest mechanical VTE prophylaxis when pharmacologic VTE is contraindicated (SSCG Section R, Recommendation 4)	(weak recommendation, low quality of evidence).
STRESS ULCER PROPHYLAXIS	76. We recommend that stress ulcer prophylaxis be given to patients with sepsis or septic shock who have risk factors for gastrointestinal (GI) bleeding (SSCG Section S, Recommendation 1)	(strong recommendation, low quality of evidence).
	77. We suggest using either proton pump inhibitors (PPIs) or histamine-2 receptor antagonists (H2RAs) when stress ulcer prophylaxis is indicated (SSCG Section S, Recommendation 2)	(weak recommendation, low quality of evidence).
	78. We recommend against stress ulcer prophylaxis in patients without risk factors for GI bleeding (SSCG Section S, Recommendation 3)	(BPS).
NUTRITION	79. We recommend against the administration of early	(strong recommendation,

	parenteral nutrition alone or parenteral nutrition in combination with enteral feedings (but rather initiate early enteral nutrition) in critically ill patients with **sepsis** or **septic shock** who can be fed enterally (SSCG Section T, Recommendation 1)	moderate quality of evidence).
	80. We recommend against the administration of parenteral nutrition alone or in combination with enteral feeds (but rather to initiate IV glucose and advance enteral feeds as tolerated) over the first 7 days in critically ill patients with **sepsis** or **septic shock** for whom early enteral feeding is not feasible (SSCG Section T, Recommendation 2)	(strong recommendation, moderate quality of evidence).
	81. We suggest the early initiation of enteral feeding rather than a complete fast or only IV glucose in critically ill patients with **sepsis** or **septic shock** who can be fed enterally (SSCG Section T, Recommendation 3)	(weak recommendation, low quality of evidence).
	82. We suggest either early trophic/hypocaloric or early full enteral feeding in critically ill patients with **sepsis** or **septic shock**; if trophic/hypocaloric feeding is the initial strategy, then feeds should be advanced according to patient tolerance (SSCG Section T, Recommendation 4)	(weak recommendation, moderate quality of evidence).
	83. We recommend against the use of omega-3 fatty acids as an immune supplement in critically ill patients with **sepsis** or **septic shock** (SSCG Section T, Recommendation 5)	(strong recommendation, low quality of evidence).
	84. We suggest against routinely monitoring gastric residual volumes (GRVs) in critically ill patients with **sepsis** or **septic shock** (weak recommendation, low quality of evidence). However, we suggest measurement of gastric residuals in patients with feeding intolerance or who are considered to be at high risk of aspiration (SSCG Section T, Recommendation 6)	(weak recommendation, very low quality of evidence).
	85. We suggest the use of prokinetic agents in critically ill patients with **sepsis** or **septic shock** and feeding intolerance (SSCG Section T, Recommendation 7)	(weak recommendation, low quality of evidence).
	86. We suggest placement of post-pyloric feeding tubes in critically ill patients with **sepsis** or **septic shock** with feeding intolerance or who are considered to be at high risk of aspiration (SSCG Section T, Recommendation 8)	(weak recommendation, low quality of evidence).
	87. We recommend against the use of IV selenium to treat **sepsis** and **septic shock** (SSCG Section T, Recommendation 9)	(strong recommendation, moderate quality of evidence).
	88. We suggest against the use of arginine to treat **sepsis** and **septic shock** (SSCG Section T, Recommendation 10)	(weak recommendation, low quality of evidence).
	89. We recommend against the use of glutamine to treat **sepsis** and **septic shock** (SSCG Section T, Recommendation 11)	(strong recommendation, moderate quality of evidence).
	90. We make no recommendation about the use of carnitine for **sepsis** and **septic shock**. (SSCG Section T, Recommendation 12)	N/A
SETTING GOALS OF CARE	91. We recommend that goals of care and prognosis be discussed with patients and families (SSCG Section U, Recommendation 1)	(BPS).
	92. We recommend that goals of care be incorporated into treatment and end-of-life care planning, utilizing palliative care principles where appropriate (SSCG Section U,	(strong recommendation, moderate quality of evidence).

	Recommendation 2)	
	93. We suggest that goals of care be addressed as early as feasible, but no later than within 72 hours of ICU admission (SSCG Section U, Recommendation 3)	(weak recommendation, low quality of evidence).

SSC Guideline provides explanation on grading of recommendations and levels of evidence.

Section 2: Development of the National Clinical Guideline

2.1 Background

What is the impact of sepsis in Ireland?
In 2018, sepsis or septic shock was documented in 14,639 non-pregnant adults and these patients had a mortality rate of 20.3%[5].

There were 12,005 patients, with a sepsis diagnosis, who were assigned to a medical diagnostic related group (DRG), and these patients had an average length of stay (aLOS) of 17.1 days, which is 49.6% longer than those who had an infection diagnosis. Medical patients with a hospital stay complicated by sepsis had a mortality rate of 19.4%.

2,634 patients were assigned to a surgical DRG and they had an aLOS of 46.4 days, 127% longer than those with an infection diagnosis. Surgical patients whose hospital stay was complicated by sepsis had a mortality rate of 24.8%.

31.7% of all hospital inpatients were documented as having an infection or sepsis as part of their discharge diagnoses and they occupied 49.4% of the acute hospital beds.

Sepsis affected 3.33% of inpatients but contributed to 27% of all hospital deaths, a documentation rate of 303 cases per 100,000 population per annum. In 2017, chart review audits were performed by the Sepsis Group Assistant Directors of Nursing (ADONS) on 523 charts nationally, with charts sampled from all acute hospitals, of patients with infection and acute kidney injury cared for by medical physicians, surgeons and emergency medicine physicians[5]. This audit demonstrated that only 52% of cases that fulfilled the criteria for sepsis were actually documented as sepsis, applying this rate to national figures would lead to sepsis affecting up to 6.7% of hospital inpatients or approximately 583 per 100,000 population per annum. This is consistent with other jurisdictions that have published data based on administrative databases[8].

Mortality from Maternal Sepsis from direct causes is currently 0.5% (HSE, 2019) and 0.48 per 100,000 maternities (MBRRACE, 2018). The Irish data is based on the number of women who developed sepsis in Ireland during 2018.

TABLE 3. DEFINITIONS OF MATERNAL DEATHS: (MBRRACE, 2018)

Maternal Death	Deaths of women while pregnant or within 42 days of the end of the pregnancy* from any cause related to or aggravated by the pregnancy or its management, but not from accidental or incidental causes
Direct	A consequent of a disorder specific to pregnancy
Indirect	Deaths resulting from previous existing disease, or disease that developed during pregnancy and which was not the result of direct obstetric causes, but which was aggravated by the physiological

	effects of pregnancy.
Late	Deaths occurring more than 42 days but less than 1 year after the end of pregnancy.
Coincidental‡	Incidental/accidental deaths not due to pregnancy or aggravated by pregnancy

* Includes giving birth, ectopic pregnancy, miscarriage or termination of pregnancy.
‡ Termed ''Fortuitous'' in the International Classification of Diseases (ICD)

What are the definitions of sepsis and septic shock?[9]

Sepsis is life-threatening organ dysfunction caused by a dysregulated host response to infection.

Maternal sepsis**:** is a life-threatening condition defined as organ dysfunction resulting from infection during pregnancy, childbirth, post-abortion or postpartum period [ref].

The clinical application of this definition requires that there be evidence to support infection as the cause of the patient being unwell based on history, examination and clinical or biochemical evidence of acute organ dysfunction consequent to that infection. The guideline recognises that there is no single test that confirms the presence of infection or sepsis but rather the diagnosis is based on the presence of a suite of symptoms and signs supported by tests and investigations. It also recognises that whilst the identification of a pathological organism is very valuable in guiding treatment, that blood cultures are only positive in 40-55% of cases[7, 10] and that a negative culture does not preclude the diagnosis of infection or sepsis.
Whilst the presence of a systemic inflammatory response (SIRS) is helpful in diagnosing infection, it is no longer a requirement for the diagnosis of sepsis[9].

The criteria for a systemic inflammatory response (SIRS) are fulfilled when 2 or more of the following are present[11].

Adult non-pregnant
Heart rate > 90 beats/minute
Respiratory rate > 20 breaths/minute
Temperature > 38.3^{o}C or < 36^{o}C
White cell count > 12 or < 4 x 10^{9} cells/L or normal with > 10% immature forms

The rationale behind the shift away from the SIRS-based definition of sepsis (Sepsis-2) is primarily three-fold.

- The over-sensitivity of the previous definition that included a cohort of patients who did not have a life-threatening illness and whose clinical course would not be impacted by escalated care [12,13].
- Its failure to recognise patients with a life-threatening acute organ dysfunction due to infection that would benefit from escalated care but who did not present with a SIRS response[13,14].

- The lack of specificity of the SIRS response that can be triggered by many non-infective insults [15].

Maternity

- Modified SIRS for pregnant and post-natal women 42 days following birth
- Heart rate ≥ 100 beats/minute [refx3]
- Respiratory rate ≥ 20 breathes/minute
- Temperature > 38.3°C or < 36°C
- White cell count > 16.9 or < 4 x 10^9 cells/L or > 10% immature bands
- Blood sugar level > 7.7 mmol/L (in the non-diabetic)
- Acutely altered mental status
- Fetal heart Rate > 160 bpm

All adults

Septic shock is a subset of sepsis with circulatory and cellular/metabolic dysfunction associated with a higher risk of mortality[9].

The sepsis definition taskforce has defined this as the requirement for vasopressors/ inotropes to achieve a mean arterial pressure of ≥ 65mmHg *AND* a lactate > 2mmols/l despite adequate fluid resuscitation[9].

The rationale behind this definition is to identify the cohort of patients with a mortality risk of > 40% for the purposes of benchmarking. Patients with a vasopressor requirement and normal lactate post resuscitation have a mortality risk of > 30%[9].

Patients who require pressors or inotropes to maintain adequate perfusion pressure post fluid resuscitation require critical care whether their lactate is raised or not. For this reason this NCG uses the persistent requirement for vasopressors/ inotropes post adequate fluid resuscitation as its definition of septic shock. This is a pragmatic decision for the purposes of facilitating clinical care, recognizing that lactate measurement is not always available and that the sepsis definition taskforce allowed for this:

'In settings in which lactate measurement is not available, the use of a working diagnosis of septic shock using hypotension and other criteria consistent with tissue hypoperfusion (e.g. delayed capillary refill) may be necessary'[9].

TABLE 4. SUMMARY OF DIAGNOSTIC CRITERIA USED BY NCG

Infection	**A clinical syndrome based on symptoms and signs caused by pathological organisms, which may or may not be identified.**
Sepsis	**One or more acute organ dysfunction consequent to infection.** Of note this was formerly defined as "Severe sepsis". When used now, severe sepsis is a descriptive term rather than a definition much like severe pneumonia.
Septic shock	**A vasopressor or inotrope requirement to maintain mean arterial pressure (MAP) ≥ 65mmHg despite adequate fluid resuscitation which has been triggered by infection.**

Why is the pre-critical care setting important?

The Centres for Disease Control in the U.S. have identified that 70-80% of sepsis cases arise in the community[3]. These patients present to the acute hospital sector via the emergency department (ED), the Acute Medical Unit (AMU), the Acute Surgical Unit (ASU) and to a lesser extent the outpatient department (OPD). The remaining 20-30% of patients deteriorate with sepsis as an inpatient.

In order for patients to have the best opportunity to survive they need to present for medical review and have sepsis recognised and managed in an appropriate and timely manner. There is an important role for primary and community care in terms of risk recognition and for public awareness of the signs and symptoms of deterioration that may signal the development of sepsis, in order to ensure the right patient is in the right place at the right time to receive the right treatment; however, this is outside the remit of this guideline.

It is recognised that the presentation of sepsis is variable in symptoms, signs and time course. Thus, sepsis may not be present or not be diagnosed on first presentation and may not become apparent until the clinical condition evolves further. Deterioration whilst on treatment (including supportive) needs to be reviewed and diagnosis and treatment amended accordingly. The National Early Warning System (NEWS)[4] and/or clinical judgment should be deployed to pick up deterioration in the in-patient. Patient information leaflets and booklets are available on www.hse.ie/sepsis.

2.2 Clinical and financial impact of condition/disease/topic

The programme uses the Hospital Inpatient Enquiry (HIPE) database to extract data on the burden of sepsis in the acute hospital sectors and to identify the common characteristics of patients with sepsis. There are a number of limitations to using this dataset:

- Causality cannot be inferred from administrative data
- Sepsis may be a direct or indirect contributor to morbidity and mortality
- In patients admitted to critical care, the sepsis event may be unrelated to the cause of critical care admission and indeed may not have occurred during the critical care stay.

The reasons contributing to the above include:

- Sepsis is not routinely coded as the main diagnosis
- There is no order of precedence in the subsequent diagnostic and procedural codes dx 2-30.

For example, a patient admitted for treatment of lymphoma might develop neutropenic sepsis and end up in ICU. Their main diagnosis, dx1, is likely to be coded as lymphoma and sepsis could appear anywhere in dx2-30, as will the ICU stay.

Another patient might be admitted electively for a surgical procedure with routine post-operative ICU admission, subsequently, on the ward, they develop sepsis but do not require or no critical care bed is available, and they have a prolonged hospital stay. Their dx1 will be the reason for the surgical procedure with sepsis anywhere between dx2-30, as will the ICU stay.

In the first example sepsis is clearly the cause of deterioration and ICU admission, in the second the sepsis episode is unrelated to the ICU admission but has clearly contributed to morbidity. In both cases the sepsis episode has had a profound effect on the patient and the healthcare costs.

Despite its limitations the use of administrative data has been validated for quality improvement programmes[22].

In 2018, there were 14,639 patients who had sepsis included in their discharge coding. 4,002 of these patients required admission to a critical care bed at some point during their hospitalisation[5].

The economic impact of sepsis can be looked at by assessing

- Direct costs
- Economic and social burden
- 'Loss of wages technique'

Direct:
The average cost per in-patient stay per night in 2017 (latest data available) was €878[23]. This cost is not specific to sepsis patients, it is the average cost of an inpatient stay per night when all diagnoses are included. Sepsis is acknowledged as one of the more expensive inpatient diagnosis[24] so this analysis is at risk of underestimating the costs of sepsis care in the Irish acute hospital sector.

The estimated direct costs of patients with sepsis causing or complicating their hospital admission is €288 million i.e. €19,667 per patient with an average length of stay (aLOS) of 22.4 days. The difference between the average hospital stay complicated by infection rather than sepsis is 9 days or €7,902 per patient.

The average length of stay for a patient in a surgical diagnostic-related group (DRG) with a sepsis diagnosis is 46.4days or €40,739. Surgical DRG patients with an infection diagnosis

have an aLOS of 20.4 days, a difference in cost of €22,828 per patient between sepsis and infection complicating the hospitalisation. This is a total cost differential of approximately €60million.

Economic and Social Burden:
The costs of sepsis to the economy can be divided into direct costs (28%), loss of productivity due to mortality (53%), loss of productivity due to morbidity (12%) and loss of productivity due to temporary morbidity (4%)[25].

Direct	€19,667 (28%)
Loss of productivity due to mortality	€39,334 (56%)
Loss of productivity due to morbidity	€8,429 (12%)
Temporary loss of productivity	€2,810 (4%)

Total costs = €70,240 per patient or €1.03 billion loss to the Irish Economy per annum.

'Loss of wages' method[26]
An alternative method to estimate the loss of productivity due to mortality, is to use the 'Loss of wages' method[26]. This is the most frequently used measure of productivity loss; using a retirement age of 65 years, there were a total of 12,600 years lost amongst 1,892 patients who died below the age of 65. It does not include direct costs or productivity loss due to morbidity. The average annual earnings in 2016 were €36,919, making a total loss of earnings of €465.2million,with an estimated income tax loss to the exchequer of €93million. This is lower than the estimated €583.6million using the previous method above and would result in a total cost of €924 million to the Irish economy per annum.

Comparisons:
Direct costs in ICU versus Non-ICU :
In the U.S., Angus et al, using the claims databases estimated the ICU septic patient cost $29,900, with an aLOS 23.3 days versus the non-ICU septic patient $13,900, aLOS 15.6 days[8].

In the same population, Chalfin et al[27] calculated the cost differential between survivors and non-survivors $38,304 versus $49,182. This has been born out in other studies which show escalating ICU costs in non-survivors. (REFS)

In France, Brun-Buisson et al.[28] reported costs from €26,256 to €35,185 depending on the severity of illness. Other European studies have given lower cost estimates, ranging from €23,000 to €29,000[29]. In Ireland, McLaughlin et al[31] performed a prospective micro-costing of ICU treatment (not limited to sepsis) with mean total ICU costs of €20,487.

In Brazil, a micro-costing analysis of ICU sepsis care showed a median total cost of $9,773 ($4,643-$19,221)[30]. In China, Cheng et al[32], showed a mean hospital cost $11,390 - $11,455 per sepsis case.

Thus, it can be seen that the hospital costs calculated for Ireland are not out of sync with other high-income countries, although direct comparisons cannot be made due to the difference in methodology.

Economic and social burden:
In Germany in 2002, using the administrative and other databases, Schmidt et al[33] did an assessment of the economic and social burden of sepsis. He identified the ratios used in the analysis for Ireland.
His results include:

- Productivity loss due to temporary morbidity €3,431 to 7,409 depending on severity (calculated at €2,810 in Ireland)
- Productivity loss due to mortality €46,000 per case (calculated at €39,334 in Ireland)
- Total burden of illness €82,886 to €178,954 (calculated at €70,240 per patient in Ireland)

Economic impact of the National Sepsis Programme
Shorr et al[34] performed an economic impact of their sepsis protocol in an academic, tertiary care hospital in the United States, and found median total hospital costs were reduced from $21,985 to $16,103, mainly due to a shorter length of stay.

This has also been seen in Ireland where the aLOS for patients with sepsis causing or complicating their hospital admission in 2011-2015 was 25.9 with estimated direct costs of €21,437, as this aLOS fell in 2016/17 to 20.9 this has resulted in a reduction of €3,583 per patient with an estimated direct cost of €17,890 per hospital stay.

TABLE 5. COST PER BED DAY ACCORDING TO YEAR (€)

Year	Cost per bed day*
2017	€878
2016	€856
2015	€839
2014	€839
2013	€815
2012	€825
2011	€820

*Average costs, across all nights, all hospitals, and all types of in-patient cases. This figure is a fully absorbed cost which means it includes treatment and care costs (such as diagnostics, theatres etc.) as well as hotel costs but excludes capital and depreciation. It excludes day case, outpatient and emergency department costs. (Healthcare Pricing Office, 2017)

In the overall sepsis population, two changes occurred as a consequence of the implementation programme, improved recognition and improved treatment. In the non-critical care population changes over time will reflect improved recognition as well as changes due to improved treatment and as such analysis of trends in this population are problematic. However, in the critical care population lower acuity would have no impact on critical care admission due to the limited number of such beds; indeed, there was a decrease in capacity over the study period suggesting a potential increase in acuity amongst the critical care population.

- Mean sepsis-associated mortality 2011-2015 in patients admitted to a critical care area: 34%,

- Mean sepsis-associated mortality 2016-2018 in patients admitted to a critical care area: 31.4%

An absolute decrease of 2.6% and a relative decrease of 7.95%.

In 2018, 4,002 patients admitted to ICU had a sepsis code on their hospital discharge.

The mortality decrease demonstrates an additional 302 lives saved over the 3 years post implementation from this subpopulation.

The hospital aLOS for this subgroup decreased from 36.72 days in 2011-15 to 33.7 days in 2016-18, a gain of 12,086 bed days and a reduction in direct costs from €30,808 to €29,589 per patient. This represents a saving of €10.6million.

2.3 Rationale for this National Clinical Guideline

Sepsis is a common time-dependent medical emergency. Whilst it can affect a person of any age, from any social background and can strike irrespective of underlying good health, 90% of adults and 70% of children who develop sepsis have underlying risk factors (CDC Vitality). International sepsis campaigns that have introduced and promoted an approach to sepsis care based on early recognition of sepsis with resuscitation and timely referral to critical care are associated with an increased compliance with sepsis bundles and a decrease in mortality (OR 0.6).

In 2016, the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) were developed by a taskforce at the request of the Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM). (JAMA. 2016;315(8):801-810).

Sepsis-3 provides a welcome rationalization of the sepsis syndrome with sepsis only being diagnosed when infection has led to acute organ dysfunction and the presence of a systemic inflammatory response no longer being a requirement. A systemic inflammatory response may be caused by infective and non-infective conditions and represents an adaptive response to an insult. It is present in about 85% of sepsis cases and many more cases that are not sepsis. Thus, although its presence can alert a clinician that a patient may have a problem it is not sufficiently discriminatory to identify the cause of the problem.

These changes go a good way to reduce concerns about over diagnosis leading to overuse of antibiotics in a climate of increasing concern about multi-drug resistant organisms by identifying a subset of patients with infection who have a high mortality risk.

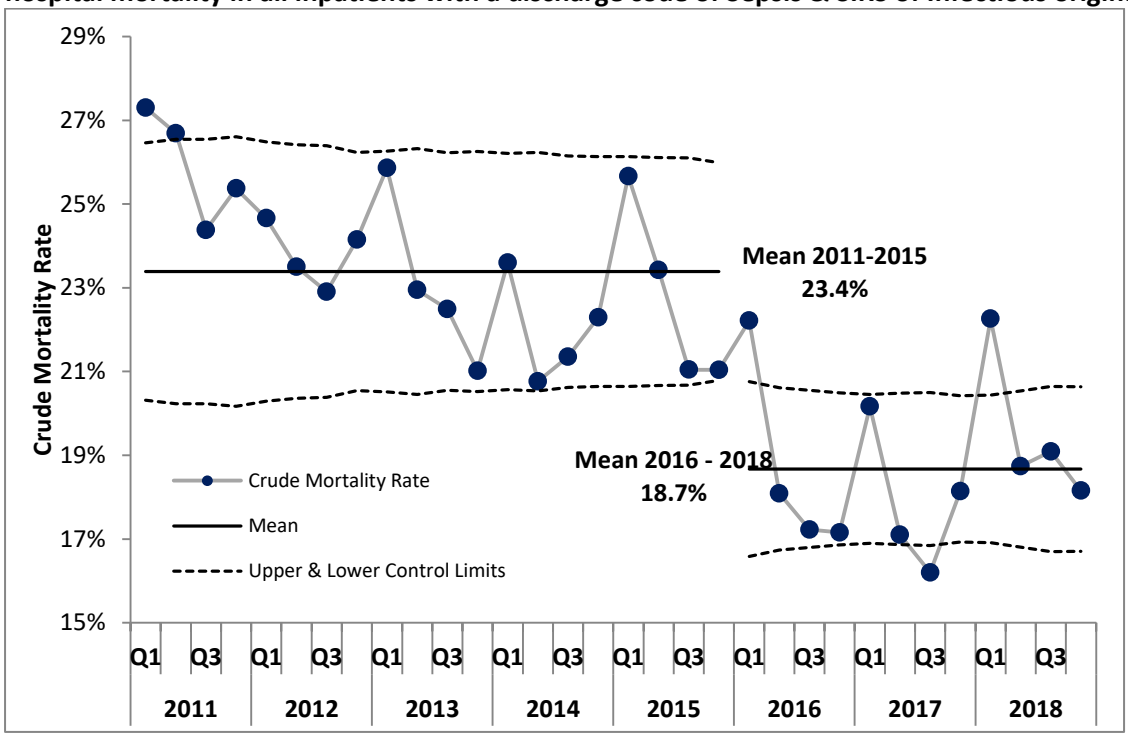
2.4 Aim and objectives

The aims of the NCG are:

1. To ensure that all acute hospitals give their patients with sepsis the best opportunity to survive.
2. To maximize the health-related quality of life in survivors of sepsis.
3. To minimize the burden of sepsis to the healthcare system by reducing the acuity and the chronic sequelae of sepsis.

The National Clinical Guideline was published in November 2014 and the implementation process started in 2015 with an education and awareness campaign. Hospital-based education was delivered by the National Sepsis Programme in all acute hospitals and clinical decision support tools and other educational aids and materials were rolled-out**.**

Figure 1. Impact of the National Clinical Guideline Implementation in Ireland; sepsis-associated hospital mortality in all inpatients with a discharge code of Sepsis & SIRS of Infectious origin. 5



Quarterly data, 2011 – 2018 (Statistical Process Control Chart).

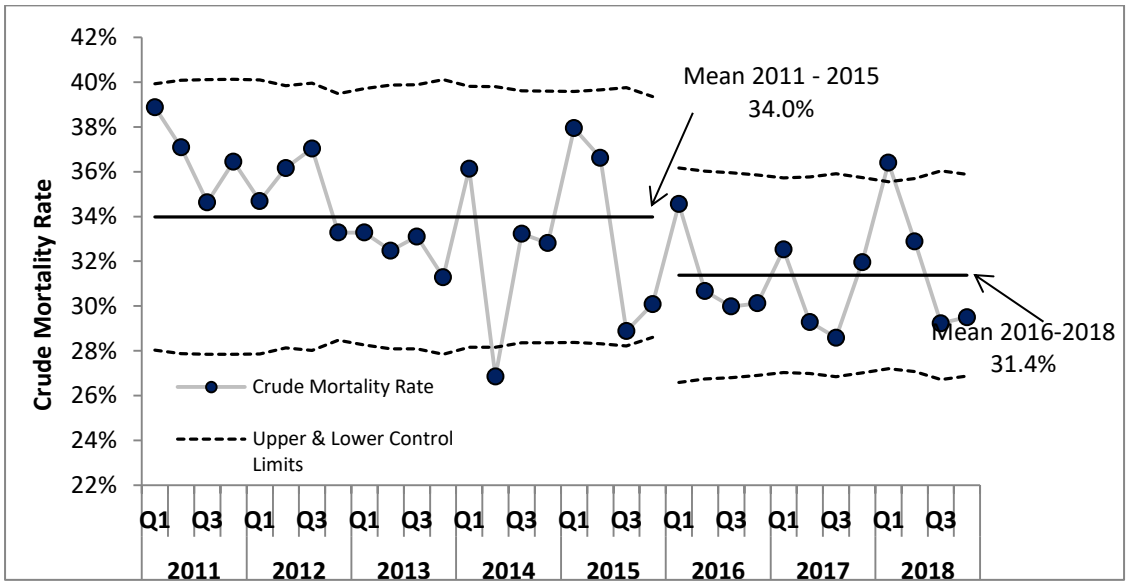
Quarterly rates of in-hospital mortality for inpatients with a diagnosis of sepsis from 2011 to 2018 were analysed using statistical process control (SPC) methods. The use of SPC methods allows us to see whether the changes made resulted in improvements and allow us to distinguish between variation that may have happened by chance alone and variation that indicates a real improvement in mortality rates. There is an important caveat and that is that the education and awareness campaign will have led to the improved documentation of lower acuity sepsis cases that bring with them a lower mortality rate and this will have impact. It is not possible to distinguish what portion of improvement is due to improved recognition and what is due to improved management, however, a 7.95% decrease in mortality is also observed in the critical care patient cohort (Figure 2), where capacity not recognition limits access and where there was a decrease in per capita bedstock. These effects are consistent with those found in other jurisdictions where sepsis quality improvement programmes were implemented.[1]

This figure demonstrates that the National Sepsis Programme had a statistically significant impact on the recognition and management of sepsis in Ireland.

Between 2011 and 2015, the average in-hospital mortality for inpatients with a diagnosis of sepsis was 23.4%. Using control limits based on SPC methods it was expected during this period that the quarterly mortality rate would vary from around 20 to 26% by chance alone. Since 2016 the quarterly mortality rate has averaged 18.7% which is below this lower control limit of 20% indicating a significant improvement in mortality rates that is not explained by chance alone.

The control limits in the statistical process control chart have been re-calculated to reflect this reduction. We now anticipate that this improvement will be sustained, and mortality will remain below 20% (with some variation due to seasonal effects).

Figure 2. Impact of the Sepsis Guideline Implementation in Ireland; sepsis-associated hospital mortality in inpatients admitted to a critical care area* with a discharge code of Sepsis & SIRS of Infectious origin.



*this includes ICU, HDU, CCU

Quarterly data, 2011 – 2018 (Statistical Process Control Chart).

SPC analysis does not identify which changes resulted in the demonstrated improvement. It is acknowledged that improved recognition and documentation of lower acuity sepsis cases, as well as improved management will have contributed to this effect. However, the average mortality rates can be benchmarked against other jurisdictions that have published[6,7,8] and this indicates that Ireland is performing as well as other high-income countries in terms of sepsis-associated mortality rates.

What are the aims of the National Sepsis Programme?

1. That all healthcare professionals have an understanding of the diagnostic criteria for sepsis and its basic pathophysiology.

2. That all medical, midwifery, and nursing staff working in the acute sector recognise patients at high risk of mortality from sepsis.
3. That all medical, nursing and midwifery staff working in the acute sector are:
    i. Familiar with the initial management of patients with a high risk of mortality from sepsis
    ii. Able to use the sepsis form which is a clinical decision support tool and forms part of the patient's clinical notes
    iii. Able to take a team approach to implementing the Sepsis 6 bundle and the sepsis management algorithms.

How should the aims be supported in the community?

70-80% of sepsis cases arise in the community thus a quality improvement campaign needs to have a 2-fold approach[4].

1. Address sepsis recognition and management by healthcare professionals who work in the community and
2. Improve Sepsis awareness in the public domain.

There is limited evidence-based data to guide recognition, management and escalation in the community and any such programme needs to have robust antimicrobial stewardship to support healthcare professionals in avoiding inappropriate usage[20] and to prevent 'protocol-driven' inappropriate emergency department, medical or surgical assessment unit referrals. It needs to be developed with the end users and tested within its context to ensure that it fulfils its purpose without unintended consequences.

Awareness of sepsis and its symptoms and signs is an important part of public health education. Such a programme should be embedded in a strategy to promote prevention of infection, antimicrobial stewardship and the recognition of signs and symptoms of deterioration that should prompt urgent medical review[21].

2.5 Guideline scope

This NCG applies to adult patients with confirmed or suspected sepsis, including pregnant women in the following settings;

- Emergency departments
- In-patient
- Maternity

The majority of recommendations and implementation points apply to both Adult non pregnant patients and pregnant women including women 42 days post birth. Recognition in the maternity patient is slightly different; therefore, maternity specific implementation points are signposted as such. Treatment and escalation is generally the same for both groups. See maternity section for more details on the pregnant woman/post parturient.

The purpose of this guideline is to implement the Surviving Sepsis Campaign Guideline (SSCG) in the management of the adult patient in the acute hospital sector in Ireland. It takes these international evidence-based recommendations and implements them in a format that applies to the structures and functions of the Irish Acute Health Care Sector. The

National Sepsis Programme would like to thank the Surviving Sepsis Campaign for permission to do this.

The recommendations of the SSCG are included so that it can be read as a standalone document. However, it is recommended that clinicians familiarise themselves with the SSCG, and is endorsed by the Critical Care Programme, the Joint Faculty of Intensive Care Medicine in Ireland and the Intensive Care Society of Ireland. An important guideline for those dealing with maternity is the 'Critically ill women in obstetrics'.[ref]

This NCG is relevant to all clinical staff in hospitals providing care to these patients.
Implementation has been divided into three phases,

1. Recognition
2. Treatment
3. Escalation

Implementation points included after SSCG recommendations are aimed, primarily, at the pre- and post-critical care setting, recognizing that much of the research that informed the SSCG occurred in the critical care setting and thus the SSCG can be more directly applied in that setting.

The NCG is designed to guide clinical judgement but not replace it. In individual cases a healthcare professional may, after careful consideration, decide not to follow guideline recommendations if it is deemed to be in the best interests of the patient and is in line with best practice. Clinical decisions and therapeutic options should be discussed with a senior clinician on a case-by-case basis as necessary and documented in the clinical notes.

Separate guidance for the paediatric patient will be produced when the paediatric SSCG is published; in the meantime, the recommendations in the 2014 guideline[2] continue to apply. The GDG recognises that the 2014 Guideline will no longer be available to access online and therefore will provide the paediatric section on the National Sepsis Website as stand-alone guidance until the paediatric SSCG becomes available.

The recommendations align with the aims of the National Sepsis Programme. Key recommendations are linked with other recommendations, practical guidance, roles, responsibilities and processes. The recommendations are linked to the best available evidence and/or expert opinion using the GRADE system for grading recommendations.

This guideline is available to all clinicians in the Republic of Ireland involved in the diagnosis and management of patients with sepsis.

A summary version of the National Clinical Guideline outlining the key recommendations and National Implementation Plan is available at: www.health.gov.ie/patient-safety/ncec

2.6 Conflict of interest statement

The guideline development process followed the conflict of interest policy set out by the NCEC. All members of the Sepsis Management GDG and the NCEC QA appraisal team were required to complete a Conflict of Interest declaration which was managed by the National Sepsis Programme Manager and the NCEC respectively. There were no conflicts of interest stated.

2.7 Sources of funding

The GDG examined the resources available to them to review and complete the update of this National Clinical Guideline and as such were satisfied that they would be able to leverage on the suitably qualified and multidisciplinary staff selected as part of the stakeholder analysis to complete the review.

2.8 Guideline methodology

In order to update the 2014 Sepsis National Clinical Guideline (NCG) the National Sepsis Programme convened a Guideline Development Group (GDG) consisting of key stakeholders, recognised experts in sepsis management and patient advocates.
A literature search was undertaken by the HSE Library Service to identify any national and international sepsis clinical guidelines published since the previous Sepsis NCG was published in 2014 which could be adopted or adapted for use in the Irish Healthcare setting.
The search strategy included a search of Medline and PubMed using search terms related to the management of sepsis and septic shock (Appendix 3). The websites of key organisations were also searched. The search identified 11 documents, the majority of which were excluded immediately as they related to pre-hospital care, non-acute care settings, paediatrics or were related to a specific type of sepsis, e.g. acute meningitis and meningococcal sepsis. When the exclusion criteria were applied only three guidelines were eligible for consideration:

- NICE Sepsis: recognition, assessment and early management (2016)
- Surviving Sepsis Campaign (SSC): International Guidelines for Management of Sepsis and Septic Shock (2016)
- The Japanese Clinical Practice Guidelines for the Management of Sepsis and Septic Shock (2018)

The prisma flow diagram illustrates the process undertaken in narrowing down the guidelines for appraisal. (Appendix 3)
In order to decide which guideline was relevant for the Irish Healthcare system and to appraise the quality of the guidelines, including the rigour and transparency in which the guidelines were developed a quality assessment was undertaken by two of the GDG Members using the Appraisal of Guidelines for Research and Evaluation II (AGREE II) tool, (Brouwers et al, 2017). The SSC Guideline ranked highest in all domains by both appraisers with overall domain percentages ranging 71-100%. Both appraisers agreed that based on the AGREE II process that the SSC Guideline should be adopted for use in the Irish Healthcare system.
The SSC Guideline which focuses on early management of sepsis and septic shock, underwent a robust process to identify the evidence relating to five areas of practice (hemodynamics, infection, adjunctive therapies, metabolic, and ventilation). An extensive search was performed for each PICO and the Grading of Recommendations Assessment,

Development and Evaluation (GRADE) system principles were used to guide the assessment of the quality of evidence and to determine the strength of the recommendations. Both of these are fully described in the SSC Guideline and are summarised in Tables 6 and 7. Table 8 identifies the grading terminology used in the 2016 guideline. All of these terms are referred to within the recommendations section of this document.

TABLE 6. DETERMINATION OF THE QUALITY OF EVIDENCE

Underlying Methodology 1. High: RCTs 2. Moderate: Downgraded RCTs or upgraded observational studies 3. Low: Well-done observational studies with RCTs 4. Very Low: Downgraded controlled studies or expert opinion or other evidence
Factors that may decrease the strength of evidence 1. Methodologic features of available RCTs suggesting high likelihood of bias 2. Inconsistency of results, including problems with subgroup analyses 3. Indirectness of evidence (differing population, intervention, control, outcomes, comparison) 4. Imprecision of results 5. High likelihood of reporting bias
Main factors that may increase the strength of evidence 1. Large magnitude of effect (direct evidence, relative risk >2 with no plausible confounders) 2. Very large magnitude of effect with relative risk >5 and no threats to validity (by two level) 3. Dose-response gradient

RCT = Randomised controlled trials

TABLE 7. FACTORS DETERMINING STRONG VERSUS WEAK RECOMMENDATIONS

What should be considered	Recommendation Process
High or moderate evidence (Is there high, or moderate, quality evidence?)	The higher the quality of evidence, the more likely a strong recommendation.
Certainty about the balance of benefits versus harms and burdens (Is there certainty?)	The larger the difference between the desirable and the undesirable consequences and the certainty around the difference, the more likely a strong recommendation. The smaller the net benefit and the lower the certainty for that benefit, the more likely a weak recommendation.
Certainty in, or similar, values (Is there certainty or similarity?)	The more certainty or similarity in values and preferences, the more likely a strong recommendation.
Resource implications (Are resources worth expected benefits?)	The lower the cost of an intervention compared to the alternative and other costs related to the decision (i.e. fewer resources consumed), the more likely a strong recommendation.

TABLE 8. GRADING TERMINOLOGY

	2016 Descriptor
Strength	Strong Weak
Quality	High Moderate Low Very low
Ungraded strong recommendation	Best practice statement (BPS)

It was agreed by the GDG to fully adopt the SSC Guideline with the addition of implementation points to aid the implementation of the guideline within the Irish Healthcare System in both pregnant and non-pregnant adults. It was also agreed by the GDG to limit the NCG to adults, non-pregnant and pregnant, and to exclude paediatrics from the scope of the guideline as the SSC Guideline refers to adults only. In addition, there is work underway internationally by the SSC on a specific paediatric sepsis guideline, therefore the decision was made to remove the paediatric section from the guideline and to publish a HSE Guidance document on paediatric sepsis which can be used in the interim.
The guideline provides recommendations for good practice that are based on the best available clinical and cost effectiveness evidence.

2.9 Consultation summary

The GDG sought to ensure that all stakeholders had an opportunity to review and contribute to the update of the National Clinical Guideline for Sepsis. The GDG gratefully acknowledges the contribution made by the all those who contributed from professional, academic and patient groups. The stakeholders are listed in Appendix 5.

2.10 External review

Two international experts were invited to review and provide feedback on an early draft of the guideline. These experts were selected based on their contribution to academic literature and clinical practice:

1. Professor Kevin Rooney is a Consultant Anesthetist and Professor of Care Improvement at University of the West of Scotland. He is the Clinical Lead for the Acute Adult Workstream of the Scottish Patient Safety Program for Healthcare Improvement Scotland and led their breakthrough series collaborative on sepsis, which resulted in a sustained relative risk reduction of 21% in sepsis mortality across Scotland.
2. Dr John Bates, Galway University Hospital, Department of Anaesthesia and Intensive Care, Dean of Joint faculty of Intensive Care Medicine.

The GDG are very grateful to these revieiwers for their time, expertise and contribution to this guideline.Their feedback and how it was used to inform the guideline is summarized in Appendix X (To be completed)

2.11 Implementation

These guidelines are divided into sections with each one pertaining to a different aspect of patient care. Recommendations from the Surviving Sepsis Campaign Guideline Update 2016 are labelled 'SSCG Recommendation' and 'SSCG Rationale'.

Implementation points are included to guide implementation of the SSCG recommendations in Ireland, particularly in the non-critical care environment. The implementation points arise from piloting clinical decision support tools in the acute hospital sector, in particular, in emergency departments (EDs) and maternity units to ensure that the implementation recommendations could be affected within the resources of our healthcare system and had the support of end-users. The feedback from these pilots was overviewed by multidisciplinary committees (the National Steering Committee and the Maternity Working Group) and the forms amended based on this feedback and re-piloted, if required. Thus, the implementation programme is informed by end-users and by multidisciplinary specialist input.

Funding for guideline implementation is subject to service planning and the estimates process.

2.12 Monitoring and audit

Outcome aims: The primary aim of optimizing patient survival should be audited by the publication of age and co-morbidity adjusted sepsis-associated (direct and in-direct) hospital mortality rates for each acute hospital and benchmarked against the national average. International benchmarking of the national sepsis-associated hospital mortality rate should be done against other high-income jurisdictions that publish such mortality rates.

Secondary outcome aims include healthcare utilization assessment such as the total number of bed days, average length of stay, critical care admission rates and average length of stay, and hospital readmission rates within three months[17] and should be reported where possible. The assessment of healthcare utilization is important as a monitor of the effectiveness of the sepsis quality improvement programme and also provides data for resource planning. As sepsis incidence increases with age with an ageing population it can be expected that healthcare provision for sepsis care will increase. An effective programme can modulate this increase.

Process audit is an important part of any quality improvement programme. It takes a snapshot of performance and benchmarks it against the guideline and thus identifies areas that may benefit from improvement. Since process audit does not contextualize the decisions made during a patient's care episode it is not designed to assess the quality of an individual care episode. However, should an area of concern be identified it should be brought to the attention of the sepsis committee for their consideration.

Maternity

Sepsis outcome audits are carried out by The Confidential Enquiry into Maternal Deaths (CEMD) in the UK and Ireland. Since June 2012, these audits have been carried out

by the MBRRACE-UK (Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries) collaboration and Maternal Death Enquiry (MDE) in the National Perinatal Epidemiology Centre-Ireland. They are published on the National Perinatal Epidemiology Unit (NPEU) website: https://www.npeu.ox.ac.uk/mbrrace-uk/reports. Each topic-specific/sepsis Confidential Enquiry chapter now appears in an annual report once every three years on a cyclical basis, in contrast to the past when a single report was produced every three years.

Practical guidance A

The GDG suggests that a tool be developed to risk adjust sepsis-associated hospital mortality (direct and in-direct) based on the Hospital In-patient Enquiry database and that each acute hospital, on this database, have annual risk-adjusted sepsis-associated mortality rates benchmarked against the national average.

Rationale:

Optimising survival from sepsis depends on the hospital system working efficiently and effectively as a whole. It requires effective communication, adequate resources and capacity both in infrastructure and staffing. Sepsis management and risk-adjusted sepsis-associated hospital mortality are robust markers of the quality of acute health care delivery.

Monitoring and acting on outcome audit ensures improvement occurs throughout the acute healthcare system and is not sporadic. It informs the population a hospital serves and its staff on the effectiveness of its sepsis management and supports improvement processes.

Outlier management:

Hospitals whose outcome measures are in excess of the control limits will, in the first instance have their data reviewed by the national sepsis audit committee (Appendix 2). There are 3 possible outcomes from this initial review

1. No action warranted
2. Monitor pending further review
3. Outlier intervention warranted

Outlier interventions:

1. The National Sepsis Team, including the Hospital Group Sepsis ADON, will discuss the findings and the outcome of the National Audit Committee data review with the Hospital Management and Clinical Director/s.
2. An improvement plan will be formulated by Hospital Management, the Clinical Director/s and the Sepsis/ Deteriorating Patient Committee, with advice from National Sepsis Team.
3. Audit of the improvement plan, its implementation and effect by the Hospital with support from the Hospital Group Sepsis ADON and the Hospital Group Leadership Team to ensure any identified issues are addressed.
4. It is the responsibility of the Hospital Management, Clinical Director/s and Sepsis/ Deteriorating Patient Committee to effect and monitor the findings of the outcome and process audits.

Practical guidance B

The GDG suggest that intermittent process audit be performed to support improvements in sepsis recognition, management and escalation.

Rationale:
The purpose of these audits is to benchmark different areas of practice against these guidelines for the purpose of informing on-going education and performance improvement initiatives. Process audit does not review the context of decision making in patient management and as such, cannot comment on the standard of care relating to an individual patient. However, if during the course of an audit, the possibility of a serious patient safety incident is considered this should be brought to the attention of the Sepsis/ Deteriorating Patient Committee. It is the responsibility of the Committee to decide if any further action is warranted.

It is the responsibility of the hospital sepsis committee to inform clinicians of the audit findings and to adjust the hospital's sepsis education programme to improve management and to effect, along with hospital management, any outlier interventions.

Practical guidance C

The GDG suggests that an annual sepsis outcome report be published which includes, but is not limited to:

- the risk-adjusted hospital mortality rates
- the incidence, patient characteristics and healthcare utilization of patients with sepsis during their hospitalization
- hospital group level amalgamated process audit results
- balancing measures.

Rationale:
A culture of openness promotes good practice and confidence in the healthcare system. It is important that the community is aware of the limitations of sepsis care, its high mortality risk and the efforts being made to reduce that risk. Sepsis guidelines are based on the best available information at the time of publication; however, they are just guidelines and cannot anticipate the complexity of an individual case. Data collection on patient characteristics and risk factors allows the identification of high-risk patients for prioritization. However, for every patient prioritized there are others who have been deemed less at risk. When capacity is challenging, getting this right is a vital and difficult component of time-dependent care especially when the clinical scenario is evolving. A hospital working within the control limits of the national average demonstrates that it is providing a service, in terms of sepsis care, that is as good as anywhere else within the state.

Balancing measures:
Audits should also include considerations of potential unintended consequences of the National Sepsis Programme including inappropriate antimicrobial use. Inappropriate antimicrobial use is a patient safety issue (e.g. adverse reactions, *Clostridium difficile* infection) and of public health concern (increased rates of multidrug resistant organisms, MDRO)[18].

In relation to antimicrobial use, there are at least three potential unintended consequences of implementing Sepsis 6 screening:

1. Patients who have deteriorated but have no evidence of potential infective source/sepsis are commenced inappropriately on antimicrobial therapy.
2. Patients with sepsis are commenced on inappropriate antimicrobial therapy that is not in line with local guidelines.
3. Empiric antimicrobial therapy that has been commenced in a patient with suspected sepsis is not reviewed at 24-48 hours as recommended by the Start Smart, then Focus Antimicrobial Care bundle[44].

All hospitals should have antimicrobial stewardship programmes in place as outlined in National Guidelines[18,19] that monitor process and outcome measures to ensure that antimicrobials are not being prescribed unnecessarily due to inappropriate application of Sepsis 6/Sepsis 6 + 1. Ensuring antimicrobials are used appropriately for all infections, not just those associated with sepsis, will help to ensure effective antimicrobial therapy is available when cases of sepsis do occur.

Roles and responsibilities:
It is the responsibility of the National Sepsis Programme to provide guidance on what outcomes, processes and patient characteristics to audit and to review audit methodology and results to ensure that they make clinical and statistical sense. It is the responsibility of the Programme to provide outlier support when indicated.

It is the responsibility of sepsis committees, Hospital Management and Hospital Group Leadership to effect recommendations arising out of outlier intervention.

It is the responsibility of the Department of Health, the HSE, Hospital Group Leadership and Hospital Management to support the audit process and to ensure that adequate resources are available to perform the audit and to effect change required based on audit results.

It is the responsibility of the Department of Health and the HSE to resource a risk-adjusted sepsis-associated hospital mortality rate audit tool as the key performance indicator for sepsis in Ireland.

2.13 Plan to update this National Clinical Guideline

This guideline will be scheduled for review 3 years after publication. In the event that new relevant evidence comes to light, particular in relation to Paediatric Sepsis, then a rapid update may be required within the three-year period.

Section 3: National Clinical Guideline recommendations

Recommendations from the Surviving Sepsis Campaign (SSC) Guideline Update 2016 and 2018 are adopted in total for this guideline. Recommendations are labelled 1-93 and are divided into sections with each one pertaining to a different aspect of patient care. Additionally, National Implementation Points are provided and are for the purpose of implementing the SSCG, in the Irish context, particularly in the non-critical care environment.
The implementation points arise from piloting clinical decision support tools in the acute hospital sector, in particular, emergency departments (EDs) and maternity units to ensure that the implementation recommendations could be affected within the resources of our healthcare system and had the support of end-users. The feedback from these pilots was overseen by multidisciplinary committees (the National Steering Committee and the Maternal Sepsis Form oversight committee) and the forms amended based on this feedback and re-piloted, if required. Thus, the implementation programme is informed by end-users and by multidisciplinary specialist input.

The following guidance is based on the best available evidence. The Surviving Sepsis Campaign Guideline Update 2016[1] and 2018[2] bundle update can be found at the links below giving details of the methods and the evidence used to develop the guidance:

https://journals.lww.com/ccmjournal/Fulltext/2017/03000/Surviving_Sepsis_Campaign___International.15.aspx

[2]http://www.survivingsepsis.org/SiteCollectionDocuments/Surviving-Sepsis-Campaign-Hour-1-Bundle-2018.pdf

3.1 Key questions, evidence statements and recommendations

3.1.1 Recognition, Screening for Sepsis and Performance Improvement

Key questions

- *Should hospitals use a formal resourced performance improvement program for sepsis including sepsis screening for acutely ill, high risk patients?*

SSCG Rationale

Performance improvement efforts for sepsis are associated with improved patient outcomes ([40]). Sepsis performance improvement programs should optimally have multi-professional representation (physicians, nurses, affiliate providers, pharmacists, respiratory therapists, dieticians, administrators) with stakeholders from all key disciplines represented in their development and implementation. Successful programs should include protocol development and implementation, targeted metrics to be evaluated, data collection, and on-going feedback to facilitate continuous performance improvement ([41]). In addition to traditional continuing education efforts to introduce guidelines into clinical practice, knowledge translation efforts can be valuable in promoting the use of high-quality evidence in changing behaviour ([42]).

Sepsis performance improvement programs can be aimed at earlier recognition of sepsis via a formal screening effort and improved management of patients once they are identified as being septic. Because lack of recognition prevents timely therapy, sepsis screening is associated with earlier treatment ([43, 44]). Notably, sepsis screening has been associated with decreased mortality in several studies ([20, 45]). The implementation of a core set of recommendations ("bundle") has been a cornerstone of sepsis performance improvement programs aimed at improving management ([46]). Note that the SSC bundles have been developed separately from the guidelines in conjunction with an educational and improvement partnership with the Institute for Healthcare Improvement ([46]). The SSC bundles that are based on previous guidelines have been adopted by the U.S.-based National Quality Forum and have also been adapted by the U.S. healthcare system's regulatory agencies for public reporting. To align with emerging evidence and U.S. national efforts, the SSC bundles were revised in 2015.

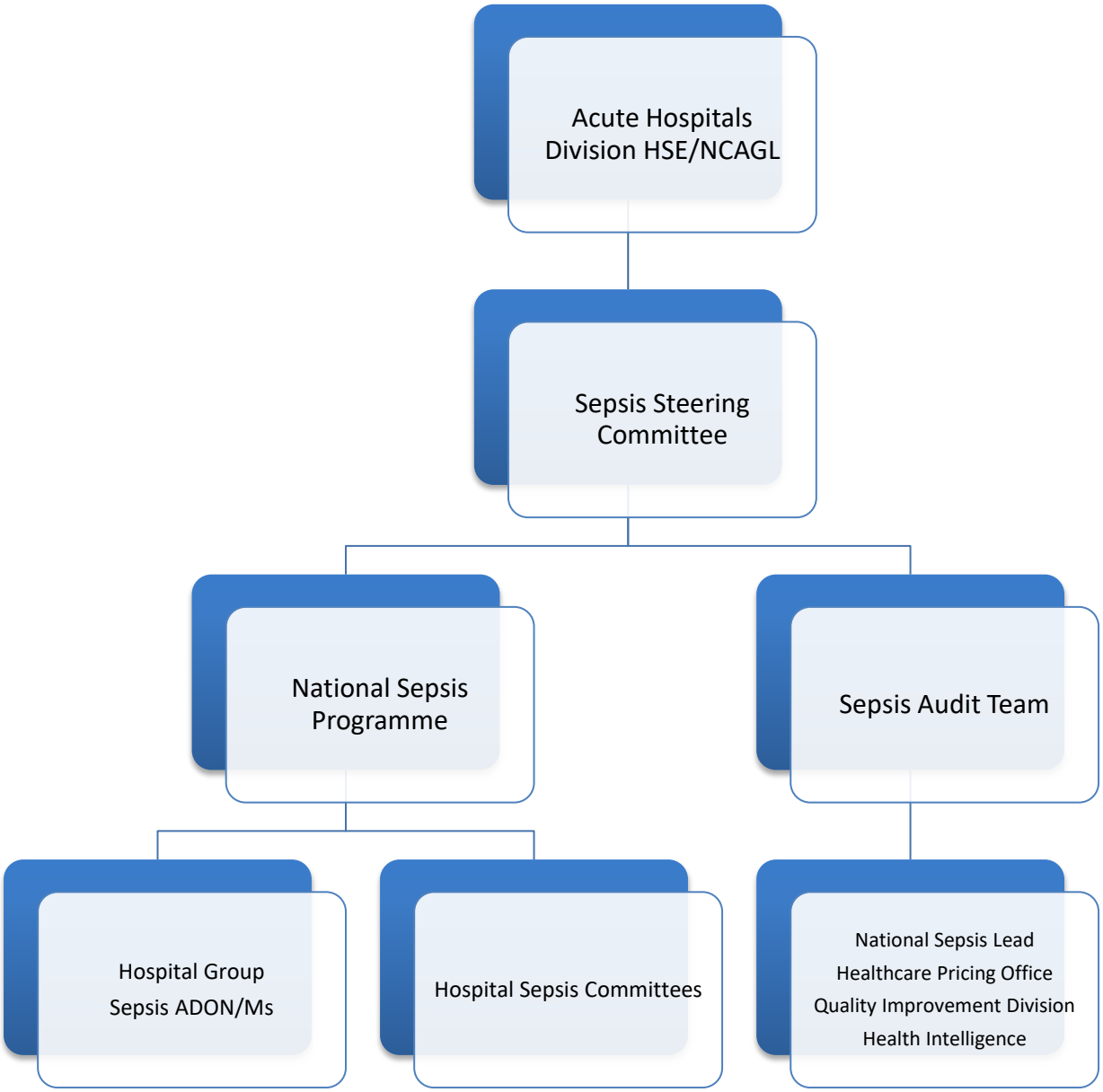
While specifics vary widely among different programs, a common theme is the drive toward improvement in compliance with sepsis bundles and practice guidelines such as SSC ([8]). A meta-analysis of 50 observational studies demonstrated that performance improvement programs were associated with a significant increase in compliance with the SSC bundles and a reduction in mortality (OR 0.66; 95% CI, 0.61–0.72) ([47]). The largest study to date examined the relationship between compliance with the SSC bundles (based on the 2004 guidelines) and mortality. A total of 29,470 patients in 218 hospitals in the United States, Europe, and South America were examined over a 7.5-year period ([21]). Lower mortality was observed in hospitals with higher compliance. Overall hospital mortality decreased 0.7% for every 3 months a hospital participated in the SSC, associated with a 4% decreased LOS for every 10% improvement in compliance with bundles. This benefit has also been shown across a wide geographic spectrum. A study of 1,794 patients from 62 countries with severe sepsis (now termed "sepsis" after the Sepsis-3 definition ([1])) or septic shock demonstrated a 36%–40% reduction of the odds of dying in the hospital with compliance with either the 3- or 6-hour SSC bundles ([48]). This recommendation met the pre-specified criteria for a BPS. The specifics of performance improvement methods varied markedly between studies; thus, no single approach to performance improvement could be recommended (Supplemental Digital Content 5, http://links.lww.com/CCM/C326).

Recommendation 1 (SSCG Section B, Recommendation 1)
We recommend that hospitals and hospital systems have a performance improvement program for sepsis, including sepsis screening for acutely ill, high-risk patients
Quality/level of evidence: Low + Strength of recommendation: BPS

Implementation Point 1 (Recommendation 1)

The National Sepsis Programme will support and monitor sepsis performance improvement to promote the population receiving safe and high-quality sepsis care.
The National Sepsis Programme with the following governance structure coordinates the implementation and audit of the Guideline.

Figure 3. The National Clinical Programme for Sepsis Governance Structure



The **National Sepsis Steering Committee** is a multi-disciplinary committee recognizing that sepsis affects all specialties and services. Its membership and terms of reference are listed in Appendix 1 & 2.

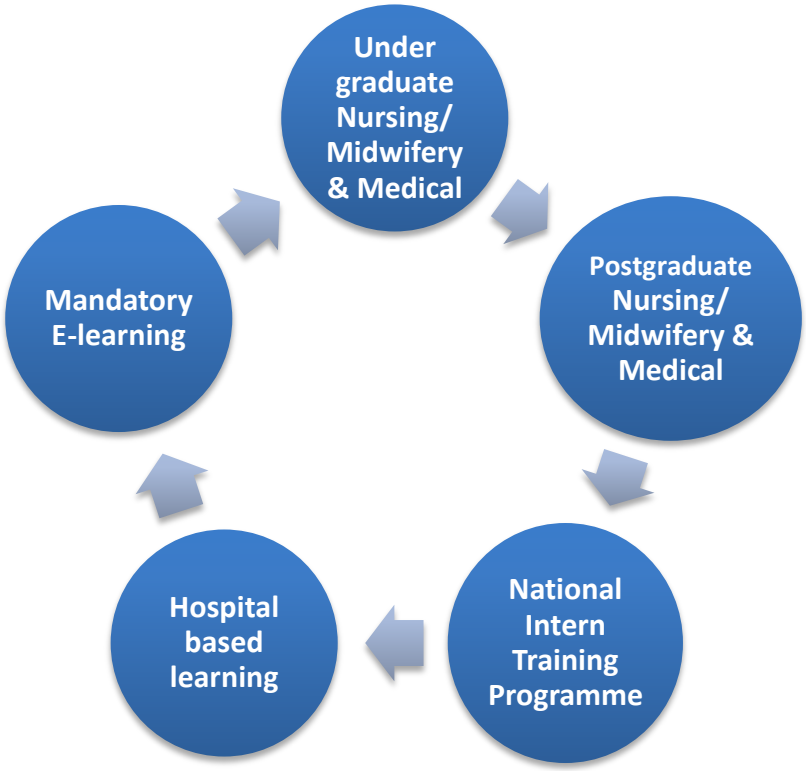
The **National Sepsis Team** reports to the steering committee and the office of the National Clinical Advisor and Group Lead for Acute Hospitals, Health Services Executive (HSE) and works with the National Clinical Effectiveness Committee for the scheduled updates of the National Clinical Guideline and advises the Department of Health on issues related to sepsis. Its membership and terms of reference are listed in Appendix 2.

Hospital Sepsis Committee: All acute hospitals are required to have a Sepsis Committee whose role is to guide the implementation of the National Clinical Guideline in their hospital by coordinating education, sepsis form rollout and reviewing audit feedback and using it to inform the education and roll-out processes. This committee, along with Hospital Management and the Clinical Directors, has responsibility for effecting and auditing the improvements identified due to audit outlier intervention. This committee is multi-disciplinary with a named medical and nursing/midwifery lead with the inclusion of NCHDs, clinical microbiology, pharmacy (e.g. antimicrobial pharmacist), coding, practice facilitators and educators and may invite other specialties as required. The committees liaise with their Group Sepsis Assistant Director of Nursing/Midwifery (ADON/M) and the National Team, this is a two-way relationship with the sepsis committees feeding back to the programme on the usefulness of aids and algorithms, suggestions to improve sepsis management and suggesting specific audits. The Sepsis Committee recommends that the Hospital Group Sepsis ADON/M be a member of each hospital committee in their group.

In turn the National Team provides tools to assist education, implementation and audit feedback. Should outlier intervention be required, the National Team can advise the Hospital Sepsis Committee and Management and offer further education and audit support. The Hospital Group Sepsis ADON/M works with the hospital, the Hospital Group Leadership Team and the National Sepsis Team to support sepsis quality improvement.

Sepsis Education: This guideline recognises that the responsibility for sepsis education falls under a number of domains and recommends that education providers ensure that their education curricula are consistent with the National Clinical Guideline and its implementation programme.

Figure 4. Sepsis Education Overview



Roles and Responsibilities

It is the responsibility of the Department of Health (DoH) to support the development, implementation and audit of this National Clinical Guideline.

It is the responsibility of the HSE to provide appropriate structured support and adequate resources for the governance, operationalization, and audit of sepsis management.

It is the responsibility of the Sepsis Steering Committee to provide clinical expertise and guidance for the National Sepsis Programme.

It is the responsibility of the National Sepsis Team to ensure that clinical guidance is in line with best international practice, to provide clinical advice and decision support tools to local hospital sepsis committees and to oversee process and outcome audit, provide feedback and to advise on outlier intervention when required.

It is the responsibility of the Hospital Group Leadership Team, Hospital Management and Clinical Directors to support sepsis quality improvement and to foster and facilitate the implementation process and audit. They are also responsible for effecting and monitoring change arising from outlier intervention.

It is the responsibility of hospital sepsis committees to co-ordinate sepsis guideline implementation in their hospital and to work with the Hospital Group Sepsis Assistant Directors of Nursing/Midwifery (ADON/Ms) and the National Sepsis Team with the aim of optimizing sepsis recognition and treatment.

It is the responsibility of the Sepsis ADON/Ms to help support the local hospital sepsis committees' aims by performing audit and feedback on the sepsis care in their institution and by liaising with the National Sepsis Programme to ensure effective communication between the Programme, the Hospital Group Leadership and Local Hospitals. The Sepsis ADONs also have a role in fostering new sepsis initiatives and international benchmarking.

It is the responsibility of Nursing/Midwifery and Medical Colleges, Under and Post-Graduate to ensure that their sepsis curricula are consistent with the National Clinical Guideline and provide their graduates with the appropriate knowledge and skillset to be able to comply with the recommendations therein.

Implementation Point 2 (Recommendation 1)

Adopt strategies for the prevention of infection and sepsis.

Hand hygiene:

Healthcare associated infections, (infections acquired during health care delivery), are common and are a risk factor for developing sepsis. Effective hand hygiene plays a key role in preventing infection. The 5 moments of hand hygiene should be incorporated into practice and patients and visitors/carers should be instructed on how to perform hand hygiene to protect themselves too.

Food hygiene:

Pregnant women should avoid 'deli' meats; prepared dairy-based dressings, raw milk, soft cheeses, pâtés and smoked fish. All these are associated with listeriosis. Pregnant women should be advised to cook food thoroughly, especially meat, ensuring that it is cooked through to the middle. Salads, fruit and raw vegetables should be washed thoroughly before eating to prevent Listeriosis and Toxoplasmosis [22]. More information is available at https://www.safefood.eu/Food-safety.aspx

Vaccination or immunization:

Sepsis cannot always be prevented but promoting the uptake of vaccinations to reduce the risk of infection may also reduce the risk of developing sepsis. Annual flu vaccine and pneumococcal vaccine should be promoted where appropriate.

Maternity only

Vaccination

Modulation of the immune system occurs in pregnancy[23]. Pregnant women are at increased risk for severe illness from influenza virus. The MBRRACE-UK confidential enquiry into maternal mortality during the H_1N_1 epidemic (2009-2012) demonstrated that one in eleven maternal mortalities were directly from the influenza virus (Knight *et al*, 2014). Kay *et al*. (2014) found that vigorous cellular immune responses to influenza during pregnancy could drive pulmonary inflammation, explaining the increased morbidity and mortality. Consideration should be made to offering seasonal influenza vaccination in antenatal clinics[25].

Anyone trying to conceive or thinking about conceiving should ensure they have the MMR vaccine, which covers measles, mumps and rubella. Rubella (German measles) is particularly harmful to a fetus in early pregnancy as it can cause major birth defects.

Breastfeeding:

Neonates have a developing immune system[18] and haven't been exposed to microorganisms in the environment. Breastfeeding protects against neonatal infections and sepsis[ref]. Mother's milk includes large amounts of secretory IgA antibodies produced by lymphocytes which have migrated from the mother's gut to the mammary glands[19, 20]. The newborn is colonized with microbes from the mother's intestinal flora at and after birth thus, breastfeeding controls the early exposure of the neonate's intestinal mucosa to microbes and limits bacterial translocation through the gut mucosa[21]. Immunoglobulin is also transferred across the placenta before birth and these give protection for the first 3 months of life, in particular [18,19,20].

Animal Borne infections

Toxoplasmosis is a disease caused by a parasite that infects warm-blooded animals, primarily cats.

Women who are pregnant or planning pregnancy should avoid contact with all rodents and their droppings, including avoiding changing cat litter. If no one else can perform the task, disposable gloves should be worn, and hands washed with soap and warm water afterwards. Adopting or handling stray cats, especially kittens, should be avoided.

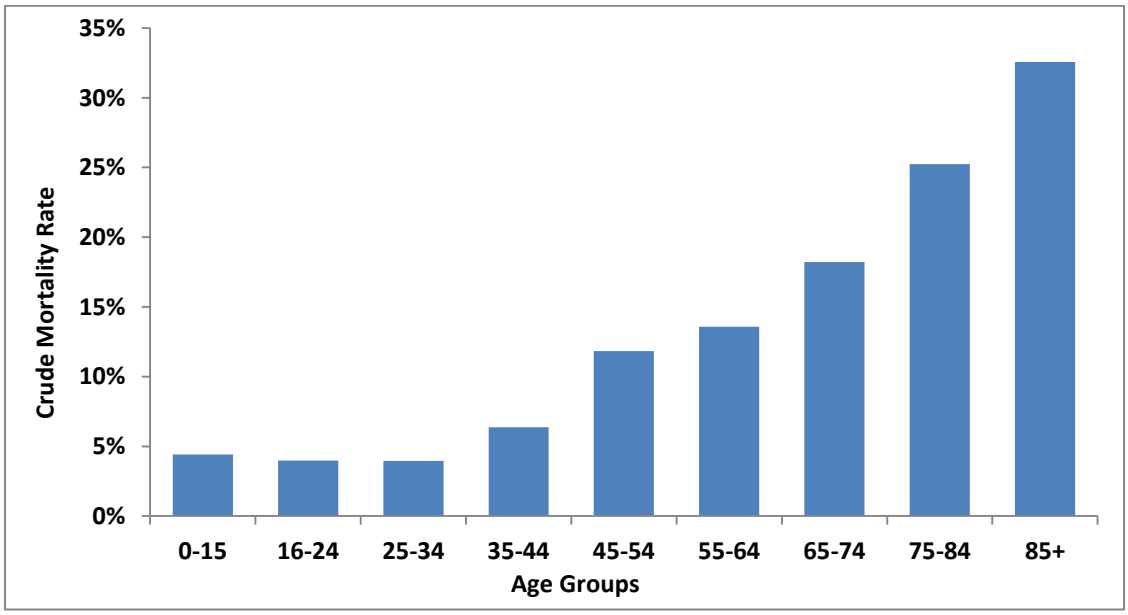
The HSE has further information on toxoplasmosis here and an information leaflet available here.

Implementation Point 3 (Recommendation 1)

Patients presenting or deteriorating as an inpatient, where infection is suspected to be the cause, are screened to identify those who are at high risk of mortality from sepsis.

Sepsis occurs most frequently at the extremes of age. It is more common and has a higher mortality when it occurs in patients with co-morbidities and as we get older, we accumulate co-morbidities. Certain medications act by suppressing the immune system and patients taking them are more susceptible to infection and sepsis. In Ireland there is no gender difference in mortality although sepsis is more common in males. This is also consistent with the published literature[5,7,8,10,16].

Figure 5. In-patient sepsis-associated hospital mortality* by age groups, 2018



* 'Sepsis-associated' includes direct and indirect deaths. Causality cannot be inferred from administrative databases.

Profiling at-risk patient groups facilitates early recognition and treatment, which is the only proven method of reducing mortality from sepsis.

Figure 6. Inpatient sepsis-associated hospital mortality according to number of co-morbidities, 2018

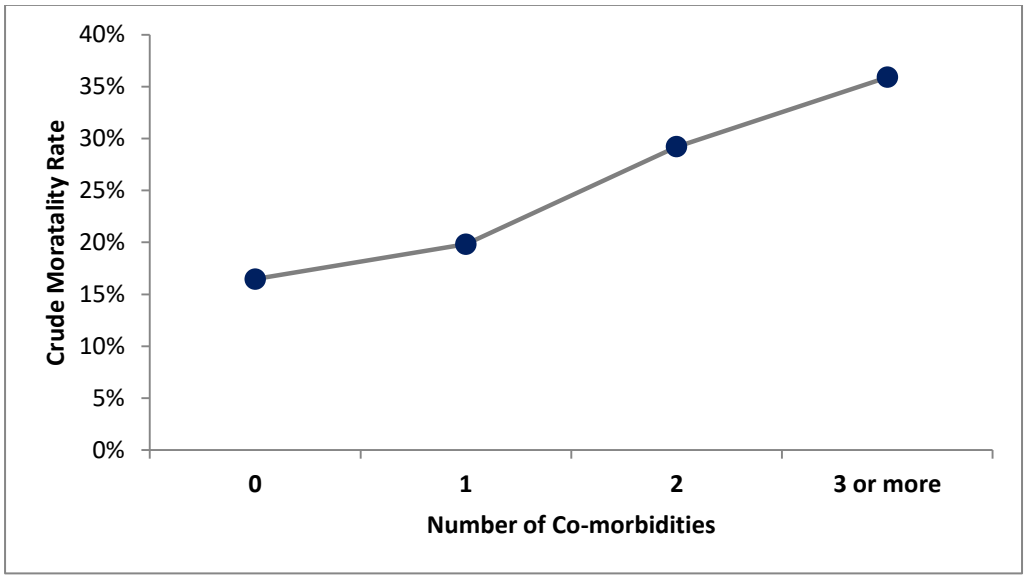
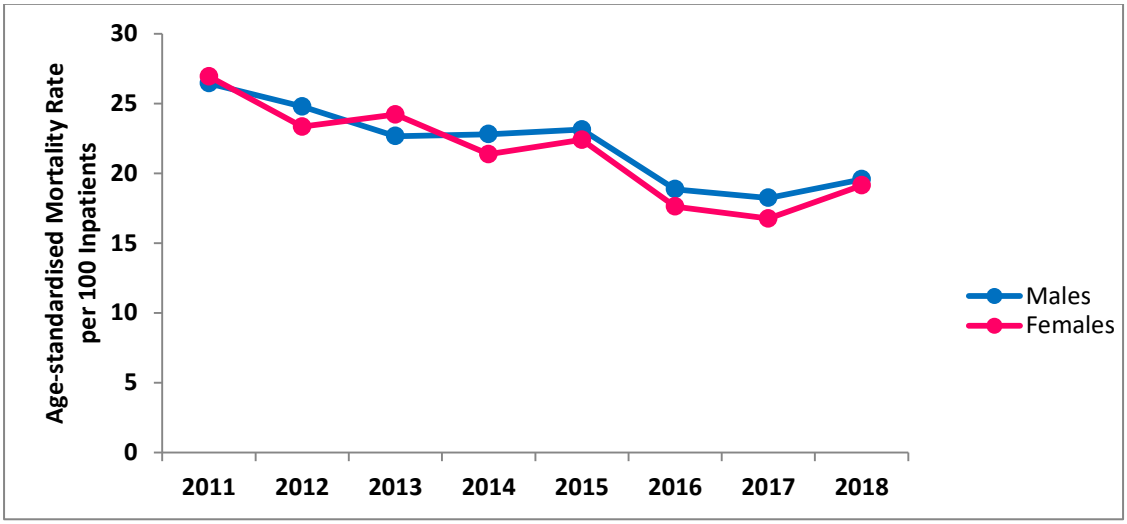


Figure 7. Inpatient sepsis-associated hospital mortality by gender, 2018



Maternity only

Sepsis was the leading cause of direct maternal mortalities in the Centre for Maternal & Child Enquiries (CMACE 2006-2008)[26], and the second leading cause of maternal mortalities in the Mothers and Babies: Reducing Risk through Audit and Confidential Enquiry (MBRRACE)[27]. The latest MBRRACE[28] publication shows sepsis as the 4th leading direct cause with an increase in direct causes due to sepsis and a decrease in indirect sepsis deaths from the previous report.

Irish data demonstrates an increase in reported diagnoses of both sepsis and infection. In 2018, there were 61,016 live births in Ireland, and 9,471 maternity patients (period from conception up to 42 days post-birth or miscarriage) were either admitted to hospital with an infection or diagnosed with an infection as an in-patient. 442 were diagnosed with sepsis. However, it must be noted these cases were diagnosed including the Sepsis-2 definition of sepsis i.e. SIRS of infectious origin and thus include a wide range of acuity[29].

Identifying pregnant women with sepsis can be particularly challenging as clinical and laboratory criteria may overlay with normal pregnant physiology[ref] The physiological changes of pregnancy, including an increase in heart rate (tachycardia), respiratory rate (tachypnoea) and cardiac output, combined with a rise in white cell count that peaks after delivery, can mask sepsis indicators normally seen in the non-pregnant population. Additionally, the altered physiology of pregnancy and the postnatal period can result in women presenting with vague signs and symptoms of sepsis. It may be difficult to distinguish between normal and pathological states. Importantly, pregnant and recently delivered women have a significant capacity to compensate physiologically to major stresses to the body (such as haemorrhage or sepsis), and therefore signs of tachycardia or hypotension (reduced blood pressure) may not appear until late, when sudden clinical deterioration becomes apparent. Sepsis, therefore, requires a high index of suspicion, as it

may be difficult to diagnose resulting in delayed initiation of appropriate treatment and significant morbidity or mortality.

Screening:
The purpose of screening is to identify patients with a high-risk presentation e.g. clinically apparent acute organ dysfunction such as acute confusion, respiratory failure or a purpuric rash AND patients who because of their medical history, e.g. on chemotherapy or having chronic co-morbidities, have a high mortality risk if they have sepsis.

Sepsis diagnosis is not always obvious as the presentation can be variable. Having clinical decision support tools can help clinicians to identify high-risk patients, in making the diagnosis of sepsis and in the initiation of treatment.

Emergency Medicine Early Warning System (EMEWS) is recommended for use in EDs when patients are waiting longer for review by a Treating Clinician than is recommended based on their Manchester Triage System (MTS) Category. National Clinical Guideline No. 18: Emergency Medicine Early Warning System (EMEWS) strongly recommends adherence to the NCEC National Clinical Guideline No. 6 Sepsis Management in patients with a clinical suspicion of infection/sepsis.

The National Early Warning Score (NEWS) is recommended as the system to be used to identify high risk and deteriorating admitted patients with infection and sepsis.

The NEWS[3] is deployed in Ireland for the identification of deterioration in admitted patients and in head to head testing has been shown to outperform qSOFA[39, 40].

Three patient groups have been identified as having a mortality risk of > 20% from sepsis[5]. All three patient presentations should be assigned Category 2 at Triage (unless Category 1 criteria apply) or have medical review within 30 minutes if an inpatient, if they present unwell or deteriorate and have signs and symptoms consistent with infection.

Patients at high risk of mortality from sepsis:

1. Patients at risk of neutropenia, due to bone marrow failure, autoimmune disorder or treatment including but not limited to, chemotherapy and radiotherapy, who present unwell, that is with specific or non-specific symptoms and signs of infection.

2. Patients presenting with clinical criteria for one or more acute organ dysfunction and a suspicion of infection as the cause.
    - i. Acutely altered mental state
        - New onset confusion/ agitation
        - Altered functional state in an individual with underlying neurological disorder/ disability
        - Decreased Glasgow Coma Scale Score
    - ii. Respiratory dysfunction
        - Sustained respiratory rate > 30 breaths per minute
        - Laboured breathing
        - Hypoxia/ cyanosis
        - Respiratory failure requiring invasive or non-invasive support

iii. Cardiovascular dysfunction
Tachycardia > 130 beats per minute
Systolic blood pressure < 100 mmHg or > 40mmHg drop from usual pressure
Pale cold peripheries with prolonged central capillary refill
Inability to stand due to sustained dizziness with signs of hypoperfusion

iv. Renal dysfunction
Oligo or anuria for > 12 hours with no urgency

v. Coagulation dysfunction
Non-blanching, mottled or petechial rash

vi. Liver dysfunction
Jaundice

3. Patients who present with a systemic inflammatory response (SIRS) to infection and who have 1 or more co-morbidity associated with higher risk of mortality in sepsis[5,7,8,10,16]

Co-morbidities include:
Chronic obstructive pulmonary disease
Diabetes mellitus
Cancer
Chronic kidney disease
Chronic liver disease
Immunosuppression
Frailty
Age ≥ 75 years
Recent major surgery or trauma

Clinical Decision Support Tools such as the 'Think Sepsis at Triage' algorithm (Figure 8) or the Screening Algorithm for In-Patients (Figure 9) will help nurses to:

a) correctly risk stratify 'at-risk' patients
b) escalate to medical review in a timely manner
c) start the appropriate sepsis form (Appendix 11). The completed sepsis form should be placed with the patient's documentation to assist in their management and diagnosis of sepsis. Clinicians should consider documenting when patients with infection screen negative for these high-risk categories. This guidance aims to support clinical decision-making and not to replace it, always exercising clinical judgment.

The outcome from screening is NOT the Sepsis 6 bundle but rather an early thorough medical review to develop a differential diagnosis for the patient's presentation. The result of the screen is communicated to the treating clinician so that sepsis is considered during the examination. If infection is included in the differential, then the Sepsis 6 bundle is administered. For this reason, 1 hour is allowed for screening and medical review and then 1 hour for the administration of the Sepsis 6 bundle. For patients who present with septic shock, it is recommended that the Sepsis 6 bundle be administered within 1 hour of this particular presentation.

In summary, patients who present to Emergency Department (ED) Triage with suspected infection or who deteriorate on the ward due to suspected infection, should be screened to see if they fit into one of the high-risk groups. Deterioration on the ward is suggested by a NEWS score that has risen to ≥ 4 (≥ 5 if already on supplementary oxygen therapy)[3] or by exercising clinical judgment. The patient should be escalated to medical review as per the 'Think Sepsis at Triage' algorithm or the NEWS escalation policy and an appropriate sepsis form (Appendix 11) placed with the patient's case notes.

Figure 8. Screening algorithm for Triage:

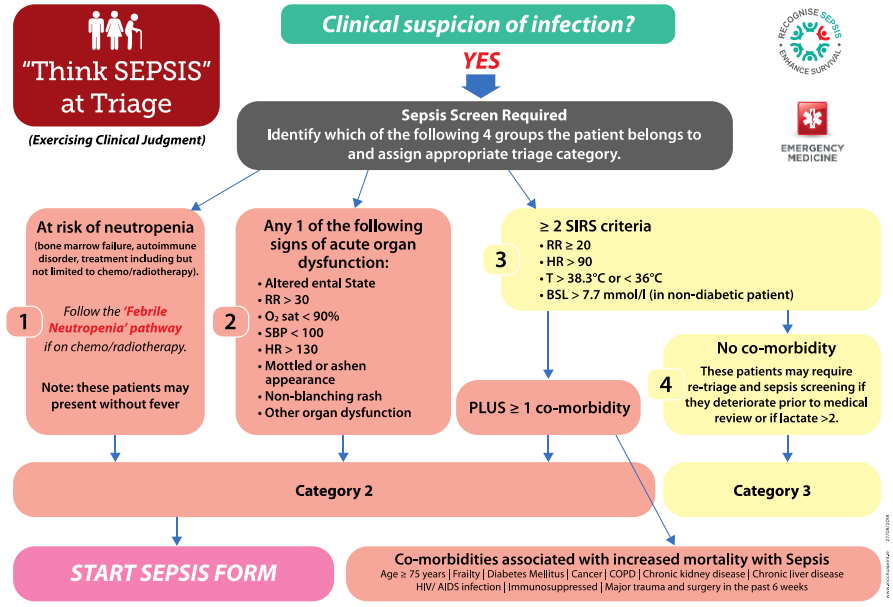
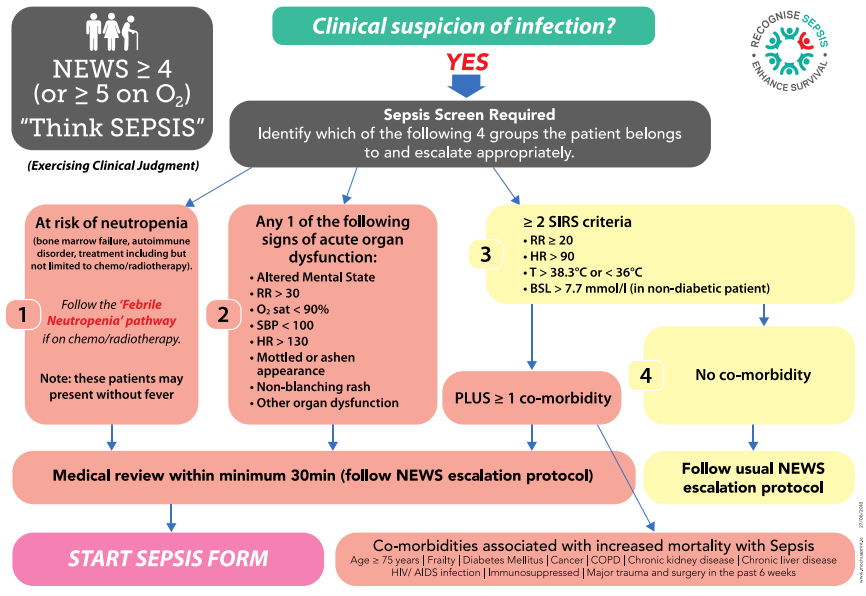


Figure 9. Screening algorithm for inpatients



Note: Sepsis may also need to be considered in patients whose NEWS score is < 4. However, it is recommended that patients with a NEWS ≥ 4 have a medical review within 30 minutes[3] and if infection is suspected as the cause sepsis needs to be considered.

Patients who are attending other departments in the hospital such as outpatients and who become a cause of concern due to infection may be screened according to the Triage or NEWS criteria as best suits the clinical circumstance.

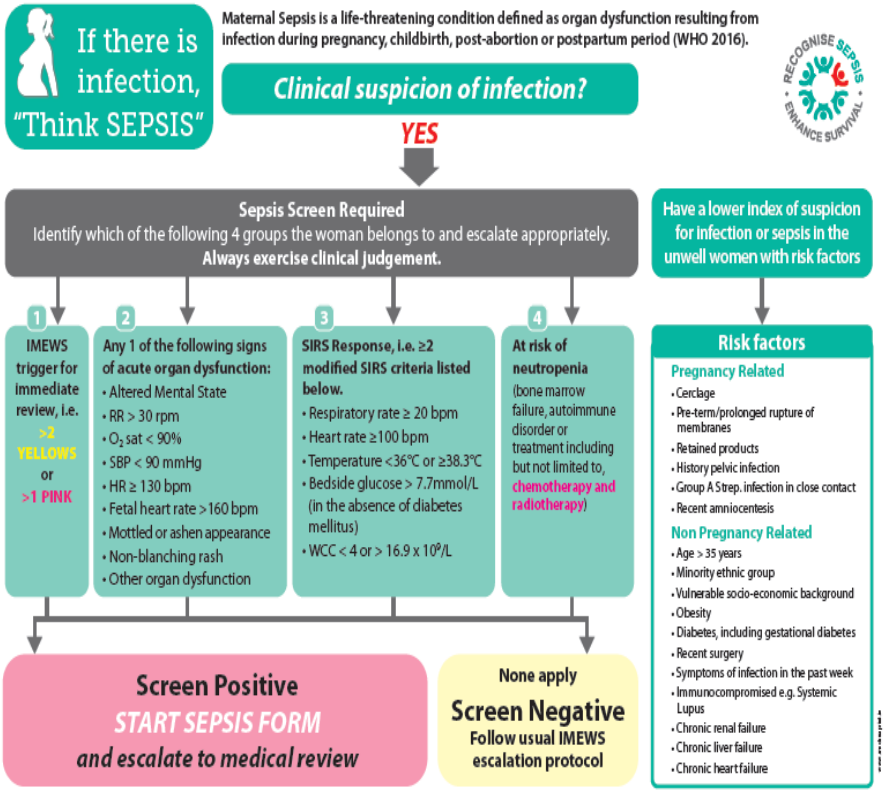
Screening
Maternity only

Sepsis is one of the leading causes of maternal mortality in obstetrics. Alongside thromboembolism and haemorrhage, sepsis is one of the leading causes of both direct and indirect morbidity (MBRRACE, 2018)[ref]. Physiological changes of pregnancy may create a vulnerable environment, predisposing women to develop sepsis. These changes can mask or mimic sepsis indicators seen in the non-obstetric population, making it difficult to recognise sepsis and possibly delaying treatment. The Irish Maternity Early Warning System (IMEWS) is recommended for the monitoring and detection of physiological deterioration inpregnant and postpartum women.

The use of maternal-specific clinical decision support tools for sepsis identification and knowledge of appropriate interventions and their effects on the woman and fetus can help clinicians obtain the best outcomes in acute care settings[ref].

The maternity sepsis form provides a time dependent pathway which aids the midwife in recognising women at risk of sepsis and supports effective communication to the medical professional. The form also supports the doctor in identifying women who should get the Sepsis 6+1 bundle and guides its completion. The form also lists the diagnostic criteria for sepsis and septic shock and the appropriate escalation for both. It can be found on the Maternal & Newborn Clinical Management System (MN-CMS) via the 'AD HOC' tab..

Figure 10. Screening algorithm for maternity



Post birth 42 days

Many women are seen in the community by the Community Midwife, Domiciliary Midwife or Public Health Nurse. A screening tool has been developed to aid early recognition of potential sepsis and advice on pathway of care (Appendix 14).

PRE-HOSPITAL

Pre-hospital emergency care is the clinical process of assessment, treatment and disposition of patients following an acute event in the community. As sepsis is a syndrome and not a specific disease, Pre-Hospital Emergency Care Council (PHECC) registered practitioners (EMT, paramedic and advanced paramedic) are advised to have a high index of suspicion in relation to sepsis for unwell patients. PHECC practitioners utilise clinical practice guidelines (CPGs) to inform their scope of practice (Appendix 15)

Roles and responsibilities:

It is the responsibility of the HSE, Hospital Group and Hospital Management to facilitate appropriate training and provide adequate resources for the screening of patients with infection for high risk of mortality from sepsis.

It is the responsibility of clinicians to be familiar with the three high-risk presentations and to escalate care according to the Triage and Inpatient algorithms.

It is the responsibility of all clinicians working in the acute hospital sector to be familiar with

the NEWS and any other relevant early warning systems.

3.1.2 Initial Treatment

Key questions

- *In patients with sepsis or septic shock, should we use crystalloid with supplemental albumin for initial resuscitation versus crystalloids alone?*
- *In patients with sepsis or septic shock, should we be using HES versus crystalloids for acute resuscitation?*
- *In patients with severe sepsis or septic shock, should we be using gelatin versus crystalloid for acute resuscitation?*
- *In patients with sepsis or septic shock, should we use using balanced crystalloid solutions versus normal saline?*
- *In patients with sepsis or septic shock, should we recommend using repeated fluid challenge based on hemodynamic variables?*
- *In patients with sepsis or septic shock, should we use early goal directed therapy protocol for resuscitation?*
- *In patients with sepsis or septic shock with elevated serum lactate, should we incorporate resuscitation goals aiming to normalize lactate levels?*
- *In patients with septic shock requiring vasopressors, should we target mean arterial pressure (MAP) of 65 mmHg vs. higher MAP?*
- *In patients with sepsis or septic shock, should we use dynamic parameters (versus static parameters) to predict fluid responsiveness?*

SSCG Rationale

Early effective fluid resuscitation is crucial for stabilization of sepsis-induced tissue hypoperfusion or septic shock. Sepsis-induced hypoperfusion may be manifested by acute organ dysfunction and/or ± decreased blood pressure and increased serum lactate. Previous iterations of these guidelines have recommended a protocolized quantitative resuscitation, otherwise known as early goal-directed therapy (EGDT), which was based on the protocol published by Rivers (16). This recommendation described the use of a series of “goals” that included central venous pressure (CVP) and central venous oxygen saturation (Scvo2). This approach has now been challenged following the failure to show a mortality reduction in three subsequent large multi-centre RCTs (17–19). No harm was associated with the interventional strategies; thus, the use of the previous targets is still safe and may be considered. Of note, the more recent trials included less severely ill patients (lower baseline lactate levels, Scvo2 at or above the target value on admission, and lower mortality in the control group). Although this protocol cannot now be recommended from its evidence base, bedside clinicians still need guidance as to how to approach this group of patients who have significant mortality and morbidity. We recommend, therefore, that these patients be viewed as having a medical emergency that necessitates urgent assessment and treatment. As part of this, we recommend that initial fluid resuscitation begin with 30 mL/kg of crystalloid within the first 3 hours. This fixed volume of fluid enables clinicians to initiate resuscitation while obtaining more specific information about the patient and while awaiting more precise measurements of hemodynamic status. Although little literature

includes controlled data to support this volume of fluid, recent interventional studies have described this as usual practice in the early stages of resuscitation, and observational evidence supports the practice (20, 21). The average volume of fluid pre-randomization given in the PROCESS and ARISE trials was approximately 30mL/kg, and approximately 2 litres in the PROMISE trial (17–19). Many patients will require more fluid than this, and for this group we advocate that further fluid be given in accordance with functional hemodynamic measurements.

One of the most important principles to understand in the management of these complex patients is the need for a detailed initial assessment and ongoing re-evaluation of the response to treatment. This evaluation should start with a thorough clinical examination and evaluation of available physiologic variables that can describe the patient's clinical state (heart rate, blood pressure, arterial oxygen saturation, respiratory rate, temperature, urine output, and others as available). Echocardiography in recent years has become available to many bedside clinicians and enables a more detailed assessment of the causes of the hemodynamic issues (22).

The use of CVP alone to guide fluid resuscitation can no longer be justified (22) because the ability to predict a response to a fluid challenge when the CVP is within a relatively normal range (8–12 mm Hg) is limited (23). The same holds true for other static measurements of right or left heart pressures
or volumes. Dynamic measures of assessing whether a patient requires additional fluid have been proposed in an effort to improve fluid management and have demonstrated better diagnostic accuracy at predicting those patients who are likely to respond to a fluid challenge by increasing stroke volume. These techniques encompass passive leg raises, fluid challenges against stroke volume measurements, or the variations in systolic pressure, pulse pressure, or stroke volume to changes in intrathoracic pressure induced by mechanical ventilation (24). Our review of five studies of the use of pulse pressure variation to predict fluid responsiveness in patients with sepsis or septic shock demonstrated a sensitivity of 0.72 (95% CI, 0.61–0.81) and a specificity of 0.91 (95% CI, 0.83–0.95); the quality of evidence was low due to imprecision and risk of bias (**Supplemental Digital Content 3,** http://links.lww.com/CCM/C324) (24). A recent multi-centre study demonstrated limited use of cardiac function monitors during fluid administration in the ICUs. Even though data on the use of these monitors in the emergency department are lacking, the availability of the devices and applicability of the parameters to all situations may influence the routine use of dynamic indices (22, 25).

MAP is the driving pressure of tissue perfusion. While perfusion of critical organs such as the brain or kidney may be protected from systemic hypotension by autoregulation of regional perfusion, below a threshold MAP, tissue perfusion becomes linearly dependent on arterial pressure. In a single-centre trial (26), dose titration of norepinephrine from 65 to 75 and 85 mm Hg raised cardiac index (from 4.7 ± 0.5 to 5.5 ± 0.6 L/min/m2) but did not change urinary flow, arterial lactate levels, oxygen delivery and consumption, gastric mucosal Pco2, RBC velocity, or skin capillary flow. Another single-centre (27) trial compared, in norepinephrine-treated septic shock, dose titration to maintain MAP at 65 mm Hg versus achieving 85 mm Hg. In this trial, targeting high MAP increased cardiac index from 4.8 (3.8–6.0) to 5.8 (4.3–6.9) L/min/m2 but did not change renal function, arterial lactate levels, or oxygen consumption. A third single-centre trial (28) found improved microcirculation, as

assessed by sublingual vessel density and the ascending slope of thenar oxygen saturation after an occlusion test, by titrating norepinephrine to a MAP of 85 mm Hg compared to 65 mm Hg. Only one multi-centre trial that compared norepinephrine dose titration to achieve a MAP of 65 mm Hg versus 85 mm Hg had mortality as a primary outcome (29). There was no significant difference in mortality at 28 days (36.6% in the high-target group and 34.0% in the low-target group) or 90 days (43.8% in the high-target group and 42.3% in the low target group). Targeting a MAP of 85 mm Hg resulted in a significantly higher risk of arrhythmias, but the subgroup of patients with previously diagnosed chronic hypertension had a reduced need for renal replacement therapy (RRT) at this higher MAP. A recent pilot trial of 118 septic shock patients (30) suggested that, in the subgroup of patients older than 75 years, mortality was reduced when targeting a MAP of 60–65 mm Hg versus 75–80 mm Hg. The quality of evidence was moderate (**Supplemental Digital Content 4,** http://links.lww.com/CCM/C325) due to imprecise estimates (wide confidence intervals). As a result, the desirable consequences of targeting MAP of 65 mm Hg (lower risk of atrial fibrillation, lower doses of vasopressors, and similar mortality) led to a strong recommendation favouring an initial MAP target of 65 mm Hg over higher MAP targets. When a better understanding of any patient's condition is obtained, this target should be individualized to the pertaining circumstances.

Serum lactate is not a direct measure of tissue perfusion (31). Increases in the serum lactate level may represent tissue hypoxia, accelerated aerobic glycolysis driven by excess beta-adrenergic stimulation, or other causes (e.g., liver failure). Regardless of the source, increased lactate levels are associated with worse outcomes (32). Because lactate is a standard laboratory test with prescribed techniques for its measurement, it may serve as a more objective surrogate for tissue perfusion as compared with physical examination or urine output. Five randomized controlled trials (647 patients) have evaluated lactate-guided resuscitation of patients with septic shock (33–37). A significant reduction in mortality was seen in lactate-guided resuscitation compared to resuscitation without lactate monitoring (RR 0.67; 95% CI, 0.53–0.84; low quality). There was no evidence for difference in ICU length of stay (LOS) (mean difference –1.51 days; 95% CI, –3.65 to 0.62; low quality). Two other meta-analyses of the 647 patients who were enrolled in these trials demonstrate moderate evidence for reduction in mortality when an early lactate clearance strategy was used, compared with either usual care (non-specified) or with a Scvo2 normalization strategy (38, 39).

The use of IV fluids in the resuscitation of patients is a cornerstone of modern therapy. Despite this, there is little available evidence from RCTs to support its practice; this is an area in which research is urgently needed. One trial of children (mostly with malaria) in Africa, in a setting where escalation to mechanical ventilation and other organ support was limited, questioned this practice ([230]). We believe that the extrapolation of these data to patients in better-resourced settings is not valid and thus recommend that clinicians restore euvolemia with IV fluids, more urgently initially, and then more cautiously as the patient stabilizes. There is some evidence that a sustained positive fluid balance during ICU stay is harmful ([231–235]). We do not recommend, therefore, that fluid be given beyond initial resuscitation without some estimate of the likelihood that the patient will respond positively.

The absence of any clear benefit following the administration of colloid compared to crystalloid solutions in the combined subgroups of sepsis, in conjunction with the expense of albumin, supports a strong recommendation for the use of crystalloid solutions in the initial resuscitation of patients with sepsis and septic shock.

We were unable to recommend one crystalloid solution over another because no direct comparisons have been made between isotonic saline and balanced salt solutions in patients with sepsis. One before-after study in all ICU patients suggested increased rates of acute kidney injury and RRT in patients managed with a chloride-liberal strategy compared to a chloride-restrictive strategy ([236]). There is indirect low-quality evidence from a network meta-analysis suggesting improved outcome with balanced salt solutions as compared to saline in patients with sepsis ([237]) (Supplemental Digital Content 6, http://links.lww.com/CCM/C327). In addition, the neutral result of the SPLIT cluster RCT in ICU patients (mainly surgical patients) in four New Zealand ICUs lowered our confidence in recommending one solution over the other ([238]). No cost-effectiveness studies compare balanced and unbalanced crystalloid solutions. Therefore, we considered the desirable and undesirable consequences to be comparable for both solutions and issued a weak recommendation to use either solution. Hyperchloremia should be avoided, however, and thus close scrutiny of serum chloride levels is advised, whichever fluid solutions are used.

The SAFE study indicated that albumin administration was safe and equally effective as 0.9% saline in ICU patients requiring fluid administration ([239]). A meta-analysis aggregated data from 17 randomized trials (n = 1,977) of albumin versus other fluid solutions in patients with sepsis or septic shock ([240]); 279 deaths occurred among 961 albumin-treated patients (29%) versus 343 deaths among 1,016 patients (34%) treated with other fluids, favouring albumin (OR, 0.82; 95% CI, 0.67–1.00). When albumin-treated patients were compared with those receiving crystalloids (seven trials, n = 144), the odds ratio of dying was significantly reduced for albumin-treated patients (OR, 0.78; 95% CI, 0.62–0.99).

Since the 2012 SSC guideline publication, six systematic reviews/meta-analyses ([237, 241–245]) were published assessing the use of albumin solutions in the management of patients with sepsis or septic shock. Each meta-analysis included different populations (adult/child, septic/nonseptic, and acute resuscitation/maintenance), different comparators and different duration of exposure to the intervention (hours, days), which made combining data challenging (Supplemental Digital Content 7, http://links.lww.com/CCM/C328).

Xu et al ([242]) evaluated albumin compared to crystalloid as a resuscitation fluid. Five studies, encompassing 3,658 sepsis and 2,180 septic shock patients, were included. Albumin use resulted in reduced septic shock 90-day mortality (OR, 0.81; 95% CI, 0.67–0.97) and trended toward reduced 90-day mortality in sepsis (OR, 0.88; 95% CI, 0.76–1.01; $p = 0.08$). Jiang et al ([245]) evaluated albumin in a mixed population of sepsis severity including adults and children. Three septic shock studies, encompassing 1,931 patients, were included. Albumin use resulted in decreased mortality (OR, 0.89; 95% CI, 0.80–0.99) with low heterogeneity ($I^2 = 0\%$). A mortality reduction trend was reported for albumin administration compared to crystalloids when given less than 6 hours from identification (11 studies; n = 5515; OR, 0.94; 95% CI, 0.86–1.03).

Patel et al ([244]) evaluated mixed populations, including resuscitation and maintenance. Additionally, a series of studies excluded from other meta-analyses due to accuracy concerns was included in this evaluation ([246–248]). When comparing crystalloid and albumin, the authors report a combined mortality benefit of albumin as compared to crystalloid (7 studies, n = 3,878; OR, 0.93; 95% CI, 0.86–1.00), but it was not consistent across individual severity subgroups. Use of albumin in septic shock trended toward mortality benefit (4 studies; n = 1,949; OR, 0.91; 95% CI, 0.82–1.01; *p* = 0.06), and the use of albumin in sepsis was not significant (4 studies; n = 1,929; OR, 0.96; 95% CI, 0.83–1.10). Evaluation of treatment within 24 hours also trended toward mortality benefit (4 studies; n = 3,832; RR, 0.93; 95% CI, 0.86–1.01). Rochwerg 2014 et al ([237]) evaluated resuscitative fluid use in a network meta-analysis of 14 trials, encompassing 18,916 patients. When comparing albumin to crystalloid, there was no significant reduction in mortality with moderate quality of evidence in both the four- and six-node analyses (four-node: OR, 0.83; credible interval [CrI] 0.65–1.04; six-node OR 0.82; Crl 0.65–1.04).

The ALBIOS trial ([249]) showed no mortality benefit of albumin in combination with crystalloids compared to crystalloids alone in patients with sepsis or septic shock (RR, 0.94; 95% CI, 0.85–1.05); a subgroup analysis suggested that the albumin group was associated with lower 90-day mortality in patients with septic shock (RR, 0.87; 95% CI, 0.77–0.99). Fluid administration continued for 28 days or until discharge and was not targeted for acute resuscitation. In addition, the amount of 20% albumin was guided by serum albumin level with the ultimate goal of achieving levels > 30 g/L. These results are limited by significant indirectness and imprecision, resulting in low quality of evidence.

HESs are colloids for which there are safety concerns in patients with sepsis. A meta-analysis of nine trials (3,456 patients) comparing 6% HES 130/0.38–0.45 solutions to crystalloids or albumin in patients with sepsis showed no difference in all-cause mortality (RR, 1.04; 95% CI, 0.89–1.22) ([250]). However, when low risk of bias trials were analysed separately, HES use resulted in higher risk of death compared to other fluids (RR, 1.11; 95% CI, 1.01–1.22; high-quality evidence), which translates to 34 more deaths per 1,000 patients. Furthermore, HES use led to a higher risk of RRT (RR, 1.36; 95% CI, 1.08–1.72; high-quality evidence) ([250]). A subsequent network meta-analysis focused on acute resuscitation of patients with sepsis or septic shock and found that HES resulted in higher risk of death (10 RCTs; OR, 1.13; CrI, 0.99–1.30; high-quality evidence) and need for RRT (7 RCTs; OR, 1.39; CrI, 1.17–1.66; high-quality evidence) compared to crystalloids. When comparing albumin to HES, albumin resulted in lower risk of death (OR, 0.73; CrI, 0.56–0.93; moderate-quality evidence) and a trend toward less need for RRT (OR, 0.74; CrI, 0.53–1.04; low-quality evidence) ([237]). Overall, the undesirable consequences of using HES (increased risk of death and need for RRT) along with moderate to high quality of available evidence resulted in a strong recommendation against the use of HES in resuscitation of patients with sepsis or septic shock.

Gelatin is another synthetic colloid that can be used for fluid resuscitation; however, high-quality studies comparing gelatins to other fluids in patients with sepsis or septic shock are lacking. Trials conducted in critically ill patients were summarized in a recent meta-analysis ([251]). Gelatin use in critically ill adult patients did not increase mortality (RR, 1.10; 95% CI, 0.85–1.43; low-quality evidence) or acute kidney injury (RR, 1.35; 95% CI, 0.58–3.14; very low-quality evidence) compared to albumin or crystalloid. These results are limited by indirectness, since the studies did not focus on critically ill patients. The aforementioned

network meta-analysis by Rochwerg et al did not identify any RCTs comparing gelatins to crystalloids or albumin; therefore, the generated estimates were imprecise and were based on indirect comparisons ([237]). Given the low quality of the available data and the cost associated with gelatin use, we issued a weak recommendation favoring the use of crystalloids over gelatins.

Recommendation 2. (SSCG Section A, Recommendation 1)
Sepsis and septic shock are medical emergencies, and we recommend that treatment and resuscitation begin immediately
Quality/level of evidence: Low + Strength of recommendation: BPS.

Recommendation 3. (SSCG Section A, Recommendation 2)
We recommend that, in the resuscitation from sepsis- induced hypoperfusion, at least 30 mL/kg of IV crystalloid fluid be given within the first 3 hours
Quality/level of evidence: Low + Strength of recommendation: Strong

Recommendation 4. (SSCG Section A, Recommendation 3)
We recommend that, following initial fluid resuscitation, additional fluids be guided by frequent reassessment of hemodynamic status
Quality/level of evidence: Low + Strength of recommendation: BPS

Recommendation 5. (SSCG Section A, Recommendation 4)
We recommend further hemodynamic assessment (such as assessing cardiac function) to determine the type of shock if the clinical examination does not lead to a clear diagnosis.
Quality/level of evidence: Low + Strength of recommendation: BPS

Recommendation 6. (SSCG Section A, Recommendation 5)
We suggest that dynamic over static variables be used to predict fluid responsiveness, where available.
Quality/level of evidence: Low + Strength of recommendation: Weak

Recommendation 7. (SSCG Section A, Recommendation 6)
We recommend an initial target mean arterial pressure (MAP) of 65 mm Hg in patients with septic shock requiring vasopressors.
Quality/level of evidence: Moderate + Strength of recommendation: Strong

Recommendation 8. (SSCG Section A, Recommendation 7)
We suggest guiding resuscitation to normalize lactate in patients with elevated lactate levels as a marker of tissue hypoperfusion.
Quality/level of evidence: Low + Strength of recommendation: Weak

Recommendation 9. (SSCG Section F, Recommendation 1).
We recommend that a fluid challenge technique be applied where fluid administration is continued as long as hemodynamic factors continue to improve
Quality/level of evidence: Low + Strength of recommendation: BPS

Recommendation 10. (SSCG Section F, Recommendation 2).
We recommend crystalloids as the fluid of choice for initial resuscitation and subsequent intravascular volume replacement in patients with sepsis and septic shock
Quality/level of evidence: Moderate + Strength of recommendation: Strong

Recommendation 11. (SSCG Section F, Recommendation 3).

We suggest using either balanced crystalloids or saline for fluid resuscitation of patients with sepsis or septic shock
Quality/level of evidence: Low + Strength of recommendation: Weak

Recommendation 12. (SSCG Section F, Recommendation 4).
We suggest using albumin in addition to crystalloids for initial resuscitation and subsequent intravascular volume replacement in patients with sepsis and septic shock when patients require substantial amounts of crystalloids
Quality/level of evidence: Low + Strength of recommendation: Weak

Recommendation 13. (SSCG Section F, Recommendation 5).
We recommend against using hydroxyethyl starches (HESs) for intravascular volume replacement in patients with sepsis or septic shock
Quality/level of evidence: High + Strength of recommendation: Strong

Recommendation 14. (SSCG Section F, Recommendation 6).
We suggest using crystalloids over gelatins when resuscitating patients with sepsis or septic shock.
Quality/level of evidence: Low + Strength of recommendation: Weak

SSC Remarks: Reassessment should include a thorough clinical examination and evaluation of available physiologic variables (heart rate, blood pressure, arterial oxygen saturation, respiratory rate, temperature, urine output, and others, as available) as well as other non-invasive or invasive monitoring, as available.

Implementation Point 5 (Recommendations 2-9)

Initial treatment: Following medical review, patients with a history and examination suggestive of systemic infection **and** who were identified as being in one of the three high-risk group for mortality from sepsis, should be given the Sepsis 6 bundle, and have their initial response reviewed with results of tests and investigations, within one hour of this differential diagnosis (i.e. **TIME ZERO**). Patients who present in extremis, for example, with profound hypotension, respiratory failure requiring ventilatory support and/or purpuric rash should receive the Sepsis 6 bundle as soon as possible.

SEPSIS 6 BUNDLE
Patients, with a clinical suspicion of infection who have screened as high risk of mortality from sepsis should have the Sepsis 6 bundle of care completed within one hour of a medical review.

A time-dependent bundled approach to sepsis resuscitation facilitates compliance with SSCG recommendations 1-3.

ACHIEVING TIME-DEPENDENT GOALS
All clinicians (medical, midwifery and nursing) should be familiar with the Sepsis 6 treatment bundle; they should work together to ensure that patients, who on history and examination have a suspicion of infection and are identified by screening as high risk of mortality from sepsis, receive the components of the Sepsis 6 bundle completed and reviewed correctly and within 1 hour of differential diagnosis.

Table 9. The Sepsis 6 bundle:

GIVE 3	TAKE 3
☐ Oxygen:……% Range 21-100%. Titrate to oxygen saturations 94- 98% (88-92% in patients with chronic lung disease).	☐ Blood cultures: Take blood cultures using aseptic (no touch) technique prior to giving antimicrobials unless this leads to a delay > 45 minutes. If a central venous catheter is *in situ*, take blood cultures through that line. Take other specimens as indicated by history and examination e.g. influenza swabs, wound swabs, sputum, urine etc.
☐ Fluids: Volume in 1st hour ……. Mls Patients who present with hypotension should receive 30mls/kg of a balanced salt solution within 1 hour of presentation. **Start vasopressors in patients who are fluid unresponsive.** Patients with hypoperfusion should receive fluid to restore perfusion using a bolus and review technique. 500mls boluses are recommended but may be amended based on clinical context. See fluid resuscitation algorithm.	☐ Blood Tests: Point of care lactate (venous or arterial). Full blood count, Urea & Electrolytes, Liver function tests +/- Coagulation screen. Other tests and investigations as indicated.
☐ Antimicrobials: Give antimicrobials as per local antimicrobial guideline based on the site of infection, community or healthcare acquired and the patient's allergy status. Assess requirement for source control. Type:…….Dose……Time Given……..	☐ Urine output: Assess urinary output as part of volume/ perfusion status assessment. For patients with sepsis/ septic shock start hourly fluid balance charts.

Give 3: three therapeutic interventions:

1. **Oxygen**: supplementary oxygen is administered to ensure oxygen saturation levels are between 94 – 98% (PaO_2 ≥ 10kPa) or 88 – 92% (PaO_2 ≥ 8kPa) in patients with chronic lung disease. For the purpose of audit this box is ticked when the desired oxygen saturations are achieved not when supplemental oxygen is administered.

2. **Fluids**: Patients who present with hypotension should receive at least 30mls/kg intravenous isotonic crystalloid fluid with the aim of restoring tissue perfusion. Patients, with hypotension, who are fluid intolerant or fluid resistant should have a critical care review with respect to invasive monitoring and advanced cardiorespiratory support.
   Apply vasopressors if the patient is hypotensive during or after fluid resuscitation to maintain mean arterial pressure (MAP) ≥ 65mmHg.

   Fluid administration to high-risk patients with infection who present without hypotension should be based on clinical need. The patient's volume status should be assessed by reviewing their heart rate, blood pressure, urinary output and serum

lactate. If a deficit is diagnosed, it should be corrected using a bolus and review method. This entails administering boluses of 500mls isotonic crystalloid given over 15 minutes followed by a prompt review to see if the patient needs further fluid or is showing signs of overload. A patient with no deficit or whose deficit has been corrected needs no further fluid. Exercise professional judgment in patients who due to chronic health issues are at high risk of fluid overload, consider 250ml boluses and more frequent review in such cases. A fluid resuscitation algorithm for non-critical care specialists is available in Appendix 12. A fluid balance chart should be started in patients who require fluid resuscitation.

3. **Antimicrobials and Source Control**: Appropriate antimicrobials should be administered according to local antimicrobial guidelines. Refer to Section D: Antimicrobial therapy for further information. Antimicrobials can only work if there is a blood supply to the source, therefore review the need for source control. See Section E: Source Control for further information.

Take 3: Three diagnostic interventions

1. **Blood cultures**: Take using aseptic (non-touch) technique before the first dose of antimicrobials unless it will delay administering the antimicrobial therapy for more than 45 minutes. If a central venous catheter is *in situ*, blood cultures should also be taken through that line. Other specimens should be sent as clinically indicated e.g. influenza swabs, wound swabs, sputum, urine etc.

SSCG remarks that appropriate routine microbiologic cultures always include at least two sets of blood cultures (aerobic and anaerobic).

2. **Blood tests**: send blood for a full blood count, urea and electrolytes and liver function tests and do a point of care lactate. These tests help support an infection diagnosis and identify any acute organ dysfunction as it's consequence. Other tests and investigations to assess the patient and aid in diagnosis should be according to the clinical assessment and based on usual management.

3. **Urine output**: assessing and quantifying urinary output is part of diagnosing a fluid deficit and response to resuscitation. This does not require all patients to have a urinary catheter. A urinary catheter may be necessary, however, for patients who are sick enough to warrant fluid resuscitation and ongoing hourly urinary output monitoring.

Maternity only

All clinicians (medical, midwifery and nursing) should be familiar with the adapted Sepsis 6+1 treatment bundle. They should work together to ensure that patients, who on history and examination have infection and who are identified by screening as at risk of sepsis, receive the components of the Sepsis 6+1 bundle, completed correctly and within 1 hour of diagnosis.

TABLE 10. MATERNITY SEPSIS 6 + 1 BUNDLE

GIVE 3	TAKE 3
OXYGEN: Titrate O2 to saturations of 94 -98% or 88-92% in chronic lung disease.	**BLOOD CULTURES:** Take blood cultures before giving antimicrobials (if no significant delay i.e. >45 minutes) and other cultures as per examination.
FLUIDS: Start IV fluid resuscitation if evidence of hypovolaemia. 500ml bolus of isotonic crystalloid over 15mins & give up to 2 litres, reassessing frequently. Call Anaesthesia/Critical Care if hypotensive or not fluid responsive. **Caution in pre-eclampsia.**	**BLOODS:** Check point of care lactate & full blood count, U&E +/- LFTs +/- Coag. Other test and investigations as indicated by history and examination.
ANTIMICROBIALS: Give IV antimicrobials according to the site of infection and following local antimicrobial guidelines.	**URINE OUTPUT:** assess urinary output as part of volume/perfusion status assessment. For patients with sepsis or septic shock start hourly urinary output measurement.
+1 If Pregnant, Assess Fetal Wellbeing Note: there is no auto regulation of the feto-placental unit. One of the earlier signs of maternal hypoperfusion may be fetal tachycardia. Resuscitating the mother resuscitates the baby.	

Antimicrobials specific to Maternal Shock

For acute maternal septic shock, as defined by the current HSE maternal sepsis form, empirical antibiotics should be administered within 1 hour. In patients with no penicillin allergy reported, in line with international and national guidance above, three antimicrobials should be given in setting of acute maternal septic shock[ref]:

a. Broad spectrum beta-lactam antimicrobial (Meropenem is recommended in to cover for extended spectrum beta-lactamases, (RCOG also give piperacillin/tazobactam as an option)[ref]

b. Gentamicin: This is for bactericidal action against Gram-negative organisms mainly

c. Clindamycin: This is to switch off exotoxin production with significantly decreased mortlity[ref]

d. A combination of either piperacillin/tazobactam or cabapenem PLUS clindamycin provides one of the broadest ranges of treatment for sepsis[ref]

If there is a strong suspicion clinically that the septic shock may be relating to group A Streptococcus, then IV immunoglobulin[ref] could be considered in line with the national Group A Streptococcal management guidelines which were produced by the Health Protection Surveillance Centre (HPSC)

+ 1: Fetal wellbeing

Resuscitating the mother will resuscitate the baby, however, it is important to assess fetal wellbeing and formulate a plan for delivery if required. Maternal sepsis with or without haemodynamic instability may present with fetal distress as the uteroplacental circulation is not auto-regulated[ref] Thus any maternal circulatory insufficiency arising from sepsis may result in compromised fetal perfusion.

Management plans need to take into consideration the altered immunological response of the woman and the altered physiological responses during pregnancy[ref]. Particular consideration needs to be taken of the physiological effects of anaesthesia, general and regional, on the pregnant septic women.

Implementation Point 6 (10-14)

Patients who present with shock should receive 30mls/kg of intravenous balanced crystalloid fluid and vasopressors started in those with fluid resistant shock within one hour of presentation[49].

The initial resuscitation of patients with tissue hypo-perfusion may be guided by physiological parameters such as normalisation of mental status, skin perfusion, blood pressure, urinary output and serum lactate measurement. A fluid resuscitation algorithm outlining the fluid bolus and review method to initial resuscitation is available (Appendix 12). Four potential scenarios need to be considered after each bolus.

1. Persistent hypoperfusion: continue fluid resuscitation.
2. Fluid intolerant:
    a. Persistent hypoperfusion, as evidenced by hypotension and/or raised lactate with clinical signs of overload. These patients should have a critical care review and consideration for inotropes and invasive monitoring for fluid responsiveness. Forced diuresis is unlikely to be helpful and may be harmful in this group due to ongoing intra-vascular hypovolaemia.
    b. Euvolaemia with signs of overload, these patients may benefit from diuresis. Before giving the diuretic check the patient's perfusion.
3. Fluid resistant: these patients have no or transient improvement in physiological parameters with fluid resuscitation due to a high degree of vascular leak, vasoplegia +/- cardiac impairment and require vasopressors and/or inotropes and invasive monitoring of fluid responsiveness with critical care input.
4. Fluid replete – the fluid deficit has been corrected, stop fluid resuscitation.

Certain patient populations, such as those with chronic renal failure, congestive cardiac failure and frailty, lead clinicians to be reluctant to administer intravenous fluid to avoid causing harm, however, these patients if they have an infection-induced perfusion deficit require restoration of tissue perfusion to avert progressive organ dysfunction and reduce mortality. Taking a bolus approach allows good control of resuscitation and early detection of signs of overload. Exercise clinical judgment, if clinically indicated, and use smaller boluses e.g. 250mls with more frequent review.

Maternity only

Pulmonary vascular resistance decreases during pregnancy. Pulmonary capillary wedge pressure and central venous pressure do not change during pregnancy, but serum colloid pressure is reduced by 10% to 15%, predisposing pregnant women to an increased risk of pulmonary oedema[ref].

Normal physiologic changes of pregnancy cause a reduction in colloid oncotic pressures [ref], allowing interstitial fluid shifts to occur and placing obstetric patients at risk of developing pulmonary oedema and acute respiratory distress syndrome

Implementation Point 7

Sepsis is diagnosed when acute organ dysfunction consequent to infection occurs. This includes acute on chronic organ dysfunction.

As the SSC guidelines were being developed, new definitions for sepsis and septic shock (Sepsis-3) were published. *Sepsis* is now defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. *Septic shock* is a subset of sepsis with circulatory and cellular/metabolic dysfunction associated with a higher risk of mortality[3].

Infection, sepsis and septic shock are clinical diagnoses. There is no one test that will confirm the presence of infection, sepsis or septic shock to the exclusion of other diagnoses. Rather the suite of symptoms and signs along with tests and investigations need to be weighed against the differential diagnoses and a clinical decision made. The presence of positive cultures does much to support an infective aetiology but only occurs in 40-60% of sepsis cases, [7, 10, 36] and has a time lag to positivity.

Much has been made of the removal of the systemic inflammatory response syndrome (SIRS) criteria from the definition of sepsis, however, this does not mean that SIRS has 'gone away' it reflects the fact that self-limiting non-life threatening infections may present with SIRS and that SIRS may be caused by infectious and non-infectious insults.

SIRS in non-pregnant adults include:

- Heart rate > 90 beats/minute
- Respiratory rate > 20 breaths/minute
- Temperature > 38.3^{o}C or < 36^{o}C
- White cell count > 12 or < 4 x 10^{9} cells/L or normal with > 10% immature forms.

The presence of a SIRS response is not required for the diagnosis of sepsis to be made but, in fact, it is present in 86.7% of critical care sepsis patients[37].

The SIRS criteria continue to be helpful in identifying patients with infection.

TABLE 11. NON-SPECIFIC SIGNS AND SYMPTOMS OF INFECTION INCLUDE:

Temperature > 38.3^{o}C or < 36^{o}C	Myalgia / arthralgia
Rigors	Vomiting
Anorexia	Diarrhoea
Fatigue	Rash

TABLE 12. LOCALISING SIGNS & SYMPTOMS OF INFECTION MAY INCLUDE (DISCLAIMER: THIS LIST IS BY NO MEANS EXHAUSTIVE):

Respiratory tract Tachypnoea Hypoxia/cyanosis Cough Purulent sputum Pleuritic pain Sore throat Ear/ Mastoid pain	**Bones & Joints** Pain Swelling Redness Dysfunction
Intra-abdominal Pain Peritonism Distension Vomiting Diarrhoea	**Brain & meninges** Altered consciousness Headache Neck stiffness Photophobia Pain with straight leg raise
Urinary tract Dysuria Flank pain Frequency Blood in the urine	**Device related** Redness Swelling Discharge May be a diagnosis of exclusion
Skin **Pain** **Redness** **Swelling** **Rash** **Discharge** **Mottling/ blistering**	**Bloodstream infection** Severe non-specific signs of infection +/- source symptoms

Note: Patients with immunocompromise may not manifest the usual signs and symptoms of infection due to their inability to mount the appropriate immune response. These patients often present unwell with evidence of new onset organ dysfunction. They may have no temperature and mount no white cell increase. A high index of suspicion must be deployed to diagnose these patients correctly and a presumption of infection and treatment with empiric antimicrobial therapy is recommended until the diagnosis is confirmed.

Maternity only

Obstetric patients with infections may present with nonspecific symptoms and early investigation is necessary to exclude severe infection[24].

- History of fevers or rigors
- Cough/sputum/breathlessness
- Flu-like symptoms
- Unexplained abdominal pain/distension
- Pelvic pain
- Vomiting and/or diarrhoea
- Line associated infection/redness/swelling/pain
- Possible intrauterine infection

- Myalgia/back pain/general malaise/headache
- New onset of confusion
- Cellulitis/wound infection/perineal infection
- Possible breast infection/mastitis
- Multiple presentations with non-specific malaise
- Others

Note: Women with severe immuno-compromise may not manifest the usual signs and symptoms of infection due to their inability to mount the appropriate immune response. These women often present unwell with evidence of new onset organ dysfunction. They may have no temperature and mount no white cell increase. A high index of suspicion must be deployed to diagnose these women correctly and a presumption of infection and treatment with empiric antimicrobial therapy is recommended until the diagnosis is confirmed.

Organ dysfunction criteria:

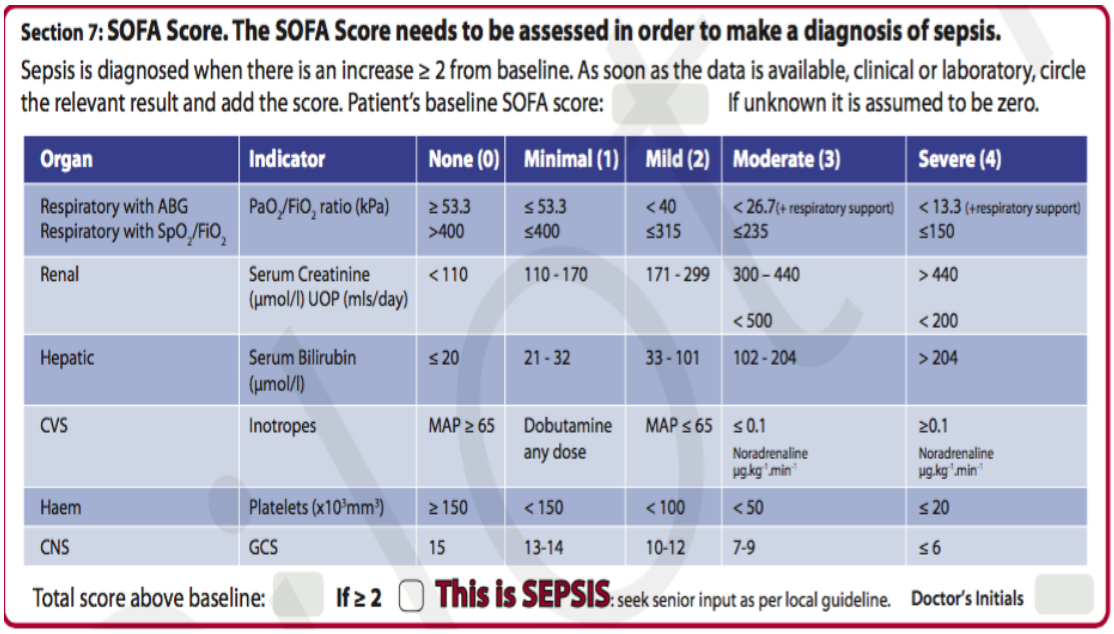
Organ dysfunction is identified if one or more of the following is diagnosed either on the blood tests sent as part of the Sepsis 6 bundle **OR** persisting clinically after the bundle has been administered. This is outlined in Table 7

TABLE 13. EVIDENCE OF ORGAN DYSFUNCTION

Central Nervous System Acutely altered mental status	**Respiratory** New need for oxygen to achieve saturation > 90% (note: this is a definition not the target)
Cardiovascular Systolic BP < 90 or Mean Arterial Pressure (MAP) < 65 or Systolic BP more than 40mmHg below the patient's normal Systolic BP Lactate ≥ 4mmol/L	**Renal** Creatinine > 170 micromol/L **or** Urine output < 500mls/24 hrs – despite adequate fluid resuscitation
Haematological Platelets < 100 x 10^9/L Petechial or purpuric rash	**Liver** Bilirubin > 32 micromol/L

The Sepsis Definition Taskforce[9] recommends the use of the SOFA score to assess for the presence of acute organ dysfunction. Two sepsis forms were trialled by the National Sepsis Team; one using the organ dysfunction list and the other using the SOFA score. Twelve Emergency Departments, nationally, participated in a PDSA cycle to inform the format. Whilst Consultants preferred the SOFA score, Non-consultant hospital doctors (NCHDs) preferred the list of organ dysfunctions[38]. As NCHDs are, by far, the more likely first treating clinicians we suggest continuing to use the list, which has been adapted to reflect the SOFA tool. The SOFA score may equally be used, if preferred.

Figure 11. The Sepsis Sofa Score Ref 9



Section 7: SOFA Score. The SOFA Score needs to be assessed in order to make a diagnosis of sepsis.

Sepsis is diagnosed when there is an increase ≥ 2 from baseline. As soon as the data is available, clinical or laboratory, circle the relevant result and add the score. Patient's baseline SOFA score: If unknown it is assumed to be zero.

Organ	Indicator	None (0)	Minimal (1)	Mild (2)	Moderate (3)	Severe (4)
Respiratory with ABG Respiratory with SpO_2/FiO_2	PaO_2/FiO_2 ratio (kPa)	≥ 53.3 >400	≤ 53.3 ≤400	< 40 ≤315	< 26.7 (+ respiratory support) ≤235	< 13.3 (+respiratory support) ≤150
Renal	Serum Creatinine (µmol/l) UOP (mls/day)	< 110	110 - 170	171 - 299	300 – 440 < 500	> 440 < 200
Hepatic	Serum Bilirubin (µmol/l)	≤ 20	21 - 32	33 - 101	102 - 204	> 204
CVS	Inotropes	MAP ≥ 65	Dobutamine any dose	MAP ≤ 65	≤ 0.1 Noradrenaline $\mu g.kg^{-1}.min^{-1}$	≥0.1 Noradrenaline $\mu g.kg^{-1}.min^{-1}$
Haem	Platelets ($x10^3 mm^3$)	≥ 150	< 150	< 100	< 50	≤ 20
CNS	GCS	15	13-14	10-12	7-9	≤ 6

Total score above baseline: **If ≥ 2** ☐ **This is SEPSIS**: seek senior input as per local guideline. **Doctor's Initials**

It is noted that the NEWS scoring system uses the AVPU (alert, responds to voice, responds to pain, unresponsive) screen for assessing mental status. It is recognised that this screening tool is not sensitive for new onset confusion or agitation as both these conditions may be scored as 'Alert'. In conditions where infection is thought to contribute to the deterioration of a patients' clinical status professional judgment should be exercised and sepsis screening performed. The sepsis forms use the more sensitive discriminator of acutely altered mental state to identify patients with neurological dysfunction as a consequence of sepsis.

The National Sepsis Programme does not support the use of the qSOFA score to identify patients with sepsis, as it was not developed as a diagnostic tool but rather as a prognostic indicator in patients with sepsis[9].

Roles and responsibilities:
It is the responsibility of all clinicians in the acute hospital sector to be familiar with the diagnostic criteria for sepsis and septic shock.

Septic Shock Diagnosis
Septic shock is diagnosed if vasopressors or inotropes are required to maintain a mean arterial blood pressure (MAP) > 65mmHg and the patient has evidence of tissue hypoperfusion after adequate fluid resuscitation.

Implementation Point 8 (Recommendation 7)
The sepsis-3 definition taskforce[9] have defined septic shock as requiring vasopressors to maintain a MAP > 65mmHg AND a lactate ≥ 2mmol/L after adequate fluid resuscitation. This identifies a cohort of patients with a mortality risk > 40% versus > 30% in those with a pressor requirement and a normal lactate.

Patients who require vasopressors or inotropes to support their blood pressure after appropriate fluid resuscitation require critical care review. Adequate fluid resuscitation, for

the purpose of this guideline, is a minimum of 30mls/kg intravenous crystalloid or that the patient is fluid intolerant. Patients with a persistent lactate > 4 despite adequate fluid resuscitation who are maintaining a MAP > 65mmHg have a high mortality risk and as such may benefit from critical care review despite not fulfilling shock criteria.

Figure 12. Adult Sepsis Pathway

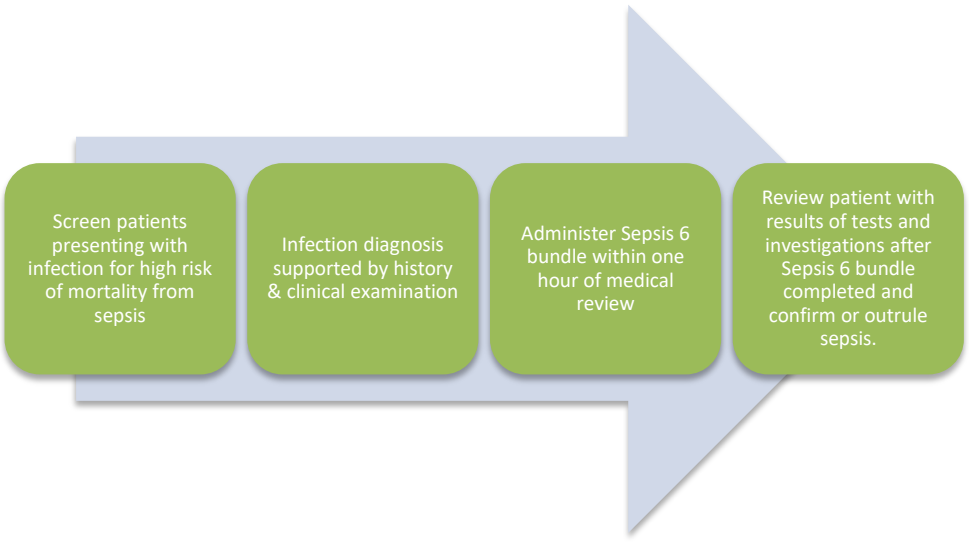
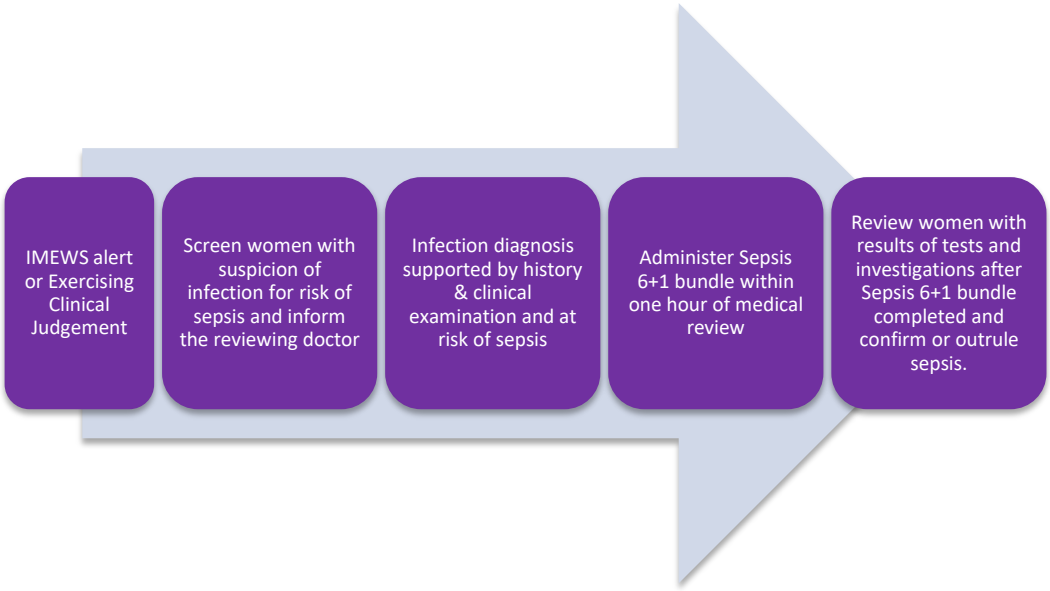


Figure 13. Maternity Sepsis Pathway



Implementation Point 9

Having administered the Sepsis 6 bundle, the patient should be reviewed with the results of the tests and investigations sent as a consequence of their medical review.

This review should be performed within 1 hour of Time Zero but may be performed earlier and as frequently as clinically indicated. This provides the first opportunity to review the working diagnosis and treatment. If a non-infective aetiology for the patients' presentation has been identified, stop antimicrobials.

If the investigations have localised the site of infection, review antimicrobial prescription using the local antimicrobial guidelines to ensure it is the most appropriate choice. If not already reviewed when empiric antimicrobial therapy was prescribed, review patients past microbiology results, as a previous history of multi-drug resistant organisms may influence choice of antimicrobial. Complex cases may benefit from Clinical Microbiology/ Infectious diseases review.

Source control is a vital component of the treatment of infection. Organise for drainage/ debridement to be performed as soon as practicable.

Suggested components of the review:

Clinical assessment:

- **Assess clinical response to Sepsis 6 bundle**
  - Has your patient improved, stabilised or deteriorated?
  - Is there clinical or biochemical evidence of acute organ dysfunction?
- **Review blood tests**
  - Do they support an infective aetiology?
  - Is there biochemical evidence of acute organ dysfunction?
- **Review other tests and investigations ordered and completed**
  - Do they support an infective aetiology?

- Is source control required?

- **Perform repeat lactate**
  - If clinically indicated or if the first was > 2mmol/l in order to monitor restoration of tissue perfusion and/or guide on-going fluid resuscitation.

Actions

- **Seek senior input if patient is not stabilized or improving.**
- **Document the diagnosis as infection, sepsis, or septic shock and amend treatment plan accordingly.**
- **Obtain critical care review for patients with septic shock and/or other organ dysfunctions requiring support.**
- **Review differential diagnoses:**

Maternity only

In a very unwell or unstable patient it is not usual to have a definitive diagnosis in the first instance. If infection is on the differential give the Sepsis 6+1 and if a non-infective aetiology is subsequently found, stop the antibiotics.

TABLE 14. DIFFERENTIAL DIAGNOSIS: COMMON MATERNAL CLINICAL FEATURES REF

Acute pulmonary embolism	Hypotension, tachypnoea, tachycardia, low-grade fever
Amniotic fluid embolism	Hypotension, tachycardia, haemorrhage
Acute pancreatitis	Fever, nausea, vomiting, abdominal pain
Acute fatty liver of pregnancy	Fatigue, nausea, vomiting, abdominal pain, jaundice, impaired level of consciousness
Adverse drug reactions, drug fever	Hypotension, relative bradycardia, fever, rash, angio-oedema
Acute liver failure-drug related viral	Jaundice, nausea, vomiting, abdominal pain impaired level of consciousness
Acute adrenal insufficiency	Weakness, fatigue, nausea, anorexia, weight loss, hypotension, fever
Acute pituitary insufficiency	Failure to lactate, hypotension, relative bradycardia, polyuria, polydipsia
Autoimmune conditions	Low-grade fever, rash (e.g. malar rash), arthritis, dry eyes or mouth, mouth ulcers, diagnostic serology
Concealed haemorrhage including ectopic pregnancy	Hypotension, tachycardia, low-grade fever
Disseminated malignancy	Low-grade fever, weight loss
Pelvic thrombosis	Pelvic pain, fever

Transfusion reactions	High fever, rigors, dysrhythmia, tachypnoea, hypotension, rash, bleeding, haematuria

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Roles and responsibilities:
It is the responsibility of the treating clinician to review the patients' clinical response to the Sepsis 6 bundle of care, the results of the tests ordered, to diagnose and document sepsis as appropriate and to escalate the patient for specialist intervention as indicated. In the circumstance where the treating clinician changes during the care episode; clear transfer of responsibility should be made and documented, outlining outstanding tasks and concerns and the name(s) of the clinicians taking over care[41]. The relevant Sepsis Form or ISBAR Communication Tool (Appendix 4) can be used for this. This information should also be communicated to other clinicians involved in the patients' immediate care. It is the responsibility of the HSE, Hospital Group Leadership and Hospital Management to ensure adequate resources are available for tests and investigations to be performed in a timely manner and for capacity to be available for escalation to critical care when required.

Maternity only
It is the responsibility of the midwife to screen for the possibility of sepsis in a woman presenting with symptoms suggestive of infection and to initiate the sepsis form in women who screen positive, then to escalate to urgent medical review and to communicate current concerns and relevant clinical history in line with the Maternity Sepsis Form and ISBAR. It is also their responsibility to assist with the timely delivery of the Sepsis 6 + 1 bundle, subsequent monitoring, care and escalation in line with the maternity sepsis form and IMEWS.

It is the responsibility of the treating clinicians to review the woman's clinical response to the sepsis 6+1 bundle of care and the results of the tests ordered and to diagnose and document sepsis as appropriate and to escalate the woman for specialist intervention as indicated.

When should a patient be escalated for critical care review?
Initial assessment of a patient presenting unwell or deteriorating should include review of airway, breathing, circulation and neurological status.

- Patients who need immediate airway management and/or ventilatory support and/or have fluid resistant or profound shock and/ or have a purpuric rash should be escalated to critical care review.
- Patients who despite adequate fluid resuscitation* have not achieved a mean arterial pressure of ≥ 65mmHg should be referred to critical care.

*For the purposes of this guideline adequate fluid resuscitation in patients presenting with hypotension is a minimum of 30mls/kg of isotonic crystalloid fluid unless the patient is or becomes fluid intolerant as evidenced by worsening cardio-respiratory status and/or oedema.

What are the goals of critical care?
The goals of critical care management are to support organ function during the diagnosis and treatment of reversible disease processes, in this instance sepsis, whilst minimizing nosocomial injury. It is recommended that this management be guided by evidence-based regimes as outlined by the Surviving Sepsis Campaign Guideline adopted in this document[1].

Roles and responsibilities:
All clinicians should familiarise themselves with the 'bolus and review' approach to the initial fluid resuscitation of patients and that, unless otherwise indicated, a balanced salt solution is the fluid of choice[1].

3.1.3 Antimicrobial therapy

Key questions

- *In patients with sepsis, should we use broad empiric antimicrobial coverage?*
- *In patients with septic shock, should we administer empirically appropriate antimicrobials (within one hour of recognition)?*
- *In patients with sepsis, should we administer empirically appropriate antimicrobials (within one hour of recognition)?*
- *In critically ill septic patients, should we implement pharmacokinetic dosing optimization for each antimicrobial?*
- *In patients with sepsis and neutropenia, should we use empiric combination antimicrobial therapy versus mono-therapy?*
- *In patients with sepsis at high risk for multi-drug resistant pathogens, should we use empiric combination antibiotic therapy (versus mono-therapy) until sensitivities are determined?*
- *In patients with septic shock, should we use empiric double-coverage antibiotic agents until hemodynamic stabilization and pathogen identification?*
- *In patients with sepsis who are receiving antimicrobials, should we assess for de-escalation of therapy daily?*
- *In patients with uncomplicated infections causing sepsis or septic shock, should we recommend a duration of therapy of 7-10 days versus longer course?*
- *In patients with sepsis or septic shock who are receiving empiric combination of antimicrobials should we assess for de-escalation of therapy daily?*
- *In patients with sepsis, should we use procalcitonin levels to support de-escalation of antimicrobial therapy?*
- *In patients with severe inflammatory state of non-infectious origin should we use systemic prophylactic antimicrobials.*

SSCG Rationale

The rapidity of administration is central to the beneficial effect of appropriate antimicrobials. In the presence of sepsis or septic shock, each hour delay in administration of appropriate antimicrobials is associated with a measurable increase in mortality ([57, 74]). Further, several studies show an adverse effect on secondary end points (e.g., LOS ([75]), acute kidney injury ([76]), acute lung injury ([77]), and organ injury assessed by Sepsis-Related Organ Assessment score ([78]) with increasing delays. Despite a meta-analysis of mostly poor-quality studies that failed to demonstrate a benefit of rapid antimicrobial therapy, the

largest and highest-quality studies support giving appropriate antimicrobials as soon as possible in patients with sepsis with or without septic shock ([57, 74, 79–81]). The majority of studies within the meta-analysis were of low quality due to a number of deficiencies, including small study size, using an initial index time of an arbitrary time point such as emergency department arrival, and indexing of outcome to delay in time to the first antimicrobial (regardless of activity against the putative pathogen) ([82, 83]). Other negative studies not included in this meta-analysis are compromised by equating bacteraemia with sepsis (as currently defined to include organ failure) and septic shock ([84–87]). Many of these studies are also compromised by indexing delays to easily accessible but non-physiologic variables such as time of initial blood culture draw (an event likely to be highly variable in timing occurrence).

While available data suggest that the earliest possible administration of appropriate IV antimicrobials following recognition of sepsis or septic shock yields optimal outcomes, one hour is recommended as a reasonable minimal target. The feasibility of achieving this target consistently, however, has not been adequately assessed. Practical considerations, for example, challenges with clinicians' early identification of patients or operational complexities in the drug delivery chain, represent poorly studied variables that may affect achieving this goal. A number of patient and organizational factors appear to influence antimicrobial delays ([88]).

Accelerating appropriate antimicrobial delivery institutionally starts with an assessment of causes of delays ([89]). These can include an unacceptably high frequency of failure to recognize the potential existence of sepsis or septic shock and of inappropriate empiric antimicrobial initiation (e.g., as a consequence of lack of appreciation of the potential for microbial resistance or recent previous antimicrobial use in a given patient). In addition, unrecognized or underappreciated administrative or logistic factors (often easily remedied) may be found. Possible solutions to delays in antimicrobial initiation include use of "stat" orders or including a minimal time element in antimicrobial orders, addressing delays in obtaining blood and site cultures pending antimicrobial administration, and sequencing antimicrobial delivery optimally or using simultaneous delivery of key antimicrobials, as well as improving supply chain deficiencies. Improving communication among medical, pharmacy, and nursing staff can also be highly beneficial.

Most issues can be addressed by quality improvement initiatives, including defined order sets. If antimicrobial agents cannot be mixed and delivered promptly from the pharmacy, establishing a supply of premixed drugs for urgent situations is an appropriate strategy for ensuring prompt administration. Many antimicrobials will not remain stable if premixed in a solution. This issue must be taken into consideration in institutions that rely on premixed solutions for rapid antimicrobial availability. In choosing the antimicrobial regimen, clinicians should be aware that some antimicrobial agents (notably β-lactams) have the advantage of being able to be safely administered as a bolus or rapid infusion, while others require a lengthy infusion. If vascular access is limited and many different agents must be infused, drugs that can be administered as a bolus or rapid infusion may offer an advantage for rapid achievement of therapeutic levels for the initial dose.

While establishing vascular access and initiating aggressive fluid resuscitation are very important when managing patients with sepsis or septic shock, prompt IV infusion of

antimicrobial agents is also a priority. This may require additional vascular access ports. Intraosseous access, which can be quickly and reliably established (even in adults), can be used to rapidly administer the initial doses of any antimicrobial ([90, 91]). In addition, intramuscular preparations are approved and available for several first-line β-lactams, including imipenem/cilastatin, cefepime, ceftriaxone, and ertapenem. Several additional first-line β-lactams can also be effectively administered intramuscularly in emergency situations if vascular and intraosseous access is unavailable, although regulatory approval for intramuscular administration for these drugs is lacking ([92–94]). Intramuscular absorption and distribution of some of these agents in severe illness has not been studied; intramuscular administration should be considered only if timely establishment of vascular access is not possible.

The initiation of appropriate antimicrobial therapy (i.e., with activity against the causative pathogen or pathogens) is one of the most important facets of effective management of life-threatening infections causing sepsis and septic shock. Failure to initiate appropriate empiric therapy in patients with sepsis and septic shock is associated with a substantial increase in morbidity and mortality ([79, 95–97]). In addition, the probability of progression from gram-negative bacteremic infection to septic shock is increased ([98]). Accordingly, the initial selection of antimicrobial therapy must be broad enough to cover all likely pathogens. The choice of empiric antimicrobial therapy depends on complex issues related to the patient's history, clinical status, and local epidemiologic factors. Key patient factors include the nature of the clinical syndrome/site of infection, concomitant underlying diseases, chronic organ failures, medications, indwelling devices, the presence of immunosuppression or other form of immunocompromise, recent known infection or colonization with specific pathogens, and the receipt of antimicrobials within the previous three months. In addition, the patient's location at the time of infection acquisition (i.e., community, chronic care institution, acute care hospital), local pathogen prevalence, and the susceptibility patterns of those common local pathogens in both the community and hospital must be factored into the choice of therapy. Potential drug intolerances and toxicity must also be considered.

The most common pathogens that cause septic shock are gram-negative bacteria, gram-positive, and mixed bacterial microorganisms. Invasive candidiasis, toxic shock syndromes, and an array of uncommon pathogens should be considered in selected patients. Certain specific conditions put patients at risk for atypical or resistant pathogens. For example, neutropenic patients are at risk for an especially wide range of potential pathogens, including resistant gram-negative *bacilli* and *Candida* species. Patients with nosocomial acquisition of infection are prone to sepsis with methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococci*.

Historically, critically ill patients with overwhelming infection have not been considered a unique subgroup comparable to neutropenic patients for purposes of selection of antimicrobial therapy. Nonetheless, critically ill patients with severe and septic shock are, like neutropenic patients, characterized by distinct differences from the typical infected patient that impact on the optimal antimicrobial management strategy. Primary among these differences are a predisposition to infection with resistant organisms and a marked increase in frequency of death and other adverse outcomes if there is a failure of rapid initiation of effective antimicrobial therapy.

Selection of an optimal empiric antimicrobial regimen in sepsis and septic shock is one of the central determinants of outcome. Survival may decrease as much as fivefold for septic shock treated with an empiric regimen that fails to cover the offending pathogen ([95]). Because of the high mortality associated with inappropriate initial therapy, empiric regimens should err on the side of over-inclusiveness. However, the choice of empiric antimicrobial regimens in patients with sepsis and septic shock is complex and cannot be reduced to a simple table. Several factors must be assessed and used in determining the appropriate antimicrobial regimen at each medical centre and for each patient. These include:

a) The anatomic site of infection with respect to the typical pathogen profile and to the properties of individual antimicrobials to penetrate that site
b) Prevalent pathogens within the community, hospital, and even hospital ward
c) The resistance patterns of those prevalent pathogens
d) The presence of specific immune defects such as neutropenia, splenectomy, poorly controlled HIV infection and acquired or congenital defects of immunoglobulin, complement or leukocyte function or production
e) Age and patient comorbidities including chronic illness (e.g., diabetes) and chronic organ dysfunction (e.g., liver or renal failure), the presence of invasive devices (e.g., central venous lines or urinary catheter) that compromise the defence to infection.

In addition, the clinician must assess risk factors for infection with multidrug-resistant pathogens including prolonged hospital/chronic facility stay, recent antimicrobial use, prior hospitalization, and prior colonization or infection with multidrug-resistant organisms. The occurrence of more severe illness (e.g., septic shock) may be intrinsically associated with a higher probability of resistant isolates due to selection in failure to respond to earlier antimicrobials.

Given the range of variables that must be assessed, the recommendation of any specific regimen for sepsis and septic shock is not possible. The reader is directed to guidelines that provide potential regimens based on anatomic site of infection or specific immune defects ([67, 99–109]).

However, general suggestions can be provided. Since the vast majority of patients with severe sepsis and septic shock have one or more forms of immunocompromise, the initial empiric regimen should be broad enough to cover most pathogens isolated in healthcare-associated infections. Most often, a broad-spectrum carbapenem (e.g., meropenem, imipenem/cilastatin or doripenem) or extended-range penicillin/β-lactamase inhibitor combination (e.g., piperacillin/tazobactam or ticarcillin/clavulanate) is used. However, several third- or higher-generation cephalosporins can also be used, especially as part of a multidrug regimen. Of course, the specific regimen can and should be modified by the anatomic site of infection if it is apparent and by knowledge of local microbiologic flora.

Multidrug therapy is often required to ensure a sufficiently broad spectrum of empiric coverage initially. Clinicians should be cognizant of the risk of resistance to broad-spectrum β-lactams and carbapenems among gram-negative bacilli in some communities and healthcare settings. The addition of a supplemental gram-negative agent to the empiric regimen is recommended for critically ill septic patients at high risk of infection with such

multidrug-resistant pathogens (e.g., *Pseudomonas, Acinetobacter*, etc.) to increase the probability of at least one active agent being administered ([110]). Similarly, in situations of a more-than-trivial risk for other resistant or atypical pathogens, the addition of a pathogen-specific agent to broaden coverage is warranted. Vancomycin, teicoplanin, or another anti-MRSA agent can be used when risk factors for MRSA exist. A significant risk of infection with *Legionella* species mandates the addition of a macrolide or fluoroquinolone.

Clinicians should also consider whether *Candida* species are likely pathogens when choosing initial therapy. Risk factors for invasive *Candida* infections include immunocompromised status (neutropenia, chemotherapy, transplant, diabetes mellitus, chronic liver failure, chronic renal failure), prolonged invasive vascular devices (haemodialysis catheters, central venous catheters), total parenteral nutrition, necrotizing pancreatitis, recent major surgery (particularly abdominal), prolonged administration of broad-spectrum antibiotics, prolonged hospital/ICU admission, recent fungal infection, and multisite colonization ([111, 112]). If the risk of *Candida* sepsis is sufficient to justify empiric antifungal therapy, the selection of the specific agent should be tailored to the severity of illness, the local pattern of the most prevalent *Candida* species, and any recent exposure to antifungal drugs. Empiric use of an echinocandin (anidulafungin, micafungin, or caspofungin) is preferred in most patients with severe illness, especially in those patients with septic shock, who have recently been treated with other antifungal agents, or if *Candida glabrata* or *Candida krusei* infection is suspected from earlier culture data ([100, 105]). Triazoles are acceptable in hemodynamically stable, less ill patients who have not had previous triazole exposure and are not known to be colonized with azole-resistant species. Liposomal formulations of amphotericin B are a reasonable alternative to echinocandins in patients with echinocandin intolerance or toxicity ([100, 105]). Knowledge of local resistance patterns to antifungal agents should guide drug selection until fungal susceptibility test results, if available, are received. Rapid diagnostic testing using β-D-glucan or rapid polymerase chain reaction assays to minimize inappropriate anti-*Candida* therapy may have an evolving supportive role. However, the negative predictive value of such tests is not high enough to justify dependence on these tests for primary decision-making.

Superior empiric coverage can be obtained using local and unit-specific antibiograms ([113, 114]) or an infectious diseases consultation ([115–117]). Where uncertainty regarding appropriate patient-specific antimicrobial therapy exists, infectious diseases consultation is warranted. Early involvement of infectious diseases specialists can improve outcome in some circumstances (e.g., *S aureus* bacteraemia) ([113–115]).

Although restriction of antimicrobials is an important strategy to reduce both the development of pathogen resistance and cost, it is not an appropriate strategy in the initial therapy for this patient population. Patients with sepsis or septic shock generally warrant empiric broad-spectrum therapy until the causative organism and its antimicrobial susceptibilities are defined. At that point, the spectrum of coverage should be narrowed by eliminating unneeded antimicrobials and replacing broad-spectrum agents with more specific agents ([118]). However, if relevant cultures are negative, empiric narrowing of coverage based on a good clinical response is appropriate. Collaboration with antimicrobial stewardship programs is encouraged to ensure appropriate choices and rapid availability of effective antimicrobials for treating septic patients.

In situations in which a pathogen is identified, de-escalation to the narrowest effective agent should be implemented for most serious infections. However, approximately one third of patients with sepsis do not have a causative pathogen identified ([95, 119]). In some cases, this may be because guidelines do not recommend obtaining cultures (e.g., community-acquired abdominal sepsis with bowel perforation) ([108]). In others, cultures may have followed antimicrobial therapy. Further, almost half of patients with suspected sepsis in one study have been adjudicated in post hoc analysis to lack infection or represent only "possible" sepsis ([120]). Given the adverse societal and individual risks to continued unnecessary antimicrobial therapy, we recommend thoughtful de-escalation of antimicrobials based on adequate clinical improvement even if cultures are negative. When infection is found not to be present, antimicrobial therapy should be stopped promptly to minimize the likelihood that the patient will become infected with an antimicrobial-resistant pathogen or develop a drug-related adverse effect. Thus, the decisions to continue, narrow, or stop antimicrobial therapy must be made on the basis of clinician judgment and clinical information.

A systemic inflammatory response without infection does not mandate antimicrobial therapy. Examples of conditions that may exhibit acute inflammatory signs without infection include severe pancreatitis and extensive burn injury. Sustained systemic antimicrobial therapy in the absence of suspected infection should be avoided in these situations to minimize the likelihood that the patient will become infected with an antimicrobial-resistant pathogen or will develop a drug-related adverse effect.

Although the prophylactic use of systemic antimicrobials for severe necrotizing pancreatitis has been recommended in the past, recent guidelines have favoured avoidance of this approach ([121]). The current position is supported by meta-analyses that demonstrate no clinical advantage of prophylactic antibiotics that would outweigh their long-term adverse effects ([122]). Similarly, prolonged systemic antimicrobial prophylaxis has been used in the past for patients with severe burns. However, recent meta-analyses suggest questionable clinical benefit with this approach ([123, 124]). Current guidelines for burn management do not support sustained antimicrobial prophylaxis ([101]). Summarizing the evidence is challenging due to the diversity of the population. The quality of evidence was low for mortality in pancreatitis ([122]) and low for burns; therefore, we believe this recommendation is better addressed as a BPS, in which the alternative of administering antibiotics without indicators of infection is implausible ([122–124]). Despite our recommendation against sustained systemic antimicrobial prophylaxis generally, brief antibiotic prophylaxis for specific invasive procedures may be appropriate. In addition, if there is a strong suspicion of concurrent sepsis or septic shock in patients with a severe inflammatory state of non-infectious origin (despite overlapping clinical presentations), antimicrobial therapy is indicated.

Early optimization of antimicrobial pharmacokinetics can improve the outcome of patients with severe infection. Several considerations should be made when determining optimal dosing for critically ill patients with sepsis and septic shock. These patients have distinct differences from the typical infected patient that affect the optimal antimicrobial management strategy. These differences include an increased frequency of hepatic and renal dysfunction, a high prevalence of unrecognized immune dysfunction, and a predisposition to infection with resistant organisms. Perhaps most importantly with respect to initial empiric antimicrobial dosing is an increased volume of distribution for most

antimicrobials, in part due to the rapid expansion of extracellular volume as a consequence of aggressive fluid resuscitation. This results in an unexpectedly high frequency of suboptimal drug levels with a variety of antimicrobials in patients with sepsis and septic shock ([125–128]). Early attention to appropriate antimicrobial dosing is central to improving outcome given the marked increase in mortality and other adverse outcomes if there is a failure of rapid initiation of effective therapy. Antimicrobial therapy in these patients should always be initiated with a full, high end-loading dose of each agent used.

Different antimicrobials have different required plasma targets for optimal outcomes. Failure to achieve peak plasma targets on initial dosing has been associated with clinical failure with aminoglycosides ([129]). Similarly, inadequate early vancomycin trough plasma concentrations (in relation to pathogen minimum inhibitory concentration [MIC]) have been associated with clinical failure for serious MRSA infections ([130]) (including nosocomial pneumonia ([131]) and septic shock ([132]). The clinical success rate for treatment of serious infections correlates with higher peak blood levels (in relation to pathogen MIC) of fluoroquinolones (nosocomial pneumonia and other serious infections) ([133–135]) and aminoglycosides (gram-negative bacteraemia, nosocomial pneumonia, and other serious infections) ([129, 136]). For β-lactams, superior clinical and microbiologic cures appear to be associated with a longer duration of plasma concentration above the pathogen MIC, particularly in critically ill patients ([137–140]).

The optimal dosing strategy for aminoglycosides and fluoroquinolones involves optimizing peak drug plasma concentrations. For aminoglycosides, this can most easily be attained with once daily dosing (5–7 mg/kg daily gentamicin equivalent). Once-daily dosing yields at least comparable clinical efficacy with possibly decreased renal toxicity compared to multiple daily dosing regimens ([141, 142]). Once-daily dosing of aminoglycosides is used for patients with preserved renal function. Patients with chronically mildly impaired renal function should still receive a once-daily-equivalent dose but would normally have an extended period (up to 3 days) before the next dose. This dosing regimen should not be used in patients with severe renal function in whom the aminoglycoside is not expected to clear within several days. Therapeutic drug monitoring of aminoglycosides in this context is primarily meant to ensure that trough concentrations are sufficiently low to minimize the potential for renal toxicity. For fluoroquinolones, an approach that optimizes the dose within a nontoxic range (e.g., ciprofloxacin, 600 mg every 12 hours, or levofloxacin, 750 mg every 24 hours, assuming preserved renal function) should provide the highest probability of a favourable microbiologic and clinical response ([127, 143, 144]).

Vancomycin is another antibiotic whose efficacy is at least partially concentration-dependent. Dosing to a trough target of 15–20 mg/L is recommended by several authorities to maximize the probability of achieving appropriate pharmacodynamic targets, improve tissue penetration, and optimize clinical outcomes ([145–147]). Pre-dose monitoring of trough concentrations is recommended. For sepsis and septic shock, an IV loading dose of 25–30 mg/kg (based on actual body weight) is suggested to rapidly achieve the target trough drug concentration. A loading dose of 1 gram of vancomycin will fail to achieve early therapeutic levels for a significant subset of patients. In fact, loading doses of antimicrobials with low volumes of distribution (teicoplanin, vancomycin, colistin) are warranted in critically ill patients to more rapidly achieve therapeutic drug levels due to their expanded extracellular volume related to volume expansion following fluid resuscitation ([148–152]).

Loading doses are also recommended for β-lactams administered as continuous or extended infusions to accelerate accumulation of drug to therapeutic levels ([153]). Notably, the required loading dose of any antimicrobial is not affected by alterations of renal function, although this may affect frequency of administration and/or total daily dose.

For β-lactams, the key pharmacodynamics correlate to microbiologic and clinical response is the time that the plasma concentration of the drug is above the pathogen MIC relative to the dosing interval (T > MIC). A minimum T > MIC of 60% is generally sufficient to allow a good clinical response in mild to moderate illness. However, optimal response in severe infections, including sepsis, may be achieved with a T > MIC of 100% ([139]). The simplest way to increase T > MIC is to use increased frequency of dosing (given an identical total daily dose). For example, piperacillin/tazobactam can be dosed at either 4.5 g every 8 hours or 3.375 g every 6 hours for serious infections; all things being equal, the latter would achieve a higher T > MIC. We suggested earlier that initial doses of β-lactams can be given as a bolus or rapid infusion to rapidly achieve therapeutic blood levels. However, following the initial dose, an extended infusion of drug over several hours (which increases T > MIC) rather than the standard 30 minutes has been recommended by some authorities ([154, 155]). In addition, some meta-analyses suggest that extended/continuous infusion of β-lactams may be more effective than intermittent rapid infusion, particularly for relatively resistant organisms and in critically ill patients with sepsis ([140, 156–158]). A recent individual patient data meta-analysis of randomized controlled trials comparing continuous versus intermittent infusion of β-lactam antibiotics in critically ill patients with severe sepsis demonstrated an independent protective effect of continuous therapy after adjustment for other correlates of outcome ([140]).

While the weight of evidence supports pharmacokinetically optimized antimicrobial dosing strategies in critically ill patients with sepsis and septic shock, this is difficult to achieve on an individual level without a broader range of rapid therapeutic drug monitoring options than currently available (i.e., vancomycin, teicoplanin and aminoglycosides). The target group of critically ill, septic patients exhibit a variety of physiologic perturbations that dramatically alter antimicrobial pharmacokinetics. These include unstable hemodynamic, increased cardiac output, increased extracellular volume (markedly increasing volume of distribution), variable kidney and hepatic perfusion (affecting drug clearance) and altered drug binding due to reduced serum albumin ([159]). In addition, augmented renal clearance is a recently described phenomenon that may lead to decreased serum antimicrobial levels in the early phase of sepsis ([160–162]). These factors make individual assessment of optimal drug dosing difficult in critically ill patients. Based on studies with therapeutic drug monitoring, under-dosing (particularly in the early phase of treatment) is common in critically ill, septic patients, but drug toxicity such as central nervous system irritation with β-lactams and renal injury with colistin is also seen ([163–166]). These problems mandate efforts to expand access to therapeutic drug monitoring for multiple antimicrobials for critically ill patients with sepsis.

In light of the increasing frequency of pathogen resistance to antimicrobial agents in many parts of the world, the initial use of multidrug therapy is often required to ensure an appropriately broad-spectrum range of coverage for initial empiric treatment. The use of multidrug therapy for this purpose in severe infections is well understood.

The phrase “combination therapy” in the context of this guideline connotes the use of two different classes of antibiotics (usually a β-lactam with a fluoroquinolone, aminoglycoside, or macrolide) for a single putative pathogen expected to be sensitive to both, particularly for purposes of accelerating pathogen clearance. The term is not used where the purpose of a multidrug strategy is to strictly broaden the range of antimicrobial activity (e.g., vancomycin added to ceftazidime, metronidazole added to an aminoglycoside or an echinocandin added to a β-lactam).

A propensity-matched analysis and a meta-analysis/meta-regression analysis have demonstrated that combination therapy produces higher survival in severely ill septic patients with a high risk of death, particularly in those with septic shock ([167, 168]). A meta-regression study ([167]) suggested benefit with combination therapy in patients with a mortality risk greater than 25%. Several observational studies have similarly shown a survival benefit in very ill patients ([169–172]). However, the aforementioned meta-regression analysis also suggested the possibility of increased mortality risk with combination therapy in low-risk (< 15% mortality risk) patients without septic shock ([167]). One controlled trial suggested that, when using a carbapenem as empiric therapy in a population at low risk for infection with resistant microorganisms, the addition of a fluoroquinolone does not improve patients’ outcomes ([173]). A close examination of the results, however, demonstrates findings consistent with the previously mentioned meta-regression (trend to benefit in septic shock with an absence of benefit in sepsis without shock). Despite the overall favourable evidence for combination therapy in septic shock, direct evidence from adequately powered RCTs is not available to validate this approach definitively. Nonetheless, in clinical scenarios of severe clinical illness (particularly septic shock), several days of combination therapy is biologically plausible and is likely to be clinically useful ([152, 167, 168]) even if evidence has not definitively demonstrated improved clinical outcome in bacteraemia and sepsis without shock ([174, 175]). Thus, we issue a weak recommendation based on low quality of evidence.

A number of other recent observational studies and some small, prospective trials also support initial combination therapy for selected patients with specific pathogens (e.g., severe pneumococcal infection, multidrug-resistant gram-negative pathogens) ([172, 176–182]). Unfortunately, in most cases and pending the development of rapid bedside pathogen detection techniques, the offending pathogen is not known at the time of presentation. Therefore, specifying combination therapy to specific identified pathogens is useful only if more prolonged, targeted combination therapy is contemplated. In addition, with respect to multidrug-resistant pathogens, both individual studies and meta-analyses yield variable results depending on the pathogen and the clinical scenario (179–184). Infectious diseases consultation may be advisable if multidrug-resistant pathogens are suspected. One area of broad consensus on the use of a specific form of combination therapy is for streptococcal toxic shock syndrome, for which animal models and uncontrolled, clinical experience demonstrate a survival advantage with penicillin and clindamycin, the latter as a transcriptional inhibitor to pyrogenic exotoxin superantigens ([109, 185, 186]).

Despite evidence suggesting benefit of combination therapy in septic shock, this approach has not been shown to be effective for ongoing treatment of most other serious infections, including bacteraemia and sepsis without shock ([168, 174, 175]). The term “ongoing treatment” includes extended empiric therapy for culture-negative infections and extended definitive/targeted therapy where a pathogen is identified. In the case of neutropenia in the

absence of septic shock, studies using modern broad-spectrum antibiotics consistently suggest that, while multidrug therapy to broaden pathogen coverage (e.g., to include *Candida* species) may be useful, combination therapy using a β-lactam and an aminoglycoside for purposes of accelerating pathogen clearance is not beneficial for less severely ill "low-risk" patients ([187]). Combination therapy of this sort for even "high-risk" neutropenic patients (inclusive of hemodynamic instability and organ failure) with sepsis is inconsistently supported by several international expert groups ([106, 188]). This position against combination therapy for a single pathogen in any form of neutropenic infection emphatically does not preclude the use of multidrug therapy for the purpose of broadening the spectrum of antimicrobial treatment.

High-quality data on clinically driven de-escalation of antimicrobial therapy for severe infections are limited ([189]). Early de-escalation of antimicrobial therapy in the context of combination therapy as described here has not been studied. However, observational studies have shown that early de-escalation of multidrug therapy is associated with equivalent or superior clinical outcomes in sepsis and septic shock ([54, 190–192]); despite this, at least one study has indicated an increased frequency of superinfection and longer ICU stay ([192]). In addition to institutional benefit with respect to limiting a driver of antimicrobial resistance, early de-escalation can also benefit the individual patient ([193–195]). Although the data are not entirely consistent, on balance, an approach that emphasizes early de-escalation is favoured when using combination therapy.

While substantial consensus on the need for early de-escalation of combination therapy exists, agreement is lacking on precise criteria for triggering de-escalation. Among approaches used by panel members are de-escalation based on: a) clinical progress (shock resolution, decrease in vasopressor requirement, etc.), b) infection resolution as indicated by biomarkers (especially procalcitonin), and c) a relatively fixed duration of combination therapy. This lack of consensus on de-escalation criteria for combination therapy reflects the lack of solid data addressing this issue (notwithstanding procalcitonin data relating to general de-escalation).

Unnecessarily prolonged administration of antimicrobials is detrimental to society and to the individual patient. For society, excessive antimicrobial use drives antimicrobial resistance development and dissemination ([196]). For individual patients, prolonged antibiotic therapy is associated with specific illnesses such as *Clostridium difficile* colitis ([195]) and, more broadly, an increased mortality risk ([54]). The basis of the increased mortality with unnecessarily prolonged and broad antimicrobial therapy has not been convincingly demonstrated, although cumulative antimicrobial toxicity; the occurrence of antimicrobial-associated secondary infections (e.g., *C difficile* colitis); and selection of, and superinfection with, multidrug-resistant pathogens are all potential contributors.

Although patient factors will influence the length of antibiotic therapy, a treatment duration of 7 to 10 days (in the absence of source control issues) is generally adequate for most serious infections ([103, 197–199]). Current guidelines recommend a 7-day course of therapy for nosocomial pneumonia (both hospital-acquired and ventilator-associated pneumonia [VAP]) ([103]). Recent data suggest that some serious infections may be treated with shorter courses especially if there is a need for and successful provision of source control ([200, 201]). Subgroup analysis of the most critically ill subjects (Acute Physiologic and Chronic Health Evaluation

[APACHE] II score greater than either 15 or 20) in the short course of antimicrobials in the intra-abdominal sepsis study of Sawyer et al demonstrated no difference in outcome based on the duration of therapy (as with the overall group) ([200, 202]). A treatment duration of 3 to 5 days or fewer was as effective as a duration of up to 10 days. Similarly, studies have shown that a treatment duration of < 7 days is as effective as longer durations in the management of acute pyelonephritis with or without bacteraemia ([201]), uncomplicated cellulitis ([203]), and spontaneous bacterial peritonitis ([204]). Some conditions are generally thought to require more prolonged antimicrobial therapy. These include situations in which there is a slow clinical response, undrainable foci of infection, bacteraemia with *S aureus* (particularly MRSA) ([67, 104]), candidemia/invasive candidiasis ([105]) and other fungal infections, some viral infections (e.g., herpes, cytomegalovirus), and immunologic deficiencies, including neutropenia ([188]).

Assessment of the required duration of therapy in critically ill patients should include host factors, particularly immune status. For example, patients with neutropenic infection and sepsis usually require therapy for at least the duration of their neutropenia. The nature of the infecting pathogen also plays a role. In particular, uncomplicated *S aureus* bacteraemia requires at least 14 days of therapy, while complicated bacteraemia requires treatment as an endovascular infection with 6 weeks of therapy. Uncomplicated bacteraemia has been defined as: 1) exclusion of endocarditis, 2) no implanted prostheses, 3) negative results of follow-up blood cultures drawn 2 to 4 days after the initial set, 4) defervescence within 72 hours after the initiation of effective antibiotic therapy, and 5) no evidence of metastatic infection ([104]). Patients with candidemia (whether or not catheter-associated) and deep *Candida* infections, whether or not associated with sepsis, require more prolonged therapy ([105, 205]). Highly resistant gram-negative pathogens with marginal sensitivity to utilized antimicrobials may be slow to clear and represent another example. The nature and site of infection may also affect duration of therapy. Larger abscesses and osteomyelitis have limited drug penetration and require longer therapy. Although it is well known that endocarditis requires prolonged antimicrobial therapy, severe disease more typically presents as cardiac failure/cardiogenic shock and emboli rather than as sepsis or septic shock ([206, 207]). A variety of other factors may play a role in determining the optimal duration of therapy, particularly in critically ill infected patients. If the clinician is uncertain, infectious diseases consultation should be sought.

Few of the studies noted focused on patients with septic shock, sepsis with organ failure, or even critical illness. To an extent, standard recommendations on duration of therapy in this document depend on inferences from less ill cohorts. Therefore, decisions to narrow or stop antimicrobial therapy must ultimately be made on the basis of sound clinical judgment

There are many reasons for unnecessarily prolonged antimicrobial therapy. For complicated, critically ill patients admitted with serious infections, non-infectious concurrent illness and medical interventions may produce signs and symptoms consistent with active infection (even following control of infection). For example, pulmonary infiltrates and shortness of breath may be caused by pulmonary oedema in addition to pneumonia; an elevated white cell count may occur as a consequence of corticosteroid administration or physiologic stress; fever may be associated with certain drugs, including β-lactams and phenytoin. In addition, there is a natural tendency to want to continue a therapy that is often seen as benign long

enough to be confident of cure. However, as discussed, antimicrobials are not an entirely benign therapy. In low-risk patients, the adverse effects can outweigh any benefit.

Given the potential harm associated with unnecessarily prolonged antimicrobial therapy, daily assessment for de-escalation of antimicrobial therapy is recommended in patients with sepsis and septic shock. Studies have shown that daily prompting on the question of antimicrobial de-escalation is effective and may be associated with improved mortality rates ([55, 208]).

During the past decade, the role of biomarkers to assist in the diagnosis and management of infections has been extensively explored. The use of galactomannan and β-D-glucan to assist in the assessment of invasive aspergillus (and a broad range of fungal pathogens) has become well accepted ([209, 210]). Similarly, measurement of serum procalcitonin is commonly used in many parts of the world to assist in the diagnosis of acute infection and to help define the duration of antimicrobial therapy. Various procalcitonin-based algorithms have been used to direct de-escalation of antimicrobial therapy in severe infections and sepsis ([211–216]). However, it is not clear that any particular algorithm provides a clinical advantage over another. A large body of literature suggests that use of such algorithms can speed safe antimicrobial de-escalation compared to standard clinical approaches with reduced antimicrobial consumption without an adverse effect on mortality. Recently, a large randomized trial on procalcitonin use in critically ill patients with presumed bacterial infection demonstrated evidence of a reduction in duration of treatment and daily defined doses of antimicrobials ([217]). However, given the design of the study, the reduction could have been related to a prompting effect as seen in other studies ([55, 218]). In addition, the procalcitonin group showed a significant reduction in mortality. This finding is congruent with studies demonstrating an association between early antimicrobial de-escalation and survival in observational studies of sepsis and septic shock ([54, 55]). This benefit is uncertain, though, because another meta-analysis of randomized controlled studies of de-escalation failed to demonstrate a similar survival advantage ([219]). Meta-analyses also suggest that procalcitonin can also be used to assist in differentiating infectious and non-infectious conditions at presentation ([211, 214, 216]). The strongest evidence appears to relate to bacterial pneumonia versus non-infectious pulmonary pathology ([216, 220]), where meta-analysis suggests that procalcitonin may assist in predicting the presence of bacteraemia, particularly in ICU patients ([221]).

No evidence to date demonstrates that the use of procalcitonin reduces the risk of antibiotic-related diarrhoea from *C difficile*. However, the occurrence of *C difficile* colitis is known to be associated with cumulative antibiotic exposure in individual patients ([195]), so such a benefit is likely. In addition, although prevalence of antimicrobial resistance has not been shown to be reduced by the use of procalcitonin, the emergence of antimicrobial resistance is known to be associated with total antimicrobial consumption in large regions ([196]).

It is important to note that procalcitonin and all other biomarkers can provide only supportive and supplemental data to clinical assessment. Decisions on initiating, altering, or discontinuing antimicrobial therapy should never be made solely on the basis of changes in any biomarker, including procalcitonin.

Sterilization of cultures can occur within minutes to hours after the first dose of an appropriate antimicrobial (49, 50). Obtaining cultures prior to the administration of antimicrobials significantly increases the yield of cultures, making identification of a pathogen more likely. Isolation of an infecting organism(s) allows for de-escalation of antimicrobial therapy first at the point of identification and then again when susceptibilities are obtained. De-escalation of antimicrobial therapy is a mainstay of antibiotic stewardship programs and is associated with less resistant microorganisms, fewer side effects, and lower costs (51). Several retrospective studies have suggested that obtaining cultures prior to antimicrobial therapy is associated with improved outcome (52, 53). Similarly, de-escalation has also been associated with improved survival in several observational studies (54, 55). The desire to obtain cultures prior to initiating antimicrobial therapy must be balanced against the mortality risk of delaying a key therapy in critically ill patients with suspected sepsis or septic shock who are at significant risk of death (56, 57).

We recommend that blood cultures be obtained prior to initiating antimicrobial therapy if cultures can be obtained in a timely manner. However, the risk/benefit ratio favours rapid administration of antimicrobials if it is not logistically possible to obtain cultures promptly. Therefore, in patients with suspected sepsis or septic shock, appropriate routine microbiologic cultures should be obtained before initiation of antimicrobial therapy from all sites considered to be potential sources of infection if it results in no substantial delay in the start of antimicrobials. This may include blood, cerebrospinal fluid, urine, wounds, respiratory secretions, and other body fluids, but does not normally include samples that require an invasive procedure such as bronchoscopy or open surgery. The decision regarding which sites to culture requires careful consideration from the treatment team. “Pan culture” of all sites that could potentially be cultured should be discouraged (unless the source of sepsis is not clinically apparent), because this practice can lead to inappropriate antimicrobial use (58). If history or clinical examination clearly indicates a specific anatomic site of infection, cultures of other sites (apart from blood) are generally unnecessary. We suggest 45 minutes as an example of what may be considered to be no substantial delay in the initiation of antimicrobial therapy while cultures are being obtained.

Two or more sets (aerobic and anaerobic) of blood cultures are recommended before initiation of any new antimicrobial in all patients with suspected sepsis (59). All necessary blood cultures may be drawn together on the same occasion. Blood culture yield has not been shown to be improved with sequential draws or timing to temperature spikes (60, 61). Details on appropriate methods to draw and transport blood culture samples are enumerated in other guidelines (61, 62).

In potentially septic patients with an intravascular catheter (in place > 48 hours) in whom a site of infection is not clinically apparent or a suspicion of intravascular catheter-associated infection exists, at least one blood culture set should be obtained from the catheter (along with simultaneous peripheral blood cultures). This is done to assist in the diagnosis of a potential catheter-related bloodstream infection. Data are inconsistent regarding the utility of differential time to blood culture positivity (i.e., equivalent volume blood culture from the vascular access device positive more than 2 hours before the peripheral blood culture) in suggesting that the vascular access device is the source of the infection (63–65). It is important to note that drawing blood cultures from an intravascular catheter in case of

possible infection of the device does not eliminate the option of removing the catheter (particular non-tunnelled catheters) immediately afterward.

In patients without a suspicion of catheter-associated infection and in whom another clinical infection site is suspected, at least one blood culture (of the two or more that are required) should be obtained peripherally. However, no recommendation can be made as to where additional blood cultures should be drawn. Options include a) all cultures drawn peripherally via venepuncture, b) cultures drawn through each separate intravascular device but not through multiple lumens of the same intravascular catheter, or c) cultures drawn through multiple lumens in an intravascular device (66–70).

In the near future, molecular diagnostic methods may offer the potential to diagnose infections more quickly and more accurately than current techniques. However, varying technologies have been described, clinical experience remains limited, and additional validation is needed before recommending these methods as an adjunct to or replacement for standard blood culture techniques (71–73). In addition, susceptibility testing is likely to require isolation and direct testing of viable pathogens for the foreseeable future.

Recommendation 15: (SSCG Section C, Recommendation 1)
We recommend that appropriate routine microbiologic cultures (including blood) be obtained before starting antimicrobial therapy in patients with suspected sepsis or septic shock if doing so results in no substantial delay in the start of antimicrobials .
Quality/level of evidence: Low + Strength of recommendation: BPS

SSC remarks: Appropriate routine microbiologic cultures always include at least two sets of blood cultures (aerobic and anaerobic).

START SMART
Recommendation 16. (SSCG Section D, Recommendation 1)
We recommend that administration of IV antimicrobials be initiated as soon as possible after recognition and within one hour for both sepsis and septic shock.
Quality/level of evidence: Moderate + Strength of recommendation: Strong

Recommendation 17. (SSCG Section D, Recommendation 2).
We recommend empiric broad-spectrum therapy with one or more antimicrobials for patients presenting with sepsis or septic shock to cover all likely pathogens (including bacterial and potentially fungal or viral coverage).
Quality/level of evidence: Moderate + Strength of recommendation: Strong

Recommendation 18. (SSCG Section D, Recommendation 5)
We recommend that dosing strategies of antimicrobials be optimized based on accepted pharmacokinetic/pharmacodynamic principles and specific drug properties in patients with **sepsis** or **septic shock**.
Quality/level of evidence: Low + Strength of recommendation: BPS

Recommendation 19. (SSCG Section D, Recommendation 6)

We suggest empiric combination therapy (using at least two antibiotics of different antimicrobial classes) aimed at the most likely bacterial pathogen(s) for the initial management of **septic shock**
Quality/level of evidence: Low **+ Strength of recommendation: Weak**

SSC Remarks: Readers should review Table 2 for definitions of empiric, targeted/definitive, broad-spectrum, combination, and multidrug therapy.

Recommendation 20. (SSCG Section D, Recommendation 7)
We suggest that combination therapy not be routinely used for ongoing treatment of most other serious infections, including bacteraemia and sepsis without shock.
Quality/level of evidence: Weak **+ Strength of recommendation: Low**

SSC Remarks: This does not preclude the use of multidrug therapy to broaden antimicrobial activity.

Recommendation 21. (SSCG Section D, Recommendation 8)
We recommend against combination therapy for the routine treatment of neutropenic sepsis/bacteraemia**.**
Quality/level of evidence: Moderate **+ Strength of recommendation: Strong**

SSC Remarks*:* This does not preclude the use of multidrug therapy to broaden antimicrobial activity.

THEN FOCUS
Recommendation 22. (SSCG Section D, Recommendation 3).
We recommend that empiric antimicrobial therapy be narrowed once pathogen identification and sensitivities are established and/or adequate clinical improvement is noted.
Quality/level of evidence: Low **+ Strength of recommendation: BPS**

Recommendation 23. (SSCG Section D, Recommendation 9)
If combination therapy is initially used for septic shock, we recommend de-escalation with discontinuation of combination therapy within the first few days in response to clinical improvement and/or evidence of infection resolution. This applies to both targeted (for culture-positive infections) and empiric (for culture-negative infections) combination therapy.
Quality/level of evidence: Low **+ Strength of recommendation: BPS**

Recommendation 24. (SSCG Section D, Recommendation 13).
We recommend daily assessment for de-escalation of antimicrobial therapy in patients with sepsis and septic shock.
Quality/level of evidence: Low **+ Strength of recommendation: BPS**

Recommendation 25. (SSCG Section D, Recommendation 4).
We recommend against sustained systemic antimicrobial prophylaxis in patients with severe inflammatory states of non-infectious origin (e.g., severe pancreatitis, burn injury)**.**
Quality/level of evidence: Low **+ Strength of recommendation: BPS**

Recommendation 26. (SSCG Section D, Recommendation 14).

We suggest that measurement of procalcitonin levels can be used to support shortening the duration of antimicrobial therapy in sepsis patients.
Quality/level of evidence: Low + Strength of recommendation: Weak

Recommendation 27. (SSCG Section D, Recommendation 15).
We suggest that procalcitonin levels can be used to support the discontinuation of empiric antibiotics in patients who initially appeared to have sepsis, but subsequently have limited clinical evidence of infection.
Quality/level of evidence: Low + Strength of recommendation: Weak

Recommendation 28. (SSCG Section D, Recommendation 10).
We suggest that an antimicrobial treatment duration of 7 to 10 days is adequate for most serious infections associated with sepsis and septic shock.
Quality/level of evidence: Low + Strength of recommendation: Weak

Recommendation 29. (SSCG Section D, Recommendation 11).
We suggest that longer courses are appropriate in patients who have a slow clinical response, undrainable foci of infection, bacteremia with S aureus, some fungal and viral infections, or immunologic deficiencies, including neutropenia.
Quality/level of evidence: Low + Strength of recommendation: Weak

Recommendation 30. (SSCG Section D, Recommendation 12).
We suggest that shorter courses are appropriate in some patients, particularly those with rapid clinical resolution following effective source control of intra-abdominal or urinary sepsis and those with anatomically uncomplicated pyelonephritis.
Quality/level of evidence: Low + Strength of recommendation: Weak

TABLE 15. IMPORTANT TERMINOLOGY FOR ANTIMICROBIAL RECOMMENDATIONS (REF)

Empiric therapy	Initial therapy started in the absence of definitive microbiologic pathogen identification. Empiric therapy may be mono- combination, or broad-spectrum, and/or multidrug in nature.
Targeted/definitive therapy	Therapy targeted to a specific pathogen (usually after microbiologic identification). Targeted/definitive therapy may be mono- or combination, but is not intended to be broad-spectrum
Broad-spectrum therapy	The use of one or more antimicrobial agents with the specific intent of broadening the range of potential pathogens covered, usually during empiric therapy (e.g., piperacillin/tazobactam, vancomycin, and anidulafungin; each is used to cover a different group of pathogens). Broadspectrum therapy is typically empiric since the usual purpose is to ensure antimicrobial coverage with at least one drug when there is uncertainty about the possible pathogen. On occasion, broadspectrum therapy may be continued into the targeted/definitive therapy phase if multiple pathogens are isolated.
Multidrug therapy	Therapy with multiple antimicrobials to deliver broad-spectrum therapy (i.e., to broaden coverage) for empiric therapy (i.e., where pathogen is unknown) or to potentially accelerate pathogen clearance (combination therapy) with respect to a specific pathogen(s) where the pathogen(s) is known or suspected (i.e., for both

	targeted or empiric therapy). This term therefore includes combination therapy.
Combination therapy	The use of multiple antibiotics (usually of different mechanistic classes) with the specific intent of covering the known or suspected pathogen(s) with more than one antibiotic (e.g., piperacillin/tazobactam and an aminoglycoside or fluoroquinolone for gram-negative pathogens) to accelerate pathogen clearance rather than to broaden antimicrobial coverage. Other proposed applications of combination therapy include inhibition of bacterial toxin production (e.g., clindamycin with β-lactams for streptococcal toxic shock) or potential immune modulatory effects (macrolides with a β-lactam for pneumococcal pneumonia).

Antimicrobial Stewardship

Implementation Point 10 (Recommendations 16 & 17)

Managing sepsis in the era of increasing rates of multi-drug resistant organisms (MDRO) should be linked tightly with antimicrobial stewardship[18, 19]. Coupled with rising rates of MDRO, few new antimicrobials are being developed, therefore, prescribing antimicrobials appropriately is essential for both patient safety (to minimise adverse effects) and for future generations (so effective antimicrobials are available to manage infection and sepsis). It is recommended that the 'Start Smart and then Focus' (Appendix 13), approach is employed for antimicrobial therapy[44].

Starting smart: Intravenous antimicrobials are administered as part of the Sepsis 6 bundle within one hour of diagnosis of infection in patients screened to be at high risk of mortality from sepsis. (See Section A; Screening).

All acute hospitals have guidelines for the empiric use of antimicrobials in adults that are appropriate for the local MDRO epidemiology. It is recommended that these guidelines be used to choose empiric therapy for patients with infection, taking the following into consideration:

1. Source of the infection
    - Community acquired
    - Health-care associated
    - Hospital acquired.
2. Site of the infection

Based on the history and the examination of the patient e.g. respiratory, abdominal, genito-urinary, device or catheter-related, cellulitis, central nervous system, bone or joint or unknown.

3. Patient considerations

Patient factors that need to be taken into consideration and may influence the choice of empiric antimicrobial therapy include:

- Group B Streptococcus
- Group A Streptococcus (associated high mortality in maternity)
- Previous infection or colonisation with MDRO such as meticillin resistant *Staphylococcus aureus* (MRSA), extended-spectrum B-lactamase (ESBL) producing /gram negative organism etc.
- Recent antimicrobial therapy
- Current outbreaks

- Recent infections in close contacts
- Recent travel or hospitalization and/or residence in another country
- Allergy status.

Penicillin allergy is frequently reported and if inaccurate may compromise patient care. Getting a clear description of the reported reaction to penicillin distinguishes between allergy and side-effect and more accurately describes an allergic response. The majority (90%-99%) of patients with a reported penicillin allergy do not have immediate hypersensitivity and approximately 1% of patients with an allergy to penicillin will also react to cephalosporins. [45] Thus a patient, who develops a rash in response to penicillin, may be considered low risk for treatment with a cephalosporin, but someone with angio-oedema or cardiovascular collapse at higher high risk.

Implementation Point 11 (Recommendation 18)

Empiric antimicrobial therapy should be prescribed at the optimal dose, frequency and duration, based on individual patient characteristics (e.g. age, weight, renal function), likely causative organism, site of infection, and pharmacokinetic and pharmacodynamic characteristics of the antimicrobial agent(s). For certain antimicrobials (e.g., aminoglycosides), it is essential that serum for therapeutic drug monitoring is measured appropriately, and the results acted upon in a timely manner. Local antimicrobial guidelines include recommendations on dosing, weight calculation and intravenous (IV) to oral (PO) switch and they should be consulted to ensure dose optimisation.

Implementation Point 12 (Recommendation 19)

The two-drug combination for septic shock is based on the likely source of the infection, rising MDRO rates and the fact that in some instances the source of infection may not be apparent. In guidelines that use the terminology of sepsis, severe sepsis and septic shock, use the guidance for severe sepsis for patients with acute organ dysfunction due to infection irrespective of the terminology used and the guidance for septic shock for patients on vasopressors/ inotropes due to acute infection.

Implementation Point 13 (Recommendations 20 & 21)

NB. Local guidelines should be taken into account when considering combination antimicrobial therapy for sepsis. The choice of single or combination agents may vary depending on local MDRO epidemiology.

Roles and responsibilities:

It is the responsibility of each acute hospital to have local antimicrobial guidelines that are readily available to clinicians at all times. These guidelines should be under the governance of the antimicrobial stewardship committee[19]. A clinical microbiologist or infectious disease specialist should be available for consultation on complex cases at a Consultant to Consultant level. It is the responsibility of treating clinicians to be familiar with accessing the local guideline and with its use in guiding empiric therapy.

THEN FOCUS:

Implementation Point 14 (Recommendations 22 & 23)

Empiric antimicrobial therapy should be rationalized on the basis of ongoing clinical review and results of laboratory investigations and diagnostic imaging, as outlined in the Start Smart Then Focus care bundle[44]. All empiric antimicrobial therapy should be reviewed on a daily basis by the clinician responsible for the patient's care. To ensure continuity of care and in light of changing work practices in hospitals, it is recommended that all antimicrobial prescriptions have a documented review date and indication for the prescription to facilitate safe handover of patient care. It is recommended that local antimicrobial prescribing guidelines are consulted for the criteria for converting parenteral antimicrobial therapy to oral therapy, once the patient's condition allows.

Implementation Point 15 (Recommendations 26, 27, 28, 29 & 30)

An essential component of antimicrobial stewardship is restricting antimicrobial prescription durations to the minimum duration required for clinical efficacy. As recommended previously in this NCG, all antimicrobial prescriptions should have the proposed duration documented and should be reviewed on a daily basis. Procalcitonin is a serum biomarker that is useful in distinguishing bacterial infection from other causes of infection or inflammation and may be useful in guiding duration of antimicrobial therapy[46]. Most data is from patients with lower respiratory infection in the critical care setting[47]. In addition, procalcitonin does not replace clinical judgment and provides only supportive and supplemental data to clinical assessment[48]. There are a number of limitations with procalcitonin as a stewardship tool, including suboptimal sensitivity and/or specificity, which makes a careful interpretation in the clinical context essential. In addition they are not available widely and knowledge regarding their use is evolving.

Implementation Point 16 (Recommendation 24 & 25)

When a patient presents unwell or deteriorates, a list of potential diagnoses is formed, based on history and examination, and tests and investigations are ordered to help confirm the diagnosis. Sepsis screening recommends the Sepsis 6 bundle/Sepsis 6 +1 be administered to patients with a clinical suspicion of infection who are in one of the three high-risk groups. If a non-infectious diagnosis is identified, and there is no reasonable suspicion of a concurrent infection, antimicrobial therapy should be stopped.

Then focus: Roles and responsibilities:

It is the responsibility of the treating team, or its delegate, to review the patient daily and to assess the antimicrobial therapy in terms of the patients' clinical response and laboratory results during the acute phase of the illness and to decide on and document the duration of treatment appropriate to the illness.

Implementation Point 17 (Recommendations 15)

Blood cultures are taken as part of the Sepsis 6 bundle prior to antimicrobial administration. This will maximize the yield of positive cultures, which can then be used to guide appropriate antimicrobial management, with reduced use of broad-spectrum empiric therapy and associated complications due to multi-drug resistant organisms and antibiotic-associated diarrhoea. Blood cultures should always be taken using an aseptic (no touch) technique. Care should be taken to prevent contamination when obtaining cultures as this may lead to the initiation of unnecessary antimicrobial therapy and investigations, potential adverse events, as well as lengthening hospital stays and costs. The acceptable rate for

contamination rates is < 3%[42]. It is recommended that units regularly audit their contamination rates and review their practices accordingly. Pre-packed blood culture sets and strategies to ensure aseptic technique have been shown to reduce contamination rates[43]. Practical considerations have to be taken into account, for example, if a unit has the practice that the blood cultures are drawn from the intravenous cannula, then that cannula must be inserted with aseptic technique and the blood culture be taken as the first draw and the culture bottle immediately inoculated. When possible, it is recommended that blood cultures be taken via a separate puncture.

Other specimens for culture will be based on the clinical history and examination and targeting the suspected site of infection. This includes cultures being taken through potential infected central lines. If source is being controlled it is recommended that specimens (e.g. pus, joint fluid) be sent for microbiological assessment, this should not lead to a delay in administering antimicrobials in patients with sepsis and septic shock.

Roles and responsibilities:
Administering the Sepsis 6 bundle/Sepsis 6 +1 correctly and in a timely fashion requires multi-disciplinary cooperation and processes to be put in place to facilitate achieving this goal. Components of the bundle can be performed by different team members depending on their training and experience and the policies of different institutions. Local policies should be developed to facilitate this, in the best interest of the patient. Resources such as "Sepsis Trolleys", or similar, with all the components required for Sepsis 6/Sepsis 6+1 delivery and "blood culture packs" may facilitate timely and appropriate care.

It is the responsibility of the treating Doctor to complete and sign off on the sepsis form. In the event of a handover occurring mid-treatment, a verbal handover of care and outstanding tasks should be given, and the Handover section of the sepsis form filled. It is then the responsibility of the receiving Doctor to complete and sign off the form.

It is the responsibility of hospital management to ensure that sepsis forms are available along with the necessary components of the Sepsis 6 bundle, in a time-accessible way, so that this intervention can be completed.

It is the responsibility of the treating team, or its delegate, to review the patient daily and to assess the antimicrobial therapy in terms of the patients' clinical response and laboratory results during the acute phase of the illness and to decide on and document the duration of treatment appropriate to the illness.

3.1.4 Source Control

Key questions

- *In patients with sepsis or septic shock, should we attempt early (within 12 hours) source control?*

SSCG Rationale

The principles of source control in the management of sepsis and septic shock include rapid diagnosis of the specific site of infection and determination of whether that infection site is amenable to source control measures (specifically the drainage of an abscess, debridement

of infected necrotic tissue, removal of a potentially infected device, and definitive control of a source of ongoing microbial contamination) ([222]). Foci of infection readily amenable to source control include intra-abdominal abscesses, gastrointestinal perforation, ischemic bowel or volvulus, cholangitis, cholecystitis, pyelonephritis associated with obstruction or abscess, necrotizing soft tissue infection, other deep space infection (e.g., empyema or septic arthritis), and implanted device infections.

Infectious foci suspected to cause septic shock should be controlled as soon as possible following successful initial resuscitation ([223, 224]). A target of no more than 6 to 12 hours after diagnosis appears to be sufficient for most cases ([223–229]). Observational studies generally show reduced survival beyond that point. The failure to show benefit with even earlier source control implementation may be a consequence of the limited number of patients in these studies. Therefore, any required source control intervention in sepsis and septic shock should ideally be implemented as soon as medically and logistically practical after the diagnosis is made.

Clinical experience suggests that, without adequate source control, some more severe presentations will not stabilize or improve despite rapid resuscitation and provision of appropriate antimicrobials. In view of this fact, prolonged efforts at medical stabilization prior to source control for severely ill patients, particularly those with septic shock, are generally not warranted ([108]).

The selection of optimal source control methods must weigh the benefits and risks of the specific intervention, risks of transfer for the procedure, potential delays associated with a specific procedure, and the probability of the procedure's success. Source control interventions may cause further complications, such as bleeding, fistulas, or inadvertent organ injury. In general, the least invasive effective option for source control should be pursued. Open surgical intervention should be considered when other interventional approaches are inadequate or cannot be provided in a timely fashion. Surgical exploration may also be indicated when diagnostic uncertainty persists despite radiologic evaluation or when the probability of success with a percutaneous procedure is uncertain and the mortality risk as a consequence of a failed procedure causing delays is high. Specific clinical situations require consideration of available choices, the patient's preferences, and the clinician's expertise. Logistic factors unique to each institution, such as surgical or interventional staff availability, may also play a role in the decision.

Intravascular devices such as central venous catheters can be the source of sepsis or septic shock. An intravascular device suspected to be a source of sepsis should generally be removed promptly after establishing another site for vascular access. In the absence of both septic shock and fungemia, some implanted, tunnelled catheter infections may be able to be treated effectively with prolonged antimicrobial therapy if removal of the catheter is not practical ([67]). However, catheter removal (with antimicrobial therapy) is definitive and is preferred where possible.

Recommendation 31. (SSCG Section E, Recommendation 1)
We recommend that a specific anatomic diagnosis of infection requiring emergent source control be identified or excluded as rapidly as possible in patients with sepsis or septic

shock, and that any required source control intervention be implemented as soon as medically and logistically practical after the diagnosis is made
Quality/level of evidence: Low + Strength of recommendation: BPS

Recommendation 32. (SSCG Section E, Recommendation 2)
We recommend prompt removal of intravascular access devices that are a possible source of sepsis or septic shock after other vascular access has been established
Quality/level of evidence: Low + Strength of recommendation: BPS

Implementation Point 17 (Recommendation 31 & 32)

In order to achieve compliance with these recommendations a number of steps need to occur:

1. Identification of the need for source control
2. Access to diagnostics
3. Feasibility of achieving source control
4. Identifying the best method available
5. Access to interventional radiology/ surgery

Infected collections and devitalised tissues cannot be effectively managed by antimicrobials alone and thus need to be drained or debrided. In patients with sepsis and/or septic shock antimicrobials should not be delayed more than 1 hour from differential diagnosis (Time Zero) to facilitate microbiological sampling of the collection. Patients with suspicion of an infectious collection but with no evidence of acute organ dysfunction or shock should be managed according to usual pathways and monitored for deterioration. In the event that deterioration occurs, as evidenced by a new NEWS score ≥ 4, the development of acute organ dysfunction or exercising professional judgment, the Sepsis 6 bundle should be administered, and source control achieved as soon as practicable but ideally within 12 hours of deterioration.

Patients whose infection is not settling on appropriate antimicrobials need to be re-assessed for source control including reviewing implanted devices and catheters as potential sources. If such devices are potential sources, they should be removed or treated where possible and sent for culture and antimicrobial susceptibility testing.

If source control is required, it should be performed promptly as soon as medically and logistically practicable.

Maternity only

If the need for source control involves evacuation of the uterus, it is recommended that this be performed as soon as practicable following usual communication and procedural pathways. Inform consultant obstetrician, anaesthetist, clinical microbiologist and as applicable, neonatologist.

Roles and responsibilities:

It is the responsibility of the treating clinician to assess and refer for source control as indicated. It is the responsibility of the effector of source control (surgery, interventional radiology, other) to take into consideration the severity of illness and the time of

presentation when organizing the time for source control which should be done as soon as practical.

It is the responsibility of the hospital management to ensure sufficient resources are in place to enable clinicians to achieve source control in a timely manner.

3.1.5 Vasoactive medications

Key questions

- *In patients with septic shock requiring vasopressors, should we use norepinephrine versus other agents?*
- *In patients with septic shock not responding to single vasopressors, should we add epinephrine?*
- *In patients with septic shock requiring vasopressors, should we use norepinephrine alone versus combination with vasopressin?*
- *In patients with septic shock requiring vasopressors, should we use of vasopressin versus other agents?*
- *In patients with septic shock requiring vasopressors, should we use dopamine versus other agents?*
- *In patients with septic shock and persistent hypoperfusion, should we use alternative inotropic agents to increase cardiac output?*

SSCG Rationale

The physiologic effects of vasopressors and combined inotrope/vasopressor selection in septic shock are outlined in an extensive number of literature reviews ([252–261]). Norepinephrine increases MAP due to its vasoconstrictive effects, with little change in heart rate and less increase in stroke volume compared with dopamine. Dopamine increases MAP and cardiac output, primarily due to an increase in stroke volume and heart rate. Norepinephrine is more potent than dopamine and may be more effective at reversing hypotension in patients with septic shock. Dopamine may be particularly useful in patients with compromised systolic function but causes more tachycardia and may be more arrhythmogenic than norepinephrine ([262]). It may also influence the endocrine response via the hypothalamic pituitary axis and may have immunosuppressive effects ([263]). However, a recent systematic review and meta-analysis that included 11 randomized trials (n =1,710) comparing norepinephrine to dopamine does not support the routine use of dopamine in the management of septic shock ([264]). Indeed, norepinephrine use resulted in lower mortality (RR, 0.89; 95% CI, 0.81–0.98, high-quality evidence) and lower risk of arrhythmias (RR, 0.48; 95% CI, 0.40–0.58; high-quality evidence) compared with dopamine (Supplemental Digital Content 8, http://links.lww.com/CCM/C329).

Human and animal studies suggest that the infusion of epinephrine may have deleterious effects on the splanchnic circulation and produces hyperlactatemia. However, clinical trials do not demonstrate worsening of clinical outcomes. One RCT comparing norepinephrine to epinephrine demonstrated no difference in mortality but an increase in adverse drug-

related events with epinephrine ([265]). Similarly, a meta-analysis of four randomized trials (n = 540) comparing norepinephrine to epinephrine found no significant difference in mortality (RR, 0.96; CI, 0.77−1.21; low-quality evidence) (Supplemental Digital Content 9, http://links.lww.com/CCM/C330) ([264]). Epinephrine may increase aerobic lactate production via stimulation of skeletal muscle β2-adrenergic receptors and thus may preclude the use of lactate clearance to guide resuscitation.

Vasopressin levels in septic shock have been reported to be lower than anticipated for a shock state ([266]). Low doses of vasopressin may be effective in raising blood pressure in patients refractory to other vasopressors and may have other potential physiologic benefits ([266–271]). Terlipressin has similar effects, but is long-acting ([272]). Studies show that vasopressin concentrations are elevated in early septic shock, but decrease to normal range in the majority of patients between 24 and 48 hours as shock continues ([273]). This finding has been called *relative vasopressin deficiency* because, in the presence of hypotension, vasopressin would be expected to be elevated. The significance of this finding is unknown. The VASST trial, an RCT comparing norepinephrine alone to norepinephrine plus vasopressin at 0.03 U/min, showed no difference in outcome in the intent-to-treat population ([274]). An a priori defined subgroup analysis demonstrated improved survival among patients receiving <15 μg/min norepinephrine at randomization with the addition of vasopressin; however, the pretrial rationale for this stratification was based on exploring potential benefit in the population requiring ≥ 15 μg/min norepinephrine. Higher doses of vasopressin have been associated with cardiac, digital, and splanchnic ischemia and should be reserved for situations in which alternative vasopressors have failed ([275]). In the VANISH trial, 409 patients with septic shock were randomized in a factorial (2 × 2) design to receive vasopressin with placebo or hydrocortisone, or norepinephrine with placebo or hydrocortisone. There was no significant difference in kidney failure-free days or death; however, the vasopressin group had less use of RRT ([276]). We conducted an updated meta-analysis to include the results of the VANISH trial. Data from nine trials (n = 1,324 patients with septic shock), comparing norepinephrine with vasopressin (or terlipressin) demonstrated no significant difference in mortality (RR, 0.89; 95% CI, 0.79–1.00; moderate-quality evidence) (Supplemental Digital Content 10, http://links.lww.com/CCM/C331) ([268, 271, 272, 277–279]). Results were similar after excluding trials that used a combination of norepinephrine and vasopressin in the intervention arm (RR, 0.89; 95% CI, 0.77–1.02). Large studies comparing vasopressin to other vasopressors in septic shock are lacking; most of the data regarding vasopressin support a sparing effect on norepinephrine dose, and there is uncertainty about the effect of vasopressin on mortality. Norepinephrine, therefore, remains the first-choice vasopressor to treat patients with septic shock. We do not recommend the use of vasopressin as a first-line vasopressor for the support of MAP and would advocate caution when using it in patients who are not euvolemic or at doses higher than 0.03 U/min.

Phenylephrine is a pure α-adrenergic agonist. Clinical trial data in sepsis are limited. Phenylephrine has the potential to produce splanchnic vasoconstriction ([280]). A network meta-analysis resulted in imprecise estimates (wide confidence intervals) when phenylephrine was compared to other vasopressors ([281]). Therefore, the impact on clinical outcomes is uncertain, and phenylephrine use should be limited until more research is available.

A large randomized trial and meta-analysis comparing low-dose dopamine to placebo found no difference in need for RRT, urine output, time to renal recovery, survival, ICU stay, hospital stay, or arrhythmias ([282, 283]). Thus, the available data do not support administration of low doses of dopamine solely to maintain renal function.

Myocardial dysfunction consequent to infection occurs in a subset of patients with septic shock, but cardiac output is usually preserved by ventricular dilation, tachycardia, and reduced vascular resistance ([284]). Some portion of these patients may have diminished cardiac reserve, and may not be able to achieve a cardiac output adequate to support oxygen delivery. Recognition of such reduced cardiac reserve can be challenging; imaging studies that show decreased ejection fraction may not necessarily indicate inadequate cardiac output. Concomitant measurement of cardiac output along with a measure of the adequacy of perfusion is preferable.

Routinely increasing cardiac output to predetermined "supranormal" levels in all patients clearly does not improve outcomes, as shown by two large prospective clinical trials of critically ill ICU patients with sepsis treated with dobutamine ([285–287]). Some patients, however, may have improved tissue perfusion with inotropic therapy aimed at increasing oxygen delivery. In this situation, dobutamine is the first-choice inotrope for patients with measured or suspected low cardiac output in the presence of adequate left ventricular filling pressure (or clinical assessment of adequate fluid resuscitation) and adequate MAP. Monitoring the response of indices of perfusion to measured increases in cardiac output is the best way to target such a therapy ([287]).

The data supporting dobutamine are primarily physiologic, with improved haemodynamics and some improvement in indices of perfusion, which may include clinical improvement, decreasing lactate levels, and improvement in $ScvO_2$. No randomized controlled trials have compared the effects of dobutamine versus placebo on clinical outcomes. Mortality in patients randomized to dobutamine added to norepinephrine was no different compared to epinephrine ([287]), although the trial may have been underpowered. Dobutamine was used as the first-line inotrope as part of standard care in clinical trials of EGDT ([16, 19, 288, 289]), and adverse effects on mortality were not detected with its use.

Although there are only a few studies, alternative inotropic agents might be used to increase cardiac output in specific situations. Phosphodiesterase inhibitors increase intracellular cyclic AMP and thus have inotropic effects independent of β-adrenergic receptors. The phosphodiesterase inhibitor milrinone was shown to increase cardiac output in one small randomized trial of 12 paediatric patients, but the trial was underpowered for assessment of outcomes ([290]). Levosimendan increases cardiac myocyte calcium responsiveness and also opens ATP-dependent potassium channels, giving the drug both inotropic and vasodilatory properties. Given the potential role for abnormal calcium handling in sepsis-induced myocardial depression, the use of levosimendan has been proposed in septic shock as well. In a trial of 35 patients with septic shock and acute respiratory distress syndrome (ARDS) randomized to levosimendan or placebo, levosimendan improved right ventricular performance and mixed venous oxygen saturation compared to placebo ([291]). Trials comparing levosimendan with dobutamine are limited but show no clear advantage for levosimendan ([292]). Levosimendan is more expensive than dobutamine and is not available in many parts of the world. Six small RCTs (116 patients in

total) compared levosimendan to dobutamine; pooled estimates showed no significant effect on mortality (RR, 0.83; 95% CI, 0.66–1.05; low quality) (Supplemental Digital Content 11, http://links.lww.com/CCM/C332). Given the low-quality evidence available and the higher cost associated with levosimendan, dobutamine remains the preferred choice in this population. An RCT enrolled 516 patients with septic shock who were randomized to receive either levosimendan or placebo; there was no difference in mortality. However, levosimendan led to significantly higher risk of supraventricular tachyarrhythmia than placebo (absolute difference, 2.7%; 95% CI, 0.1%–5.3%) ([293]). The results of this trial question the systematic use of this agent in patients with septic shock. Of note, cardiac function was not evaluated in that trial, and inotropic stimulation may be of benefit in patients with a low cardiac output due to impaired cardiac function.

In shock states, estimation of blood pressure using a cuff, especially an automated measurement system, may be inaccurate. Use of an arterial cannula provides a more accurate and reproducible measurement of arterial pressure ([287, 294]) and also allows beat-to-beat analysis so that decisions regarding therapy can be based on immediate and reproducible blood pressure information ([295]). Insertion of radial arterial catheters is generally safe; a systematic review of observational studies showed an incidence of limb ischemia and bleeding to be less than 1%, with the most common complication being localized hematoma (14%) ([296]). Complication rates may be lower if an ultrasound-guided technique is used ([297]). A recent systematic review showed higher risk of infections when femoral arterial catheters were used compared to radial artery catheters (RR, 1.93; 95% CI, 1.32–2.84), and the overall pooled incidence of bloodstream infection was 3.4 per 1,000 catheters ([298]). Large randomized trials that compare arterial blood pressure monitoring versus non-invasive methods are lacking.

In view of the low complication rate and likely better estimation of blood pressure but potentially limited resources in some countries, and the lack of high-quality studies, the benefits of arterial catheters probably outweigh the risks. Therefore, we issued a weak recommendation in favour of arterial catheter placement. Arterial catheters should be removed as soon as continuous hemodynamic monitoring is not required to minimize the risk of complications.

Recommendation 33. (SSCG Section G, Recommendation 1).
We recommend norepinephrine as the first-choice vasopressor.
Quality/level of evidence: Moderate + Strength of recommendation: Strong

Recommendation 34. (SSCG Section G, Recommendation 2).
We suggest adding either vasopressin (up to 0.03 U/min) (weak recommendation, moderate quality of evidence) or epinephrine (weak recommendation, low quality of evidence) to norepinephrine with the intent of raising MAP to target, or adding vasopressin (up to 0.03 U/min).
Quality/level of evidence: Moderate + Strength of recommendation: Weak

Recommendation 35. (SSCG Section G, Recommendation 3).
We suggest using dopamine as an alternative vasopressor agent to norepinephrine only in highly selected patients (e.g. patients with low risk of tachyarrhythmias and absolute or relative bradycardia).

Quality/level of evidence: Low + Strength of recommendation: Weak

Recommendation 36. (SSCG Section G, Recommendation 4).
We recommend against using low-dose dopamine for renal protection
Quality/level of evidence: High + Strength of recommendation: Strong

Recommendation 37. (SSCG Section G, Recommendation 5).
We suggest using dobutamine in patients who show evidence of persistent hypoperfusion despite adequate fluid loading and the use of vasopressor agents.
Quality/level of evidence: Low + Strength of recommendation: Weak

Remarks: *If initiated, vasopressor dosing should be titrated to an end point reflecting perfusion, and the agent reduced or discontinued in the face of worsening hypotension or arrhythmias.*

Recommendation 38. (SSCG Section G, Recommendation 6).
We suggest that all patients requiring vasopressors have an arterial catheter placed as soon as practical if resources are available.
Quality/level of evidence: Very low + Strength of recommendation: Weak

Implementation Point 18 (Recommendations 33-38)

Patients who present with profound shock may require simultaneous pressor/ inotrope and fluid administration. The end point of resuscitation is to restore flow rather than pressure, however, available monitors measure pressure rather than flow so surrogates are used which assess organ and tissue perfusion. These include urinary output, serum lactate, capillary refill, mental status and central venous oxygen saturations.

Persistently high serum lactates and central venous oxygen saturations despite adequate fluid resuscitation may represent established cellular dysfunction and an inability to extract or utilise oxygen rather than hypoperfusion or due to other causes[50] and as such will not respond to further fluid administration. Lactate physiology is complex and should be used only as one of a number of markers of tissue perfusion.

The suggested approach to resuscitation is early aggressive fluid resuscitation aiming to restore tissue perfusion and then a conservative post resuscitation phase avoiding excessive fluid accumulation with careful monitoring of input and output and assessing for de-resuscitation by diuresis/ fluid removal as soon as tolerated using perfusion parameters [49, 51, 52, 53, 54, 55].

Roles and responsibilities:
Vasopressors and inotropes are most usually prescribed by critical care staff and unless familiar with them, it is prudent to obtain critical care support when starting them. Phenylephrine is not the first line pressor for septic shock[1]. Noradrenaline is the first line. It has both α and β receptor effects so it improves cardiac output as well as having a vasoconstrictor effect. Phenylephrine, if used urgently as a temporary pressor, should be replaced by noradrenaline as soon as possible.

Starting vasopressors requires multidisciplinary support for central venous access, constitution and delivery of the vasopressors and aseptic technique.
It is the responsibility of hospital management to ensure the appropriate equipment and staff is available to provide this service.

It is the responsibility of the clinicians to be familiar with the procedures and to know the advantages and limitations of any advanced haemodynamic monitoring equipment deployed.

3.1.6 Corticosteroids

Key questions

4. *In patients with septic shock, should we use intravenous corticosteroids (versus not)?*

SSCG Rationale

The response of septic shock patients to fluid and vasopressor therapy seems to be an important factor in selection of patients for optional hydrocortisone therapy. One French multicentre RCT of patients in vasopressor-unresponsive septic shock (systolic blood pressure < 90 mm Hg despite fluid resuscitation and vasopressors for more than one hour) showed significant shock reversal and reduction of mortality rate in patients with relative adrenal insufficiency (defined as a maximal post-adrenocorticotropic hormone [ACTH] cortisol increase ≤ 9 µg/dL) ([299]). Two smaller RCTs also showed significant effects on shock reversal with steroid therapy ([300, 301]). In contrast, a large, European multicentre trial (CORTICUS) that enrolled patients with systolic blood pressure of < 90 mm Hg despite adequate fluid replacement or need for vasopressors had a lower risk of death than the French trial and failed to show a mortality benefit with steroid therapy ([302]). There was no difference in mortality in groups stratified by ACTH response.

Several systematic reviews have examined the use of low-dose hydrocortisone in septic shock with contradictory results. Annane et al ([299]) analysed the results of 12 studies and calculated a significant reduction in 28-day mortality with prolonged low-dose steroid treatment in adult septic shock patients (RR, 0.84; 95% CI, 0.72−0.97; p = 0.02). In parallel, Sligl et al ([303]) used a similar technique, but identified only eight studies for their meta-analysis, six of which had a high-level RCT design with low risk of bias. In contrast to the aforementioned review, this analysis revealed no statistically significant difference in mortality (RR, 1.00; 95% CI, 0.84−1.18). Both reviews, however, confirmed the improved shock reversal by using low-dose hydrocortisone. More recently, Annane et al included 33 eligible trials (n = 4,268) in a new systematic review ([304]). Of these 33 trials, 23 were at low risk of selection bias; 22 were at low risk of performance and detection bias; 27 were at low risk of attrition bias; and 14 were at low risk of selective reporting. Corticosteroids reduced 28-day mortality (27 trials; n = 3,176; RR, 0.87; 95% CI, 0.76–1.00). Treatment with a long course of low-dose corticosteroids significantly reduced 28-day mortality (22 trials; RR, 0.87; 95% CI, 0.78–0.97). Corticosteroids also reduced ICU mortality (13 trials; RR, 0.82; 95% CI, 0.68–1.00) and in hospital mortality (17 trials; RR, 0.85; 95% CI, 0.73–0.98). Corticosteroids increased the proportion of shock reversal by day 7 (12 trials; RR, 1.31; 95% CI, 1.14–1.51) and by day 28 (seven trials; n = 1,013; RR, 1.11; 95% CI, 1.02–1.21). Finally, an additional systematic review by Volbeda et al including a total of 35 trials randomizing 4,682 patients has been published (all but two trials had high risk of bias) ([305]). Conversely, in this review,

no statistically significant effect on mortality was found for any dose of steroids versus placebo or for no intervention at maximal follow-up. The two trials with low risk of bias also showed no statistically significant difference (random-effects model RR, 0.38; 95% CI, 0.06–2.42). Similar results were obtained in subgroups of trials stratified according to hydrocortisone (or equivalent) at high (> 500 mg) or low (≤ 500 mg) doses (RR, 0.87; trial sequential analysis [TSA]-adjusted CI; 0.38–1.99; and RR, 0.90; TSA-adjusted CI, 0.49–1.67, respectively). No statistically significant effects on serious adverse events other than mortality were reported (RR, 1.02; TSA-adjusted CI, 0.7–1.48). In the absence of convincing evidence of benefit, we issue a weak recommendation against the use of corticosteroids to treat septic shock patients if adequate fluid resuscitation and vasopressor therapy are able to restore hemodynamic stability.

In one study, the observation of a potential interaction between steroid use and ACTH test was not statistically significant ([306]). Furthermore, no evidence of this distinction was observed between responders and nonresponders in a recent multicentre trial ([302]). Random cortisol levels may still be useful for absolute adrenal insufficiency; however, for septic shock patients who have relative adrenal insufficiency (no adequate stress response), random cortisol levels have not been demonstrated to be useful. Cortisol immunoassays may over- or underestimate the actual cortisol level, affecting the assignment of patients to responders or nonresponders ([307]). Although the clinical significance is not clear, it is now recognized that etomidate, when used for induction for intubation, will suppress the hypothalamic-pituitary-adrenal axis ([308, 309]). Moreover, a sub analysis of the CORTICUS trial revealed that the use of etomidate before application of low-dose steroids was associated with an increased 28-day mortality rate ([302]).

There has been no comparative study between a fixed-duration and clinically guided regimen or between tapering and abrupt cessation of steroids. Three RCTs used a fixed-duration protocol for treatment ([300, 302, 306]), and therapy was decreased after shock resolution in two RCTs ([301, 310]). In four studies, steroids were tapered over several days ([300–302, 310]) and steroids were withdrawn abruptly in two RCTs ([306, 311]). One crossover study showed hemodynamic and immunologic rebound effects after abrupt cessation of corticosteroids ([312]). Further, one study revealed no difference in outcome of septic shock patients if low-dose hydrocortisone is used for 3 or 7 days; hence, we suggest tapering steroids when vasopressors are no longer needed ([313]).

Steroids may be indicated when there is a history of steroid therapy or adrenal dysfunction, but whether low-dose steroids have a preventive potency in reducing the incidence of sepsis and septic shock in critically ill patients cannot be answered. A recent large multicentre RCT demonstrated no reduction in the development of septic shock in septic patients treated with hydrocortisone versus placebo ([314]); steroids should not be used in septic patients to prevent septic shock. Additional studies are underway that may provide additional information to inform clinical practice.

Several randomized trials on the use of low-dose hydrocortisone in septic shock patients revealed a significant increase of hyperglycaemia and hypernatremia ([306]) as side effects. A small prospective study demonstrated that repetitive bolus application of hydrocortisone leads to a significant increase in blood glucose; this peak effect was not detectable during continuous infusion. Further, considerable inter-individual variability was seen in this blood

glucose peak after the hydrocortisone bolus ([315]). Although an association of hyperglycaemia and hypernatremia with patient outcome measures could not be shown, good practice includes strategies for avoidance and/or detection of these side effects.

Recommendation 39. (SSCG Section H, Recommendation 1).
We suggest against using IV hydrocortisone to treat septic shock patients if adequate fluid resuscitation and vasopressor therapy are able to restore hemodynamic stability. If this is not achievable, we suggest IV hydrocortisone at a dose of 200 mg per day (weak recommendation, low quality of evidence).
Quality/level of evidence: Low + Strength of recommendation: Weak

Implementation Point 19 (Recommendation 39)
Patients with fluid resistant, pressor-resistant shock should have a trial of IV hydrocortisone 50mg qds or by continuous infusion, consider adding fludrocortisone 50 micrograms once daily orally or via nasogastric tube[56, 57].

3.1.7 Blood Products

Key questions

- *In patients with sepsis, should we use a restrictive transfusion strategy versus liberal transfusion?*
- *In patients with sepsis and anemia, should we use erythropoietin to treat anemia?*
- *In non-bleeding patients with sepsis and coagulation abnormalities, should we use prophylactic FFP?*
- *In non-bleeding patients with sepsis and thrombocytopenia, should we use prophylactic platelet transfusion based on specific platelet levels?*

SSCG Rationale

Two clinical trials in septic patients evaluated specific blood transfusion thresholds. The Transfusion Requirements In Septic Shock (TRISS) trial addressed a transfusion threshold of 7 g/dL versus 9 g/dL in septic shock patients after admission to the ICU ([316]). Results showed similar 90-day mortality, ischemic events, and use of life support in the two treatment groups with fewer transfusions in the lower-threshold group. The haemoglobin targets in two of the three treatment arms in the Protocol-Based Care for Early Septic Shock (ProCESS) trial were a subpart of a more comprehensive sepsis management strategy ([18]). The EGDT group received transfusion at a haematocrit < 30% (haemoglobin 10 g/dL) when the $ScvO_2$ was < 70% after initial resuscitation interventions compared to the protocol-based standard care group that received blood transfusion only when the haemoglobin was < 7.5 g/dL. No significant differences were found between the two groups for 60-day in-hospital mortality or 90-day mortality. Although the ProCESS trial is a less direct assessment of blood transfusion therapy, it does provide important information in regard to transfusion in the acute resuscitative phase of sepsis. We judge the evidence to be high certainty that there is little difference in mortality, and, if there is, that it would favour lower haemoglobin thresholds.

No specific information regarding erythropoietin use in septic patients is available, and clinical trials of erythropoietin administration in critically ill patients show a small decrease

in red cell transfusion requirement with no effect on mortality ([317, 318]). The effect of erythropoietin in sepsis and septic shock would not be expected to be more beneficial than in other critical conditions. Erythropoietin administration may be associated with an increased incidence of thrombotic events in the critically ill. Patients with sepsis and septic shock may have coexisting conditions that meet indications for the use of erythropoietin or similar agents.

No RCTs exist related to prophylactic fresh frozen plasma transfusion in septic or critically ill patients with coagulation abnormalities. Current recommendations are based primarily on expert opinion that fresh frozen plasma be transfused when there is a documented deficiency of coagulation factors (increased prothrombin time, international normalized ratio, or partial thromboplastin time) and the presence of active bleeding or before surgical or invasive procedures ([319]). In addition, transfusion of fresh frozen plasma usually fails to correct the prothrombin time in nonbleeding patients with mild abnormalities. No studies suggest that correction of more severe coagulation abnormalities benefits patients who are not bleeding.

No RCTs of prophylactic platelet transfusion in septic or critically ill patients exist. Current recommendations and guidelines for platelet transfusion are based on clinical trials of prophylactic platelet transfusion in patients with therapy-induced thrombocytopenia (usually leukaemia and stem cell transplant) ([320–327]). Thrombocytopenia in sepsis is likely due to a different pathophysiology of impaired platelet production and increased platelet consumption. Factors that may increase the bleeding risk and indicate the need for a higher platelet count are frequently present in patients with sepsis.

Recommendation 40. (SSCG Section I, Recommendation 1).
We recommend that RBC transfusion occur only when hemoglobin concentration decreases to < 7.0g/dL in adults in the absence of extenuating circumstances, such as myocardial ischemia, severe hypoxemia, or acute hemorrhage
Quality/level of evidence: High + Strength of recommendation: Strong

Recommendation 41. (SSCG Section I, Recommendation 2).
We recommend against the use of erythropoietin for treatment of anemia associated with sepsis
Quality/level of evidence: Moderate + Strength of recommendation: Strong

Recommendation 42. (SSCG Section I, Recommendation 3).
We suggest against the use of fresh frozen plasma* to correct clotting abnormalities in the absence of bleeding or planned invasive procedures
**Known as frozen plasma in Ireland and often by a tradename.*
Quality/level of evidence: Very low + Strength of recommendation: Weak

Recommendation 43. (SSCG Section I, Recommendation 4).
We suggest prophylactic platelet transfusion when counts are < 10,000/mm^3 (10 × 10^9/L) in the absence of apparent bleeding and when counts are < 20,000/mm^3 (20 × 10^9/L) if the patient has a significant risk of bleeding. Higher platelet counts (≥ 50,000/mm^3 [50 × 10^9/L]) are advised for active bleeding, surgery, or invasive procedures

Quality/level of evidence: Very low + Strength of recommendation: Weak

3.1.8 Immunoglobulins

Key questions

- *In adult patients with sepsis or septic shock, should we use intravenous immunoglobulins (versus not)?*

SSCG Rationale

There were no new studies informing this guideline recommendation. One larger multicentre RCT (n = 624) ([328]) in adult patients found no benefit for IV immunoglobulin (IVIg). The most recent Cochrane meta-analysis ([329]) differentiates between standard polyclonal IV immunoglobulins (IVIgG) and immunoglobulin M-enriched polyclonal Ig (IVIgGM). In 10 studies with IVIgG (1,430 patients), mortality between 28 and 180 days was 29.6% in the IVIgG group and 36.5 % in the placebo-group (RR, 0.81; 95% CI, 0.70–0.93), and for the seven studies with IVIgGM (528 patients), mortality between 28 and 60 days was 24.7% in the IVIgGM group and 37.5% in the placebo-group (RR, 0.66; 95% CI, 0.51–0.85). The certainty of the studies was rated as low for the IVIgG trials, based on risk of bias and heterogeneity, and as moderate for the IVIgGM trials, based on risk of bias. Comparable results were found in other meta-analyses ([330]). However, after excluding low-quality trials, the recent Cochrane analysis ([329]) revealed no survival benefit.

These findings are in accordance with those of two older meta-analyses ([331, 332]) from other Cochrane authors. One systematic review ([332]) included a total of 21 trials and showed a reduction in death with immunoglobulin treatment (RR, 0.77; 95% CI, 0.68−0.88); however, the results of only high-quality trials (total of 763 patients) did not show a statistically significant difference (RR, 1.02; 95% CI, 0.84−1.24). Similarly, Laupland et al ([331]) found a significant reduction in mortality with the use of IVIg treatment (OR, 0.66; 95% CI, 0.53−0.83; $p < 0.005$). When only high-quality studies were pooled, the results were no longer statistically significant (OR, 0.96); OR for mortality was 0.96 (95% CI, 0.71−1.3; $p = 0.78$). Two meta-analyses that used less strict criteria to identify sources of bias or did not state their criteria for the assessment of study quality found significant improvement in patient mortality with IVIg treatment ([333–335]). Finally, there are no cut-offs for plasma IgG levels in septic patients, for which substitution with IVIgG improves outcome data ([334]).

Most IVIg studies are small, and some have a high risk of bias; the only large study (n = 624) showed no effect ([328]). Subgroup effects between IgM-enriched and non-enriched formulations reveal significant heterogeneity. Indirectness and publication bias were considered, but not invoked in grading this recommendation. The low certainty of evidence led to the grading as a weak recommendation. The statistical information that comes from the high-quality trials does not support a beneficial effect of polyclonal IVIg. We encourage conduct of large multicentre studies to further evaluate the effectiveness of other IV polyclonal immunoglobulin preparations in patients with sepsis.

Recommendation 44. (SSCG Section J, Recommendation 1).
We suggest against the use of IV immunoglobulins in patients with sepsis or septic shock
Quality/level of evidence: Low + Strength of recommendation: Weak

3.1.9 Blood purification

Key questions

- *In patients with sepsis, should we use plasma filtration therapy?*
- *In patients with sepsis, should we use a hemoperfusion therapy?*

SSCG Rationale

Blood purification includes various techniques, such as high-volume hemofiltration and hemadsorption (or hemoperfusion), where sorbents, removing either endotoxin or cytokines, are placed in contact with blood; plasma exchange or plasma filtration, through which plasma is separated from whole blood, removed, and replaced with normal saline, albumin, or fresh frozen plasma; and the hybrid system: coupled plasma filtration adsorption (CPFA), which combines plasma filtration and adsorption by a resin cartridge that removes cytokines.

When these modalities of blood purification are considered versus conventional treatment, the available trials are, overall, small, unblinded, and with high risk of bias. Patient selection was unclear and differed with the various techniques. Hemadsorption is the technique most largely investigated, in particular with polymyxin B-immobilized polystyrene-derived fibres to remove endotoxin from the blood. A recent meta-analysis demonstrated a favourable effect on overall mortality with this technique ([336]). The composite effect, however, depends on a series of studies performed in a single country (Japan), predominantly by one group of investigators. A recent large RCT performed on patients with peritonitis related to organ perforation within 12 hours after emergency surgery found no benefit of polymyxin B hemoperfusion on mortality and organ failure, as compared to standard treatment ([337]). Illness severity of the study patients, however, was low overall, which makes these findings questionable. A multicentre blinded RCT is ongoing, which should provide stronger evidence regarding this technique ([338]).

Few RCTs evaluated plasma filtration, alone or combined with adsorption for cytokine removal (CPFA). A recent RCT comparing CPFA with standard treatment was stopped for futility ([339]). About half of the patients randomized to CPFA were undertreated, primarily because of clotting of the circuit, which raises doubts about CPFA feasibility.

In consideration of all these limitations, our confidence in the evidence is very low either in favour of or against blood purification techniques; therefore, we do not provide a recommendation. Further research is needed to clarify the clinical benefit of blood purification techniques.

Recommendation 45. (SSCG Section K, Recommendation 1).
We make no recommendation regarding the use of blood purification techniques.
Quality/level of evidence: N/A + Strength of recommendation: N/A

3.1.10 Anticoagulants

Key questions

- *In adult patients with sepsis or septic shock, should we use antithrombin (versus not)?*

SSCG Rationale

Antithrombin is the most abundant anticoagulant circulating in plasma. The decrease of its plasma activity at onset of sepsis correlates with disseminated intravascular coagulation (DIC) and lethal outcome. However, a phase III clinical trial of high-dose antithrombin for adults with sepsis and septic shock as well as systematic reviews of antithrombin for critically ill patients did not demonstrate any beneficial effect on overall mortality. Antithrombin was associated with an increased risk of bleeding ([340, 341]). Although post hoc subgroup analyses of patients with sepsis associated with DIC showed better survival in patients receiving antithrombin, this agent cannot be recommended until further clinical trials are performed.

Most RCTs of recombinant soluble thrombomodulin have been targeted for sepsis associated with DIC, and a systematic review suggested a beneficial effect on survival without an increase of bleeding risk ([342, 343]). A phase III RCT is ongoing for sepsis associated with DIC. The guideline panel has elected to make no recommendation pending these new results. Two systematic reviews showed a potential survival benefit of heparin in patients with sepsis without an increase in major bleeding ([344]). However, overall impact remains uncertain, and heparin cannot be recommended until further RCTs are performed.

Recombinant activated protein C, which was originally recommended in the 2004 and 2008 SSC guidelines, was not shown to be effective for adult patients with septic shock by the PROWESS-SHOCK trial, and was withdrawn from the market ([345]).

Recommendation 46. (SSCG Section L, Recommendation 1).
We recommend against the use of antithrombin for the treatment of sepsis and septic shock
Quality/level of evidence: Moderate + Strength of recommendation: Strong

Recommendation 47. (SSCG Section L, Recommendation 2).
We make no recommendation regarding the use of thrombomodulin or heparin for the treatment of sepsis or septic shock.
Quality/level of evidence: N/A + Strength of recommendation: N/A

3.1.11 Mechanical Ventilation

Key questions

- *In patients with sepsis induced ARDS, should we use low tidal volume ventilation?*
- *In patients with sepsis induced ARDS who are mechanically ventilated, should we use plateau pressures less than 30 cm H2O?*
- *In patients with sepsis induced ARDS who are mechanically ventilated, should we use high PEEP strategy?*
- *In patients with sepsis induced ARDS, should we use recruitment manoeuvres?*
- *In patients with sepsis induced severe ARDS, should we use prone ventilation?*
- *In patients with sepsis who are mechanically ventilated, should we elevate the head of the bed?*
- *In patients with sepsis induced ARDS, should we use non-invasive ventilation?*

- *In patients with sepsis who are mechanically ventilated and ready for weaning, should we use weaning protocol versus physician guided weaning?*
- *In patients with sepsis who are mechanically ventilated and ready for weaning, should we use spontaneous breathing trials (SBT)?*
- *In patients with sepsis induced ARDS, should we use pulmonary artery catheter (PAC)?*
- *In patients with sepsis induced ARDS, should we use conservative fluid strategy?*
- *In patients with sepsis induced ARDS, should we use inhaled Beta agonists?*
- *In patients with sepsis induced ARDS, should we use ECMO treatment?*
- *In patients with sepsis induced ARDS, should we use High Frequency Oscillation (HFO) versus conventional ventilation?*
- *In patients with sepsis induced respiratory failure without ARDS, should we use low tidal volume ventilation?*
- *In patients with severe ARDS who are mechanically ventilated, should we use neuromuscular blocking agents?*

SSCG Rationale

This recommendation is unchanged from the previous guidelines. Of note, the studies that guide the recommendations in this section enrolled patients using criteria from the American-European Consensus Criteria Definition for Acute Lung Injury and ARDS ([346]). For the current document, we used the 2012 Berlin definition and the terms *mild, moderate*, and *severe ARDS* (PaO_2/FIO_2 ≤ 300, ≤ 200, and ≤ 100 mm Hg, respectively) ([347]). Several multicentre randomized trials have been performed in patients with established ARDS to evaluate the effects of limiting inspiratory pressure through moderation of tidal volume ([348–351]). These studies showed differing results, which may have been caused by differences in airway pressures in the treatment and control groups ([347], [350], [352]). Several meta-analyses suggest decreased mortality in patients with a pressure- and volume-limited strategy for established ARDS ([353], [354]).

The largest trial of a volume- and pressure-limited strategy showed 9% absolute decrease in mortality in ARDS patients ventilated with tidal volumes of 6 mL/kg compared with 12 mL/kg PBW, and aiming for plateau pressure ≤ 30 cm H_2O ([350]). The use of lung-protective strategies for patients with ARDS is supported by clinical trials and has been widely accepted; however, the precise tidal volume for an individual ARDS patient requires adjustment for factors such as the plateau pressure, the selected positive end-expiratory pressure (PEEP), thoracoabdominal compliance, and the patient's breathing effort. Patients with profound metabolic acidosis, high minute ventilation, or short stature may require additional manipulation of tidal volumes. Some clinicians believe it may be safe to ventilate with tidal volumes > 6 mL/kg PBW as long as plateau pressure can be maintained ≤ 30 cm H_2O ([355], [356]). The validity of this ceiling value will depend on the patient's effort, because those who are actively breathing generate higher transpulmonary pressures for a given plateau pressure than patients who are passively inflated. Conversely, patients with very stiff chest/abdominal walls and high pleural pressures may tolerate plateau pressures > 30 cm H_2O because transpulmonary pressures will be lower. A retrospective study suggested that tidal volumes should be lowered even with plateau pressures ≤ 30 cm H_2O ([357]) because lower plateau pressures were associated with reduced hospital mortality ([358]).

A recent patient-level mediation analysis suggested that a tidal volume that results in a driving pressure (plateau pressure minus set PEEP) below 12–15 cm H_2O may be advantageous in patients without spontaneous breathing efforts ([359]). Prospective validation of tidal volume titration by driving pressure is needed before this approach can be recommended.

High tidal volumes coupled with high plateau pressures should be avoided in ARDS. Clinicians should use as a starting point the objective of reducing tidal volume over 1 to 2 hours from its initial value toward the goal of a "low" tidal volume (≈6 mL/kg PBW) achieved in conjunction with an end-inspiratory plateau pressure ≤ 30 cm H_2O. If plateau pressure remains > 30 cm H_2O after reduction of tidal volume to 6 mL/kg PBW, tidal volume may be further reduced to as low as 4 mL/kg PBW. Respiratory rate should be increased to a maximum of 35 breaths/minute during tidal volume reduction to maintain minute ventilation. Volume- and pressure-limited ventilation may lead to hypercapnia even with these maximum tolerated set respiratory rates; this appears to be tolerated and safe in the absence of contraindications (e.g., high intracranial pressure, sickle cell crisis).

No single mode of ventilation (pressure control, volume control) has consistently been shown to be advantageous when compared with any other that respects the same principles of lung protection.

Raising PEEP in ARDS may open lung units to participate in gas exchange. This may increase Pa_{O_2} when PEEP is applied through either an endotracheal tube or a face mask ([360–362]). In animal experiments, avoidance of end-expiratory alveolar collapse helps minimize ventilator-induced lung injury when relatively high plateau pressures are in use. Three large multicentre trials and a pilot trial using higher versus lower levels of PEEP in conjunction with low tidal volumes did not show benefit or harm ([363–366]). A patient-level meta-analysis showed no benefit in all patients with ARDS; however, patients with moderate or severe ARDS (Pa_{O_2}/F_{IO_2} ≤ 200 mm Hg) had decreased mortality with the use of higher PEEP, whereas those with mild ARDS did not ([367]). A patient-level analysis of two of the randomized PEEP trials suggested a survival benefit if Pa_{O_2}/F_{IO_2} increased with higher PEEP and harm if Pa_{O_2}/F_{IO_2} fell ([368]). A small randomized trial suggested that adjusting PEEP to obtain a positive transpulmonary pressure as estimated by esophageal manometry improved outcomes; a confirmatory trial is underway ([369]). An analysis of nearly all the randomized trials of lung-protective ventilation suggested a benefit of higher PEEP if driving pressure fell with increased PEEP, presumably indicating increased lung compliance from opening of lung units ([359]).

While moderate-quality evidence suggests that higher PEEP improves outcomes in moderate to severe ARDS, the optimal method for selecting a higher PEEP level is unclear. One option is to titrate PEEP according to bedside measurements of thoracopulmonary compliance with the objective of obtaining the best compliance or lowest driving pressure, reflecting a favourable balance of lung recruitment and overdistension ([370]). The second option is to titrate PEEP upward on a tidal volume of 6 mL/kg PBW until the plateau airway pressure is 28 cm H_2O ([365]). A third option is to use a PEEP/F_{IO_2} titration table that titrates PEEP based on the combination of F_{IO_2} and PEEP required to maintain adequate oxygenation ([350], [363–365], [368]). A PEEP > 5 cm H_2O is usually required to avoid lung collapse ([371]).

Many strategies exist for treating refractory hypoxemia in patients with severe ARDS ([372]). Temporarily raising transpulmonary pressure may facilitate opening atelectatic alveoli to permit gas exchange ([371]), but could also over distend aerated lung units, leading to ventilator-induced lung injury and transient hypotension. The application of sustained continuous positive airway pressure (CPAP) appears to improve survival (RR, 0.84; 95% CI, 0.74–0.95) and reduce the occurrence of severe hypoxia requiring rescue therapy (RR, 0.76; 95% CI, 0.41–1.40) in patients with ARDS. Although the effects of recruitment manoeuvres improve oxygenation initially, the effects can be transient ([373]). Selected patients with severe hypoxemia may benefit from recruitment manoeuvres in conjunction with higher levels of PEEP, but little evidence supports the routine use in all ARDS patients ([373]). Any patient receiving this therapy should be monitored closely and recruitment manoeuvres discontinued if deterioration in clinical variables is observed.

In patients with ARDS and a Pa_{O_2}/F_{IO_2} ratio < 150, the use of prone compared with supine position within the first 36 hours of intubation, when performed for > 16 hours a day, showed improved survival ([374]). Meta-analysis including this study demonstrated reduced mortality in patients treated with prone compared with supine position (RR, 0.85; 95% CI, 0.71–1.01) as well as improved oxygenation as measured by change in Pa_{O_2}/F_{IO_2} ratio (median 24.03 higher, 95% CI, 13.3–34.7 higher) ([375]). Most patients respond to the prone position with improved oxygenation and may also have improved lung compliance ([374], [376–379]). While prone position may be associated with potentially life-threatening complications including accidental removal of the endotracheal tube, this was not evident in pooled analysis (RR, 1.09; 95% CI, 0.85–1.39). However, prone position was associated with an increase in pressure sores (RR, 1.37; 95% CI, 1.05–1.79) ([375]), and some patients have contraindications to the prone position ([374]).

In patients with refractory hypoxia, alternative strategies, including airway pressure release ventilation and extracorporeal membrane oxygenation, may be considered as rescue therapies in experienced centres ([372], [380–383]).

HFOV has theoretical advantages that make it an attractive ventilator mode for patients with ARDS. Two large RCTs evaluating routine HFOV in moderate-severe ARDS have been recently published ([384], [385]). One trial was stopped early because the mortality was higher in patients randomized to HFOV ([384]). Including these recent studies, a total of five RCTs (1,580 patients) have examined the role of HFOV in ARDS. Pooled analysis demonstrates no effect on mortality (RR, 1.04; 95% CI, 0.83–1.31) and an increased duration of mechanical ventilation (MD, 1.1 days higher; 95% CI, 0.03–2.16) in patients randomized to HFOV. An increase in barotrauma was seen in patients receiving HFOV (RR, 1.19; 95% CI, 0.83–1.72); however, this was based on very low-quality evidence.

The role of HFOV as a rescue technique for refractory ARDS remains unclear; however, we recommend against its early use in moderate-severe ARDS given the lack of demonstrated benefit and a potential signal for harm.

NIV may have theoretical benefits in patients with sepsis-induced respiratory failure, such as better communication abilities, reduced need for sedation, and avoidance of intubation. However, NIV may preclude the use of low tidal volume ventilation or achieving adequate

levels of PEEP, two ventilation strategies that have shown benefit even in mild-moderate ARDS ([365], [386]). Also, in contrast to indications such as cardiogenic pulmonary oedema or chronic obstructive pulmonary disease exacerbation where NIV use is brief, ARDS often takes days or weeks to improve, and prolonged NIV use may lead to complications such as facial skin breakdown, inadequate nutritional intake, and failure to rest respiratory muscles.

A few small RCTs have shown benefit with NIV for early or mild ARDS or de novo hypoxic respiratory failure; however, these were in highly selected patient populations ([387], [388]). More recently, a larger RCT in patients with hypoxemic respiratory failure compared NIV to traditional oxygen therapy or high-flow nasal cannula ([389]). This study demonstrated improved 90-day survival with high-flow oxygen compared with standard therapy or NIV; however, the NIV technique was not standardized and the experience of the centres varied. Although high-flow oxygen has not been addressed here, it is possible that this technique may play a more prominent role in the treatment of hypoxic respiratory failure and ARDS moving forward.

Given the uncertainty regarding whether clinicians can identify ARDS patients in whom NIV might be beneficial, we have not made a recommendation for or against this intervention. If NIV is used for patients with ARDS, we suggest close monitoring of tidal volumes

The most common indication for NMBA use in the ICU is to facilitate mechanical ventilation ([390]). When appropriately used, these agents may improve chest wall compliance, prevent respiratory dyssynchrony, and reduce peak airway pressures ([391]). Muscle paralysis may also reduce oxygen consumption by decreasing the work of breathing and respiratory muscle blood flow ([392]). However, a placebo-controlled RCT in patients with severe sepsis demonstrated that oxygen delivery, oxygen consumption, and gastric intramucosal pH were not improved during deep neuromuscular blockade ([393]).

An RCT of continuous infusions of cisatracurium in patients with early ARDS and a Pa_{O_2}/F_{IO_2} < 150 mm Hg showed improved adjusted survival rates and more organ failure-free days without an increased risk in ICU-acquired weakness compared with placebo-treated patients ([394]). The investigators used a high fixed dose of cisatracurium without train-of-four monitoring; half of the patients in the placebo group received at least a single NMBA dose. Of note, groups in both the intervention and control groups were ventilated with volume-cycled and pressure-limited mechanical ventilation. Although many of the patients in this trial appeared to meet sepsis criteria, it is not clear whether similar results would occur in sepsis patients or in patients ventilated with alternate modes. Pooled analysis including three trials that examined the role of NMBAs in ARDS, including the one above, showed improved survival (RR, 0.72; 95% CI, 0.58–0.91) and a decreased frequency of barotrauma (RR, 0.43; 95% CI, 0.20–0.90) in those receiving NMBAs ([395]).

An association between NMBA use and myopathies and neuropathies has been suggested by case studies and prospective observational studies in the critical care population ([391], [396–399]), but the mechanisms by which NMBAs produce or contribute to myopathies and neuropathies in these patients are unknown. Pooled analysis of the RCT data did not show an increase in neuromuscular weakness in those who received NMBAs (RR, 1.08; 95% CI, 0.83–1.41); however, this was based on very low quality of evidence ([395]). Given the uncertainty that still exists pertaining to these important outcomes and the balance

between benefits and potential harms, the panel decided that a weak recommendation was most suitable. If NMBAs are used, clinicians must ensure adequate patient sedation and analgesia ([400], [401]); recently updated clinical practice guidelines are available for specific guidance ([402]).

Mechanisms for the development of pulmonary oedema in patients with ARDS include increased capillary permeability, increased hydrostatic pressure, and decreased oncotic pressure ([403]). Small prospective studies in patients with critical illness and ARDS have suggested that low weight gain is associated with improved oxygenation ([404]) and fewer days of mechanical ventilation ([405], [406]). A fluid-conservative strategy to minimize fluid infusion and weight gain in patients with ARDS, based on either a CVP or a pulmonary artery (PA) catheter (PA wedge pressure) measurement, along with clinical variables to guide treatment, led to fewer days of mechanical ventilation and reduced ICU LOS without altering the incidence of renal failure or mortality rates ([407]). This strategy was only used in patients with established ARDS, some of whom had shock during their ICU stay, and active attempts to reduce fluid volume were conducted only outside periods of shock.

Patients with sepsis-induced ARDS often develop increased vascular permeability; preclinical data suggest that β-adrenergic agonists may hasten resorption of alveolar oedema ([408]). Three RCTs (646 patients) evaluated β-agonists in patients with ARDS ([408–410]). In two of these trials, salbutamol (15 µg/kg of ideal body weight) delivered intravenously ([408], [409]) was compared with placebo, while the third trial compared inhaled albuterol versus placebo ([410]). Group allocation was blinded in all three trials, and two trials were stopped early for futility or harm ([409], [411]). More than half of the patients enrolled in all three trials had pulmonary or non-pulmonary sepsis as the cause of ARDS.

Pooled analysis suggests β-agonists may reduce survival to hospital discharge in ARDS patients (RR, 1.22; 95% CI, 0.95–1.56) while significantly decreasing the number of ventilator-free days (MD, –2.19; 95% CI, –3.68 to –0.71) ([412]). β-agonist use also led to more arrhythmias (RR, 1.97; 95% CI, 0.70–5.54) and more tachycardia (RR, 3.95; 95% CI, 1.41–11.06).

β-2 agonists may have specific indications in the critically ill, such as the treatment of bronchospasm and hyperkalaemia. In the absence of these conditions, we recommend against the use of β-agonists, either in IV or aerosolized form, for the treatment of patients with sepsis-induced ARDS.

This recommendation is unchanged from the previous guidelines. Although insertion of a PA catheter may provide useful information regarding volume status and cardiac function, these benefits may be confounded by differences in interpretation of the results ([413], [414]), poor correlation of PA occlusion pressures with clinical response ([415]), and lack of a PA catheter-based strategy demonstrated to improve patient outcomes ([416]). Pooled analysis of two multicentre randomized trials, one with 676 patients with shock or ARDS ([417]) and another with 1,000 patients with ARDS ([418]), failed to show any benefit associated with PA catheter use on mortality (RR, 1.02; 95% CI, 0.96–1.09) or ICU LOS (mean difference 0.15 days longer; 95% CI, 0.74 days fewer – 1.03 days longer) ([407], [419–421]) This lack of demonstrated benefit must be considered in the context of the increased resources

required. Notwithstanding, selected sepsis patients may be candidates for PA catheter insertion if management decisions depend on information solely obtainable from PA catheter measurements.

Low tidal volume ventilation (4–6 mL/kg) has been shown to be beneficial in patients with established ARDS ([422]) by limiting ventilator-induced lung injury. However, the effect of volume- and pressure-limited ventilation is less clear in patients with sepsis who do not have ARDS. Meta-analysis demonstrates the benefits of low tidal volume ventilation in patients without ARDS, including a decrease in the duration of mechanical ventilation (MD, 0.64 days fewer; 95% CI, 0.49–0.79) and the decreased development of ARDS (RR, 0.30; 95% CI, 0.16–0.57) with no impact on mortality (RR, 0.95; 95% CI, 0.64–1.41). Importantly, the certainty in this data is limited by indirectness because the included studies varied significantly in terms of populations enrolled, mostly examining perioperative patients and very few focusing on ICU patients. The use of low tidal volumes in patients who undergo abdominal surgery, which may include sepsis patients, has been shown to decrease the incidence of respiratory failure, shorten LOS, and result in fewer postoperative episodes of sepsis ([423]). Subgroup analysis of only the studies that enrolled critically ill patients ([424]) suggests similar benefits of low tidal volume ventilation on duration of mechanical ventilation and development of ARDS, but is further limited by imprecision given the small number of studies included. Despite these methodologic concerns, the benefits of low tidal volume ventilation in patients without ARDS are thought to outweigh any potential harm. Planned RCTs may inform future practice.

The semi-recumbent position has been demonstrated to decrease the incidence of VAP ([425]). Enteral feeding increased the risk of developing VAP; 50% of the patients who were fed enterally in the supine position developed VAP, compared with 9% of those fed in the semi-recumbent position ([425]). However, the bed position was monitored only once a day, and patients who did not achieve the desired bed elevation were not included in the analysis ([425]). One study did not show a difference in incidence of VAP between patients maintained in supine and semi-recumbent positions ([426]); patients assigned to the semi-recumbent group did not consistently achieve the desired head-of-bed elevation, and the head-of-bed elevation in the supine group approached that of the semi-recumbent group by day 7 ([426]). When necessary, patients may be laid flat when indicated for procedures, hemodynamic measurements, and during episodes of hypotension. Patients should not be fed enterally while supine. There were no new published studies since the last guidelines that would inform a change in the strength of the recommendation for the current iteration. The evidence profile for this recommendation demonstrated low quality of evidence. The lack of new evidence, along with the low harms of head-of-bed and high feasibility of implementation given the frequency of the practice resulted in the strong recommendation. There is a small subgroup of patients, such as trauma patients with a spine injury, for whom this recommendation would not apply.

Spontaneous breathing trial options include a low level of pressure support, CPAP (≈5 cm H_2O), or use of a T-piece. A recently published clinical practice guideline suggests the use of inspiratory pressure augmentation rather than T-piece or CPAP for an initial spontaneous breathing trial for acutely hospitalized adults on mechanical ventilation for more than 24 hours ([427]). Daily spontaneous breathing trials in appropriately selected patients reduce the duration of mechanical ventilation and weaning duration both in individual trials as well as

with pooled analysis of the individual trials ([428–430]). These breathing trials should be conducted in conjunction with a spontaneous awakening trial ([431]). Successful completion of spontaneous breathing trials leads to a high likelihood of successful early discontinuation of mechanical ventilation with minimal demonstrated harm.

Protocols allow for standardization of clinical pathways to facilitate desired treatment ([432]). These protocols may include both spontaneous breathing trials, gradual reduction of support, and computer-generated weaning. Pooled analysis demonstrates that patients treated with protocolized weaning compared with usual care experienced shorter weaning duration (–39 hours; 95% CI, –67 hours to –11 hours), and shorter ICU LOS (–9 hours; 95% CI, –15 to –2). There was no difference between groups in ICU mortality (OR, 0.93; 95% CI, 0.58–1.48) or need for reintubation (OR, 0.74; 95% CI, 0.44–1.23) ([428]).

Recommendation 48. (SSCG Section M, Recommendation 1).
We recommend using a target tidal volume of 6mL/kg predicted body weight (PBW) compared with 12 mL/kg in adult patients with sepsis-induced ARDS
Quality/level of evidence: High + Strength of recommendation: Strong

Recommendation 49. (SSCG Section M, Recommendation 2).
We recommend using an upper limit goal for plateau pressures of 30cm H_2O over higher plateau pressures in adult patients with sepsis-induced severe ARDS
Quality/level of evidence: Moderate + Strength of recommendation: Strong

Recommendation 50. (SSCG Section M, Recommendation 3).
We suggest using higher PEEP over lower PEEP in adult patients with sepsis-induced moderate to severe ARDS
Quality/level of evidence: Moderate + Strength of recommendation: Weak

Recommendation 51. (SSCG Section M, Recommendation 4).
We suggest using recruitment maneuvers in adult patients with sepsis-induced, severe ARDS
Quality/level of evidence: Moderate + Strength of recommendation: Weak

Recommendation 52. (SSCG Section M, Recommendation 5).
We recommend using prone over supine position in adult patients with sepsis-induced ARDS and a PaO_2/FIO_2 ratio < 150
Quality/level of evidence: Moderate + Strength of recommendation: Strong

Recommendation 53. (SSCG Section M, Recommendation 6).
We recommend against using high-frequency oscillatory ventilation (HFOV) in adult patients with sepsis-induced ARDS
Quality/level of evidence: Moderate + Strength of recommendation: Strong

Recommendation 54. (SSCG Section M, Recommendation 7).
We make no recommendation regarding the use of noninvasive ventilation (NIV) for patients with sepsis-induced ARDS.
Quality/level of evidence: N/A + Strength of recommendation: N/A

Recommendation 55. (SSCG Section M, Recommendation 8).

We suggest using neuromuscular blocking agents (NMBAs) for ≤ 48 hours in adult patients with sepsis- induced ARDS and a PaO_2/FiO_2 ratio < 150 mm Hg
Quality/level of evidence: Moderate + Strength of recommendation: Weak

Recommendation 56. (SSCG Section M, Recommendation 9).
We recommend a conservative fluid strategy for patients with established sepsis-induced ARDS who do not have evidence of tissue hypoperfusion
Quality/level of evidence: Moderate + Strength of recommendation: Strong

Recommendation 57. (SSCG Section M, Recommendation 10).
We recommend against the use of β-2 agonists for the treatment of patients with sepsis-induced ARDS without bronchospasm
Quality/level of evidence: Moderate + Strength of recommendation: Strong

Recommendation 58. (SSCG Section M, Recommendation 11).
We recommend against the routine use of the PA catheter for patients with sepsis-induced ARDS
Quality/level of evidence: High + Strength of recommendation: Strong

Recommendation 59. (SSCG Section M, Recommendation 12).
We suggest using lower tidal volumes over higher tidal volumes in adult patients with sepsis-induced respiratory failure without ARDS
Quality/level of evidence: Low + Strength of recommendation: Weak

Recommendation 60. (SSCG Section M, Recommendation 13).
We recommend that mechanically ventilated sepsis patients be maintained with the head of the bed elevated between 30 and 45 degrees to limit aspiration risk and to prevent the development of VAP
Quality/level of evidence: Low + Strength of recommendation: Strong

Recommendation 61. (SSCG Section M, Recommendation 14).
We recommend using spontaneous breathing trials in mechanically ventilated patients with sepsis who are ready for weaning
Quality/level of evidence: High + Strength of recommendation: Strong

Recommendation 62. (SSCG Section M, Recommendation 15).
We recommend using a weaning protocol in mechanically ventilated patients with sepsis-induced respiratory failure who can tolerate weaning
Quality/level of evidence: Moderate + Strength of recommendation: Strong

Implementation Point 20 (Recommendation 48)

Ventilated patients should be routinely measured for height to facilitate ideal body weight-based calculations of tidal volumes and where possible, for weight to facilitate drug dosing and nutritional requirements calculations.

3.1.12 Sedation and Analgesia

Key questions

- *In mechanically ventilated patients with sepsis, should we use sedation targets?*

SSCG Rationale

Limiting the use of sedation in critically ill ventilated patients reduces the duration of mechanical ventilation and ICU and hospital LOS, and allows earlier mobilization ([433], [434]). While these data arise from studies performed in a wide range of critically ill patients, there is little reason to believe that septic patients will not derive the same benefits from sedation minimization.

Several strategies have been shown to reduce sedative use and the duration of mechanical ventilation. Nurse-directed protocols that incorporate a sedation scale likely result in improved outcomes; however, the benefit depends on the existing local culture and practice ([435], [436]). Another option for systematically limiting the use of sedation is the administration of intermittent rather than continuous sedation ([437], [438]). Daily sedation interruption (DSI) was associated with improved outcomes in a single-centre randomized trial compared with usual care ([430]); however, in a multicentre RCT there was no advantage to DSI when patients were managed with a sedation protocol, and nurses perceived a higher workload ([439]). A recent Cochrane meta-analysis did not find strong evidence that DSI alters the duration of mechanical ventilation, mortality, ICU or hospital LOS, adverse event rates, or drug consumption for critically ill adults receiving mechanical ventilation compared to sedation strategies that do not include DSI; however, interpretation of the results is limited by imprecision and clinical heterogeneity ([440]). Another strategy is the primary use of opioids alone and avoidance of sedatives, which was shown to be feasible in the majority of ventilated patients in a single-centre trial, and was associated with more rapid liberation from mechanical ventilation ([441]). Finally, the use of short-acting drugs such as propofol and dexmedetomidine may result in better outcomes than the use of benzodiazepines ([442–444]). Recent pain, agitation, and delirium guidelines provide additional detail on implementation of sedation management, including nonpharmacologic approaches for the management of pain, agitation, and delirium ([445]).

Regardless of approach, a large body of indirect evidence is available demonstrating the benefit of limiting sedation in those requiring mechanical ventilation and without contraindication. As such, this should be best practice for any critically ill patient, including those with sepsis.

Recommendation 63. (SSCG Section N, Recommendation 1).
We recommend that continuous or intermittent sedation be minimized in mechanically ventilated sepsis patients, targeting specific titration end points

Quality/level of evidence: Low **+ Strength of recommendation: BPS**

Implementation Point 22 (Recommendation 63)

Practice guidelines for the management of pain, agitation and delirium should be adopted in all intensive care units.

Patients should receive the minimum sedation to reduce delirium and facilitate early rehabilitation. The aims of sedation should be outlined, and levels monitored. Pain, agitation and delirium are common complications among sepsis patients admitted to the

ICU and are associated with extended ICU length of stay and increased risk of developing neuropathic pain, cognitive impairment, and post-traumatic stress disorder[58]. Implementation of care bundles recommended by clinical practice guidelines could improve clinical outcomes in this domain[59, 60].

3.1.13 Glucose Control

Key questions

- *Should we use intensive insulin therapy in patients with sepsis or septic shock?*
- *Should we use arterial blood glucose level (versus point of care testing) in critically ill patients with severe sepsis or septic shock on insulin infusion?*

SSCG Rationale

A large single-centre RCT in 2001 demonstrated a reduction in ICU mortality with intensive IV insulin (Leuven protocol) targeting blood glucose to 80–110 mg/dL ([446]). A second randomized trial of intensive insulin therapy using the Leuven protocol enrolled medical ICU patients with an anticipated ICU LOS of more than three days in three medical ICUs; overall mortality was not reduced ([447]).

Since these studies ([446], [447]) appeared, several RCTs ([448–455]) and meta-analyses ([456–462]) of intensive insulin therapy have been performed. The RCTs studied mixed populations of surgical and medical ICU patients and found that intensive insulin therapy did not significantly decrease mortality, whereas the NICE-SUGAR trial demonstrated an increased mortality ([451]). All studies reported a much higher incidence of severe hypoglycaemia (glucose ≤ 40 mg/dL) (6%–29%) with intensive insulin therapy. Several meta-analyses confirmed that intensive insulin therapy was not associated with a mortality benefit in surgical, medical, or mixed ICU patients. The meta-analysis by Song et al ([462]) evaluated only septic patients and found that intensive insulin therapy did not change 28-day or 90-day mortality, but was associated with a higher incidence of hypoglycaemia. The trigger to start an insulin protocol for blood glucose levels > 180 mg/dL with an upper target blood glucose level < 180 mg/dL derives from the NICE-SUGAR trial, which used these values for initiating and stopping therapy. The NICE-SUGAR trial is the largest, most compelling study to date on glucose control in ICU patients given its inclusion of multiple ICUs and hospitals and a general patient population. Several medical organizations, including the American Association of Clinical Endocrinologists, American Diabetes Association, American Heart Association, American College of Physicians, and Society of Critical Care Medicine, have published consensus statements for glycaemic control of hospitalized patients ([463], [464]). These statements usually targeted glucose levels between 140 and 180 mg/dL. Because there is no evidence that targets between 140 and 180 mg/dL are different from targets of 110 to 140 mg/dL, the present recommendations use an upper target blood glucose ≤ 180 mg/dL without a lower target other than hypoglycaemia. Stricter ranges, such as 110–140 mg/dL, may be appropriate for selected patients if this can be achieved without significant hypoglycaemia ([463], [465]). Treatment should avoid hyperglycaemia (> 180 mg/dL), hypoglycaemia, and wide swings in glucose levels that have been associated with higher mortality ([466–471]). The continuation of insulin infusions, especially with the cessation of nutrition, has been identified as a risk factor for hypoglycaemia ([454]). Balanced nutrition may be associated with a reduced risk of hypoglycaemia ([472]). Hyperglycaemia and glucose variability seem to be unassociated with increased mortality rates in diabetic patients compared to nondiabetic patients ([473–475]). Patients with diabetes and chronic

hyperglycaemia, end-stage renal failure, or medical versus surgical ICU patients may require higher blood glucose ranges ([476], [477]).

Several factors may affect the accuracy and reproducibility of point-of-care testing of blood capillary blood glucose, including the type and model of the device used, user expertise, and patient factors, including haematocrit (false elevation with anaemia), PaO_2, and drugs ([478]). Plasma glucose values by capillary point-of-care testing have been found to be potentially inaccurate, with frequent false elevations ([479–481]) over the range of glucose levels, but especially in the hypoglycaemic and hyperglycaemic ranges ([482]) and in shock patients (receiving vasopressors) ([478], [480]). A review of studies found the accuracy of glucose measurements by arterial blood gas analysers and glucose meters by using arterial blood significantly higher than measurements with glucose meters using capillary blood ([480]). The U.S. Food and Drug Administration has stated that "critically ill patients should not be tested with a glucose meter because results may be inaccurate," and Centres for Medicare and Medicaid Services have plans to enforce the prohibition of off-label use of point-of-care capillary blood glucose monitor testing in critically ill patients ([483]). Several medical experts have stated the need for a moratorium on this plan ([484]). Despite the attempt to protect patients from harm because of inaccurate capillary blood testing, a prohibition might cause more harm because a central laboratory test may take significantly longer to provide results than point-of-care glucometer testing.

A review of 12 published insulin infusion protocols for critically ill patients showed wide variability in dose recommendations and variable glucose control ([485]). This lack of consensus about optimal dosing of IV insulin may reflect variability in patient factors (severity of illness, surgical versus medical settings), or practice patterns (e.g., approaches to feeding, IV dextrose) in the environments in which these protocols were developed and tested. Alternatively, some protocols may be more effective than others, a conclusion supported by the wide variability in hypoglycaemia rates reported with protocols. Thus, the use of established insulin protocols is important not only for clinical care, but also for the conduct of clinical trials to avoid hypoglycaemia, adverse events, and premature termination of trials before the efficacy signal, if any, can be determined. Several studies have suggested that computer-based algorithms result in tighter glycaemic control with a reduced risk of hypoglycaemia ([486], [487]). Computerized decision support systems and fully automated closed-loop systems for glucose control are feasible, but not yet standard care. Further study of validated, safe, and effective protocols and closed-loop systems for controlling blood glucose concentrations and variability in the sepsis population is needed.

Recommendation 64. (SSCG Section O, Recommendation 1).
We recommend a protocolized approach to blood glucose management in ICU patients with sepsis, commencing insulin dosing when two consecutive blood glucose levels are > 180mg/dL. This approach should target an upper blood glucose level ≤ 180 mg/dL (10mmol/L) rather than an upper target blood glucose level ≤ 110 mg/dL (6.1mmol/L).
Quality/level of evidence: High + Strength of recommendation: Strong

Recommendation 65: (SSCG Section O, Recommendation 2).
We recommend that blood glucose values be monitored every 1 to 2 hours until glucose values and insulin infusion rates are stable, then every 4 hours thereafter in patients receiving insulin infusions

Quality/level of evidence: Low **+ Strength of recommendation: BPS**

Recommendation 66. (SSCG Section O, Recommendation 3).
We recommend that glucose levels obtained with point- of-care testing of capillary blood be interpreted with caution because such measurements may not accurately estimate arterial blood or plasma glucose values.
Quality/level of evidence: Low **+ Strength of recommendation: BPS**

Recommendation 67. (SSCG Section O, Recommendation 4).
We suggest the use of arterial blood rather than capillary blood for point-of-care testing using glucose meters if patients have arterial catheters.
Quality/level of evidence: Low **+ Strength of recommendation: Weak**

3.1.14 Renal replacement therapy

Key questions

- *In patients with sepsis and indication for haemodialysis, should we use CRRT versus intermittent haemodialysis?*
- *In patients with sepsis and AKI with no indication for hemodialysis, should we use renal replacement therapy versus not?*

SSCG Rationale

Although numerous nonrandomized studies have reported a nonsignificant trend toward improved survival using continuous methods (488–494), two meta-analyses (495, 496) reported the absence of significant differences in hospital mortality between patients who receive CRRT and intermittent RRT. This absence of apparent benefit of one modality over the other persists even when the analysis is restricted to RCTs (496). To date, five prospective RCTs have been published (497–501); four found no significant difference in mortality (497, 498, 500, 501), whereas one found significantly higher mortality in the continuous treatment group (499); but imbalanced randomization had led to a higher baseline severity of illness in this group. When a multivariable model was used to adjust for severity of illness, no difference in mortality was apparent between the groups. Most studies comparing modes of RRT in the critically ill have included a small number of outcomes and had a high risk of bias (e.g., randomization failure, modifications of therapeutic protocol during the study period, combination of different types of CRRT, small number of heterogeneous groups of enrolees). The most recent and largest RCT (501) enrolled 360 patients and found no significant difference in survival between the continuous and intermittent groups. We judged the overall certainty of the evidence to be moderate and not in support of continuous therapies in sepsis independent of renal replacement needs.

For this revision of the guidelines, no additional RCTs evaluating the hemodynamic tolerance of continuous versus intermittent RRT were identified. Accordingly, the limited and inconsistent evidence persists. Two prospective trials (497, 502) have reported a better hemodynamic tolerance with continuous treatment, with no improvement in regional perfusion (502) and no survival benefit (497). Four other studies did not find any significant difference in MAP or drop in systolic pressure between the two methods (498, 500, 501,

503). Two studies reported a significant improvement in goal achievement with continuous methods (497, 499) regarding fluid balance management.

Two additional RCTs reporting the effect of dose of CRRT on outcomes in patients with acute renal failure were identified in the current literature review (504, 505). Both studies enrolled patients with sepsis and acute kidney injury and did not demonstrate any difference in mortality associated with a higher dose of RRT. Two large, multicentre, randomized trials comparing the dose of renal replacement (Acute Renal Failure Trial Network in the United States and RENAL Study in Australia and New Zealand) also failed to show benefit of more aggressive renal replacement dosing (506, 507). A meta-analysis of the sepsis patients included in all relevant RCTs (n = 1,505) did not demonstrate any significant relationship between dose and mortality; the point estimate, however, favors CRRT doses > 30 mL/kg/hr. Because of risk of bias, inconsistency, and imprecision, confidence in the estimate is very low; further research is indicated. A typical dose for CRRT would be 20–25 mL/kg/hr of effluent generation.

One small trial from 2002 (504) evaluated early versus "late" or "delayed" initiation of RRT; it included only four patients with sepsis and did not show any benefit of early CRRT. Since then, two relevant RCTs (508, 509) were published in 2016. Results suggest the possibility of either benefit (509) or harm (508) for mortality, increased use of dialysis, and increased central line infections with early RRT. Enrollment criteria and timing of initiation of RRT differed in the two trials. Results were judged to be of low certainty based on indirectness (many nonseptic patients) and imprecision for mortality. The possibility of harm (e.g., central line infections) pushes the balance of risk and benefit against early initiation of RRT. Meanwhile, the undesirable effects and costs appear to outweigh the desirable consequences; therefore, we suggest not using RRT in patients with sepsis and acute kidney injury for increase in creatinine or oliguria without other definitive indications for dialysis.

Recommendation 68. (SSCG Section P, Recommendation 1).
We suggest that either continuous RRT (CRRT) or intermittent RRT be used in patients with sepsis and acute kidney injury
Quality/level of evidence: Moderate + Strength of recommendation: Weak

Recommendation 69. (SSCG Section P, Recommendation 2).
We suggest using CRRT to facilitate management of fluid balance in hemodynamically unstable septic patients.
Quality/level of evidence: Very low + Strength of recommendation: Weak

Recommendation 70. (SSCG Section P, Recommendation 3).
We suggest against the use of RRT in patients with sepsis and acute kidney injury for increase in creatinine or oliguria without other definitive indications for dialysis.
Quality/level of evidence: Low + Strength of recommendation: Weak

3.1.15 Bicarbonate therapy

Key questions

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

SSCG Rationale

Although sodium bicarbonate therapy may be useful in limiting tidal volume in ARDS in some situations of permissive hypercapnia, no evidence supports the use of sodium bicarbonate therapy in the treatment of hypoperfusion-induced lactic acidaemia associated with sepsis. Two blinded, crossover RCTs that compared equimolar saline and sodium bicarbonate in patients with lactic acidosis failed to reveal any difference in hemodynamic variables or vasopressor requirements (510, 511). The number of patients with < 7.15 pH in these studies was small, and we downgraded the certainty of evidence for serious imprecision; further, patients did not have exclusively septic shock, but also had other diseases, such as mesenteric ischemia. Bicarbonate administration has been associated with sodium and fluid overload, an increase in lactate and Paco2, and a decrease in serum ionized calcium, but the directness of these variables to outcome is uncertain. The effect of sodium bicarbonate administration on haemodynamics and vasopressor requirements at lower pH, as well as the effect on clinical outcomes at any pH level, is unknown. No studies have examined the effect of bicarbonate administration on outcomes. This recommendation is unchanged from the 2012 guidelines.

Recommendation 71. (SSCG Section Q, Recommendation 1).
We suggest against the use of sodium bicarbonate therapy to improve hemodynamics or to reduce vasopressor requirements in patients with hypoperfusion-induced lactic acidemia with pH ≥ 7.15.
Quality/level of evidence: Moderate + Strength of recommendation: Weak

3.1.16 Venous thromboembolism prophylaxis

Key questions

- *Should we use pharmacologic VTE prophylaxis (UFH or LMWH) in critically ill patients with sepsis or septic shock?*
- *Should we use LMWH (versus UFH) for VTE prophylaxis in critically ill patients with sepsis or septic shock?*
- *Should we use mechanical VTE prophylaxis in critically ill patients with sepsis or septic shock?*
- *Should we use a combination of pharmacologic and mechanical prophylaxis vs. either alone in critically ill patients with sepsis or septic shock?*

SSCG Rationale

ICU patients are at risk for deep vein thrombosis (DVT) as well as pulmonary embolism (PE). The incidence of DVT acquired in the ICU may be as high as 10% (512); the incidence of acquired PE may be 2%–4% (513, 514). Patients with sepsis and septic shock are likely at increased risk for this complication. Vasopressor use, which is frequent in these patients, has been found to be an independent risk factor for ICU-acquired DVT.

A meta-analysis of pharmacologic prophylaxis with UFH or LMWH in critically ill patients showed significant reductions in both DVT and PE, with no significant increase in bleeding complications. Mortality was lower in the patients receiving prophylaxis, although this did

not reach statistical significance (514). All studies included in the meta-analysis were cited in the 2012 guideline, which recommended pharmacologic prophylaxis. No additional prospective randomized controlled trials related to this topic have been identified since the meta-analysis and the previous guideline were published (Supplemental Digital Content 12, http://links.lww.com/CCM/C333). Data in support of pharmacologic prophylaxis are considered somewhat indirect. Except for a large prospective randomized controlled trial comparing VTE in septic patients treated with drotrecogin alfa who were randomized to receive placebo versus UFH versus LWMH (515), all studies have been in an undifferentiated population of critically ill patients. Overall, we made a strong recommendation in favor of pharmacologic prophylaxis against VTE in critically ill patients based on the overall efficacy of this intervention, although the evidence was downgraded to moderate because of indirectness of the populations studied.

A number of studies have also compared use of LMWH to UFH for prevention of VTE prophylaxis in critically ill patients. Four trials were included in the meta-analysis of Alhazzani et al (514). We did not identify any new trials since then. In this meta-analysis, the overall rate of DVT was lower in patients receiving LWMH compared to UFH, and overall mortality was reduced by 7%; however, these differences did not reach statistical significance. In those trials evaluating PE, the rates were significantly lower in patients receiving LWMH. As with all studies of pharmacologic VTE prophylaxis, only one trial (515) was restricted to septic patients, and that trial utilized drotrecogin alfa in all patients. An additional meta-analysis found that LWMH was more effective than UFH in reducing the incidence of DVT and PE in critically ill patients (516). However, the authors of this meta-analysis included studies of critically ill trauma patients.

All studies of LMWH have compared these agents against UFH administered twice daily. No high-quality studies in critically ill patients have directly compared LWMH against UFH administered thrice daily. An indirect comparison meta-analysis published in 2011 failed to identify a significant difference in efficacy between twice-daily and thrice-daily heparin in medical patients (517). However, another review and meta-analysis (also using indirect comparison) suggested greater efficacy but higher rates of bleeding with thrice-daily UFH (518). A Cochrane review demonstrated a substantial decrease in the incidence of HIT in postoperative patients receiving LMWH compared to UFH (519), although the studies were not specific to either septic or critically ill patients. Finally, a cost-effectiveness analysis based on one trial of LMWH versus UFH (520) suggested that use of LMWH resulted in an overall decrease in costs of care, despite the higher acquisition cost of the pharmaceutical agent (521). Overall, the desirable consequences (i.e., reduction in PE, HIT, cost savings, and ease of administration) of using LMWH clearly outweigh the undesirable consequences; therefore, we made a strong recommendation in favour of LMWH instead of UFH, whenever feasible. However, the evidence for this was considered only of moderate quality because of indirectness, both with respect to the populations studied and also because LMWH has only been systematically compared to UFH administered twice daily, and not thrice daily.

Precautions are generally suggested regarding use of LMWH in patients with renal dysfunction. In a preliminary trial, no accumulation of anti-Xa levels was demonstrated with dalteparin in patients with a calculated creatinine clearance < 30 mL/min (522). Thus, these patients were included in the PROTECT study (520). In the actual trial, 118 patients with renal failure were analysed, 60 of whom were randomized to dalteparin and 58 to UFH.

There was no evidence of untoward reactions in patients receiving dalteparin compared to UFH. However, dalteparin was not more efficacious than UFH in this small number of patients. These investigators speculated that other types of LMWH might be safe to use in patients with renal failure, but acknowledged no other high-quality data to support this theory. Thus, use of LMWH in septic patients with renal dysfunction might be an option, but data in support of that remain quite limited.

Combined pharmacologic prophylaxis and mechanical prophylaxis with intermittent pneumatic compression (IPC) and/or graduated compression stockings (GCS) is a potential option in critically ill patients with sepsis and septic shock. No high-quality studies of this approach in septic patients, or even critically ill patients in general, exist; however, further research is ongoing (523). A Cochrane review (524) of 11 studies in surgical patients suggested that combined prophylaxis was more effective than either modality used alone. However, the quality of evidence was low due to indirectness of population and imprecision of estimates. Therefore, we can make only a weak recommendation for combined modality therapy for VTE prophylaxis in critically ill patients with sepsis or septic shock. Recent American College of Chest Physicians guidelines made no recommendation regarding the use of combined modality in critically ill patients, but do suggest use of combined mechanical and pharmacologic prophylaxis in high-risk surgical patients (525, 526).

A significant number of septic patients may have relative contraindications to the use of pharmacologic prophylaxis. These patients may be candidates for mechanical prophylaxis using IPC and/or GCS. However, relatively little data exist regarding this approach in critically ill patients. Two meta-analyses have been published comparing use of mechanical prophylaxis with no prophylaxis in combined patient groups, primarily those undergoing orthopedic surgery (527, 528). The former meta-analysis focused on use of GCS and the latter on use of IPC. In these analyses, both modalities appeared more effective than no mechanical prophylaxis, but variable numbers of patients received pharmacologic prophylaxis in both arms, making this evidence indirect. A cohort study of 798 patients using propensity scores for risk adjustment concluded that IPC was the only effective means for mechanical VTE prophylaxis in critically ill patients; however, there was heavy use of pharmacologic prophylaxis in all groups (529). Overall, based on these data, we made a weak recommendation for using mechanical prophylaxis in critically ill septic patients with contraindications to use of pharmacologic prophylaxis. Very limited evidence indicates that IPC may be more effective than GCS alone in critically ill patients, making it the preferred modality for mechanical prophylaxis.

Recommendation 72. (SSCG Section R, Recommendation 1).
We recommend pharmacologic prophylaxis (unfractionated heparin [UFH] or low-molecular-weight heparin [LMWH]) against venous thromboembolism (VTE) in the absence of contraindications to the use of these agents (SSCG Section G, Recommendation 6).
Quality/level of evidence: Moderate + Strength of recommendation: Strong

Recommendation 73. (SSCG Section R, Recommendation 2).
We recommend LMWH rather than UFH for VTE prophylaxis in the absence of contraindications to the use of LMWH (SSCG Section G, Recommendation 6).
Quality/level of evidence: Moderate + Strength of recommendation: Strong

Recommendation 74. (SSCG Section R, Recommendation 3).
We suggest combination pharmacologic VTE prophylaxis and mechanical prophylaxis, whenever possible (SSCG Section G, Recommendation 6).
Quality/level of evidence: Low + Strength of recommendation: Weak

Recommendation 75. (SSCG Section R, Recommendation 4).
We suggest mechanical VTE prophylaxis when pharmacologic VTE is contraindicated (SSCG Section G, Recommendation 6).
Quality/level of evidence: Low + Strength of recommendation: Weak

3.1.17 Stress ulcer prophylaxis

Key questions

- *Should we use stress ulcer prophylaxis in critically ill septic patients?*
- *Should we use PPIs (versus H2RA) for stress ulcer prophylaxis in critically ill septic patients?*

SSCG Rationale

Stress ulcers develop in the GI tract of critically ill patients and can be associated with significant morbidity and mortality ([530]). The exact mechanism is not completely understood, but is believed to be related to disruption of protective mechanisms against gastric acid, gastric mucosal hypoperfusion, increased acid production, and oxidative injury to the digestive track ([531]). The strongest clinical predictors of GI bleeding risk in critically ill patients are mechanical ventilation for > 48 hours and coagulopathy ([532]). A recent international cohort study showed that preexisting liver disease, need for RRT, and higher organ failure scores were independent predictors of GI bleeding risk ([533]). A multicentre prospective cohort study found the incidence of clinically important GI bleeding to be 2.6% (95% CI, 1.6%–3.6%) in critically ill patients ([533]); however, other observational studies showed lower rates of GI bleeding ([534–537]).

A recent systematic review and meta-analysis of 20 RCTs examined the efficacy and safety of stress ulcer prophylaxis ([538]). Moderate quality of evidence showed that prophylaxis with either H2RAs or PPIs reduced the risk of GI bleeding compared to no prophylaxis (RR, 0.44; 95% CI, 0.28–0.68; low quality of evidence showed a nonsignificant increase in pneumonia risk (RR, 1.23; 95% CI, 0.86–1.78) ([538]). Recently, a large, retrospective cohort study examined the effect of stress ulcer prophylaxis in patients with sepsis and found no significant difference in the risk of *C difficile* infection compared to no prophylaxis ([539]) (Supplemental Digital Content 13, http://links.lww.com/CCM/C334). The choice of prophylactic agent should depend on patients' characteristics, patients' values and preferences, and the local incidence of *C difficile* infections and pneumonia.

Although published RCTs did not exclusively include septic patients, risk factors for GI bleeding are frequently present in patients with sepsis and septic shock ([532]); therefore, using the results to inform our recommendations is acceptable. Based on the available evidence, the desirable consequences of stress ulcer prophylaxis outweigh the undesirable consequences; therefore, we made a strong recommendation in favor of using stress ulcer prophylaxis in patients with risk factors. Patients without risk factors are unlikely to develop clinically important GI bleeding during their ICU stay ([532]); therefore, stress ulcer prophylaxis

should only be used when risk factors are present, and patients should be periodically evaluated for the continued need for prophylaxis.

While there is variation in practice worldwide, several surveys showed that PPIs are the most frequently used agents in North America, Australia, and Europe, followed by H2RAs ([540–544]). A recent meta-analysis including 19 RCTs (n = 2,177) showed that PPIs were more effective than H2RAs in preventing clinically important GI bleeding (RR, 0.39; 95% CI, 0.21–0.71; *p* = 0.002; moderate quality), but led to a nonsignificant increase in pneumonia risk (RR, 1.17; 95% CI, 0.88–1.56; *p* = 0.28; low quality) ([544]) prior meta-analyses reached a similar conclusion ([545], [546]). None of the RCTs reported the risk of *C difficile* infection; nonetheless, a large retrospective cohort study demonstrated a small increase in the risk of *C difficile* infection with PPIs compared to H2RAs (2.2% vs. 3.8%; *p* < 0.001; very low-quality evidence). Studies reporting patients' values and preferences concerning the efficacy and safety of these agents are essentially lacking. Furthermore, cost-effectiveness analyses reached different conclusions ([547], [548]).

Consequently, the benefit of preventing GI bleeding (moderate-quality evidence) must be weighed against the potential increase in infectious complications (very low- to low-quality evidence). The choice of prophylactic agent will largely depend on individual patients' characteristics; patients' values; and the local prevalence of GI bleeding, pneumonia, and *C difficile* infection. Because of the uncertainties, we did not recommend one agent over the other. Ongoing trials aim to investigate the benefit and harm of withholding stress ulcer prophylaxis (clinicaltrials.gov registration NCT02290327, NCT02467621). The results of these trials will inform future recommendations.

Recommendation 76. (SSCG Section S, Recommendation 1).
We recommend that stress ulcer prophylaxis be given to patients with sepsis or septic shock who have risk factors for gastrointestinal (GI) bleeding.
Quality/level of evidence: Low + Strength of recommendation: Strong

Recommendation 77. (SSCG Section S, Recommendation 2).
We suggest using either proton pump inhibitors (PPIs) or histamine-2 receptor antagonists (H2RAs) when stress ulcer prophylaxis is indicated.
Quality/level of evidence: Low + Strength of recommendation: Weak

Recommendation 78. (SSCG Section S, Recommendation 3).
We recommend against stress ulcer prophylaxis in patients without risk factors for GI bleeding.
Quality/level of evidence: Low + Strength of recommendation: BPS

3.1.18 Nutrition

Key questions

- *Should we use early TPN versus early full enteral feeding in critically ill patients with sepsis or septic shock who can be fed enterally?*
- *Should we use early TPN versus no or early trophic enteral feeding in critically ill patients with sepsis or septic shock who have contraindications for early full enteral feeding?*

- *Should we use early full enteral feeding versus no initial enteral feeding (except IV glucose/dextrose) in critically ill patients with sepsis or septic shock without contraindications to enteral feeding?*
- *Should we use early full enteral feeding versus early trophic enteral feeding in patients with sepsis or septic shock without contraindications to enteral feeding?*
- *Should we use early trophic enteral feeding versus no early enteral feeding (except IV glucose/dextrose) in patients with sepsis or septic shock without contraindications to enteral feeding?*
- *Should we use omega-3 supplementation in patients with sepsis or septic shock?*
- *Should we measure gastric residuals when enterally feeding critically ill patients with sepsis or septic shock?*
- *Should we use enteral feeding via a gastric tube versus a post-pyloric tube in patients with sepsis or septic shock?*
- *Should we use prokinetic agents for enterally fed patients with sepsis or septic shock?*
- *Should we use selenium therapy in patients with severe sepsis or septic shock?*
- *Should we recommend glutamine therapy in critically ill patients with severe sepsis or septic shock?*
- *Should we use arginine therapy in patients with sepsis or septic shock?*
- *Should we use carnitine therapy patients with sepsis or septic shock?*

SSCG Rationale

Parenteral nutrition delivery can secure the intended amount of calories. This may represent an advantage over enteral nutrition, especially when patients may be underfed due to GI intolerance, which may be pertinent over the first days of care in the ICU. However, parenteral delivery is more invasive and has been associated with complications, including an increased risk of infections. Further, purported physiologic benefits are associated with enteral feeding, which make this strategy the mainstay of care (549). To address the question of the superiority of parenteral nutrition for patients with sepsis and septic shock, we evaluated the evidence for patients who could be fed enterally early versus those for whom early enteral feeding was not feasible.

Our first systematic review examined the impact of an early parenteral feeding strategy alone or in combination with enteral feeding versus enteral feeding alone on mortality in patients who could be fed enterally. We identified a total of 10 trials with 2,888 patients that were conducted in heterogeneous critically ill and surgical patients, trauma and traumatic brain injury, and those with severe acute pancreatitis (550–559). No evidence showed that early parenteral nutrition reduced mortality (RR 0.97; 95% CI, 0.87–1.08; n = 2,745) or infection risk (RR, 1.52; 95% CI, 0.88–2.62; n = 2,526), but ICU LOS was increased (MD, 0.90; 95% CI, 0.38–1.42; n = 46). The quality of the evidence was graded as moderate to very low. In the largest randomized trial that addressed this study question (CALORIES, n = 2,400), there were fewer episodes of hypoglycaemia and vomiting in the early parenteral group, but no differences in death between the study groups (553, 560). Due to the lack of mortality benefit, the added cost of parenteral nutrition in absence of clinical benefit (550, 551, 555, 560), and the potential physiologic benefits of enteral feeding (549, 561, 562), we

recommend early enteral nutrition as the preferred route of administration in patients with sepsis or septic shock who can be fed enterally.

In some patients with sepsis or septic shock, feeding enterally early may not be feasible because of contraindications related to surgery or feeding intolerance. These patients represent another subgroup of critically ill patients for whom the clinician may question whether to start parenteral nutrition early with or without some enteral feeding to meet nutritional goals, versus trophic/hypocaloric enteral feeding alone, or nothing except the addition of IV glucose/dextrose for the provision of some calories. To address this question, we conducted a systematic review, which included a total of four trials and 6,087 patients (563–566). Two of the included trials accounted for 98.5% of the patients included in the review and, of these trials, more than 65% of the patients were surgical critically ill patients (564, 567). Seven (20%) of the patients from these two trials were considered septic and patients with malnourishment were either excluded or represented a very small fraction (n = 46, 3.3%) of the included patients. In three of the included trials, parenteral nutrition was initiated if enteral feeding was not tolerated after the first 7 days of care (564, 566, 567). Our review found that early parenteral nutrition with or without supplementation of enteral nutrition was not associated with reduced mortality (RR, 0.96; 95% CI, 0.79–1.16; n = 6,087; moderate-quality evidence), but was associated with increased risk of infection (RR, 1.12; 95% CI, 1.02–1.24; 3 trials; n = 6,054; moderate-quality evidence) (Supplemental Digital Content 14, http://links.lww.com/CCM/C335). Length of ventilation outcomes were reported divergently in the two large trials, with one suggesting an increase (567) and the other a decrease (564) in ventilation time associated with early parenteral nutrition. One trial also reported less muscle wasting and fat loss in the early parenteral nutrition group according to a Subjective Global Assessment Score (564). In summary, due to the lack of mortality benefit, the increased risk of infection, and the extra cost for parenteral nutrition in the absence of clinical benefit (568), current evidence does not support the initiation of early parenteral nutrition over the first 7 days of care for patients with contraindications or intolerance to enteral nutrition. Specific patient groups may benefit more or incur more harm with early initiation of parenteral nutrition in this context. We encourage future research according to individual patient level meta-analyses to characterize these subgroups and plan for future randomized trials. It is important to note that patients who were malnourished were either excluded or rarely represented in the included trials from our systematic review. Since so few malnourished patients were enrolled, evidence to guide practice is lacking. Malnourished patients may represent a subgroup of critically ill patients for whom the clinician may consider initiating parenteral nutrition early when enteral feeding is not feasible.

The early administration of enteral nutrition in patients with sepsis and septic shock has potential physiologic advantages related to the maintenance of gut integrity and prevention of intestinal permeability, dampening of the inflammatory response, and modulation of metabolic responses that may reduce insulin resistance ([561], [562]). To examine evidence for this nutrition strategy, we asked if early full feeding (started within the first 48 hours and feeding goals to be met within 72 hours of ICU admission or injury) as compared to a delayed strategy (feeds delayed for at least 48 hours) improved the outcome of our critically ill patients. In our systematic review, we identified a total of 11 trials in heterogeneous critically ill patient populations (n = 412 patients) ([569–579]). Only one trial was specifically conducted in patients with sepsis (n = 43 patients) ([577]). The risk of death was not

significantly different between the groups (RR, 0.75; 95% CI, 0.43–1.31; n = 188 patients), and infections were not significantly reduced (RR, 0.60; 95% CI, 0.34–12.07; n = 122 patients). Other recent systematic reviews in the critically ill focused specifically on trauma (three trials, 126 patients) or more heterogeneous critically ill populations (6 trials, n = 234 patients) and found that early enteral feeding reduced death and pneumonia ([580], [581]). However, in contrast to our systematic review, these latter reviews did not include studies in which enteral feeding in the intervention arm was both early and full and where the control arm feeding strategy was delayed for at least the first 48 hours. We also examined whether the provision of an early trophic/hypocaloric feeding strategy (defined by enteral feeding started within the first 48 hours and up to 70% of target caloric goals for at least 48 hours) was superior to a delayed enteral feeding strategy. In the two trials that fit these criteria, there were no statistical differences in death (RR, 0.67; 95% CI, 0.35–1.29; n = 229; low-quality evidence) or infection (RR, 0.92; 95% CI, 0.61–1.37; n = 229; very low-quality evidence) between the groups ([582], [583]). Since the present evidence does not suggest harm with early versus delayed institution of enteral feeding, and there is possible benefit from physiologic evidence suggesting reduced gut permeability, inflammation, and infection risk, the committee issued a weak recommendation to start feeding early in patients with sepsis and septic shock.

Some evidence suggests that intentional early underfeeding as compared to early full feeding of critically ill patients may lead to immune hyporesponsiveness and an increase in infectious complications ([549]). Further, because critical illness is associated with loss of skeletal mass, it is possible that not administering adequate protein may lead to challenges weaning from the ventilator and more general weakness. However, a biological rationale for a trophic/hypocaloric or hypocaloric feeding strategy exists, at least as the initial approach to feeding the critically ill as compared to a fully fed strategy. Limiting caloric intake stimulates autophagy, which is considered a defence mechanism against intracellular organisms and therefore raises the possibility that this approach could reduce infection risk ([584], [585]).

We defined feeds as trophic/hypocaloric if goal feeds were 70% or less of standard caloric targets for at least a 48-hour period before they were titrated toward goal. Our systematic review identified seven randomized trials and 2,665 patients studied ([584], [586–591]). Patient populations included heterogeneous critically ill patients and those with acute lung injury and/or ARDS. Patients who were malnourished were excluded from four of the trials ([588–591]) and the average body mass index in the remaining three trials ranged from 28 to 30 ([584], [586], [587]). Targets for trophic/hypocaloric feeding groups ranged from 10 to 20 kcal/hr to up to 70% of target goal. Study intervention periods ranged from 6 to 14 days (or until ICU discharge). In three of the trials, protein (0.8–1.5 g/kg/d) was administered to the trophic/hypocaloric group to meet protein requirements ([584], [586], [587]). Overall, there were no differences in mortality (RR, 0.95; 95% CI, 0.82–1.10; n = 2,665; high-quality evidence), infections (RR, 0.96; 95% CI, 0.83–1.12; n = 2,667; moderate-quality evidence), or ICU LOS (MD, –0.27 days; 95% CI, –1.40 to 0.86, n = 2,567; moderate-quality evidence between the study groups) (Supplemental Digital Content 15, http://links.lww.com/CCM/C336). One trial that instituted hypocaloric feeding (goal 40%–60% target feeds for up to 14 days) reported a subgroup of 292 patients with sepsis; there were also no detectable differences in death at 90 days between the study groups (RR, 0.95; 95% CI, 0.71–1.27; p = 0.82 for interaction) ([584]). A recently published systematic review of normocaloric versus hypocaloric feeding also

found no differences in hospital mortality, infections, ICU LOS, or ventilator-free days between the study groups ([585]). Some evidence also suggests a lack of adverse consequences even with longer-term outcomes. A trophic/hypocaloric feeding trial of 525 patients, which instituted the most significant restrictions in enteral feeding (20% of caloric goal) for up to 6 days, found no differences in muscle strength, muscle mass, and 6-minute walk test at 6 months or 1 year, although patients in the trophic/hypocaloric feeding group were more likely to be admitted to a rehabilitation facility during the first 12 months of follow-up ([592]). The current evidence base would suggest that a trophic/hypocaloric or early full enteral feeding strategy is appropriate. However, for patients with sepsis or septic shock who are not tolerating enteral feeds, trophic/hypocaloric feeding may be preferred, with feeds titrated over time according to patient tolerance. There is insufficient evidence to confirm that a trophic/hypocaloric feeding strategy is effective and safe in patients who are malnourished (body mass index < 18.5) because these patients were either excluded or rarely represented in the clinical trials from our systematic review. Until further clinical evidence is generated for this subpopulation, the clinician may consider titrating enteral feeds more aggressively in accordance with patient tolerance while monitoring for re-feeding syndrome. Current evidence did not specifically address patients with high vasopressor requirements, and the decision about withholding the feeds should be individualized.

Use of omega-3 fatty acids in the context of clinical trials in the critically ill has been a subject of interest during the past several years because of the immunomodulatory potential ([593]). However, systematic reviews of parenteral or enteral omega-3 supplementation in critically ill and ARDS patients have not confirmed their therapeutic benefit ([594], [595]). Further, a recent randomized trial of 272 patients with acute lung injury found excess harm related to mortality as well as fewer ventilator- and ICU-free days in the omega-3 arm as compared to the control arm ([596]). A limitation of this trial as well as several other omega-3 trials is that the intervention arm also contained vitamins and trace mineral supplementation, making omega-3 fatty acids alone difficult to isolate as the cause for harm or benefit. For these reasons, we conducted a systematic review of clinical trials in the critically ill that administered omega-3 alone in the intervention arm. In a total of 16 trials (n = 1,216 patients), there were no significant reductions in death (RR, 0.86; 95% CI, 0.71–1.03; low quality evidence); however, ICU LOS was significantly reduced in the omega-3 group (MD, –3.84 days; 95% CI, –5.57 to –2.12, very low-quality evidence). The overall quality of the evidence was graded as low. Due to the uncertainty of benefit, the potential for harm, and the excess cost and varied availability of omega-3 fatty acids, we make a strong recommendation against the use of omega-3 fatty acids for patients with sepsis and septic shock outside the conduct of RCTs.

Critically ill patients are at significant risk for GI dysmotility, which may then predispose them to regurgitation or vomiting, aspiration, and the development of aspiration pneumonia. The rationale for measurement of GRVs is to reduce the risk for aspiration pneumonia by either ceasing or modifying the enteral feeding strategy based on the detection of excess gastric residuals. The inherent controversy is that observational and interventional studies have not consistently confirmed a relationship between the measurement of GRVs (with thresholds ranging from 200 mL to no monitoring of GRVs) and outcomes of vomiting, aspiration, or pneumonia ([597–603]). In our systematic review, we identified one multicentre non-inferiority trial of 452 critically ill patients who were randomized to not monitoring GRVs versus monitoring GRVs at 6-hour intervals ([602]).

Intolerance to feeds was defined as vomiting in the intervention group versus a GRV of > 250 mL, vomiting, or both in the control group. Although vomiting was more frequent (39.6% versus 27%; median difference, 12.6; 95% CI, 5.4–19.9) in the group in which GRVs were not monitored, a strategy of not monitoring GRVs was found to be non-inferior compared to monitoring at 6-hour intervals with regard to the primary outcome of VAP (16.7% versus 15.8% respectively; difference, 0.9%; 95% CI, –4.8% to 6.7%). No detectable differences in death were shown between the study groups at 28 and 90 days. Patients who had surgery up to one month prior to study eligibility were not included in this study, so these results should not be applied to surgical critically ill patients. However, the results of this trial question the need to measure GRVs as a method to reduce aspiration pneumonia in all critically ill patients. Due to the absence of harm and the potential reduction in nursing resources needed to monitor patients, we suggest against routine monitoring of GRVs in all patients with sepsis unless the patient has demonstrated feeding intolerance (e.g., vomiting, reflux of feeds into the oral cavity) or for patients who are considered to be at high risk for aspiration (e.g., surgery, hemodynamic instability). We recommend the generation of further evidence through the conduct of future randomized controlled trials targeted to higher-risk patient groups such as the surgical population or those in shock to determine the threshold and frequency with which GRVs should be monitored.

Feeding intolerance is defined as vomiting, aspiration of gastric contents, or high GRVs. For multiple reasons, feeding intolerance commonly develops in critically ill patients. Patients with preexisting gastroparesis or diabetes or those who are receiving sedatives and vasopressors are at risk. Prokinetic agents, including metoclopramide, domperidone, and erythromycin, are frequently used in the ICU. Each of these agents has different pharmacodynamics and pharmacokinetic properties; however, these agents may be associated with prolongation of QT interval and ventricular arrhythmias. A large case-control study in non-ICU patients showed a threefold increase in risk of sudden cardiac death with domperidone use at doses > 30 mg/day ([604]). Another retrospective cohort study showed that outpatient use of erythromycin is associated with a twofold increase in the risk of sudden cardiac death, especially if concomitantly used with other CYP3A inhibitors ([605]). The impact on ventricular arrhythmias in ICU patients is less clear.

A recent systematic review and meta-analysis included 13 RCTs enrolling 1,341 critically ill patients showed that prokinetic agent use was associated with lower risk of feeding intolerance (RR, 0.73; 95% CI, 0.55–0.97; moderate-quality evidence). This was equivalent to an absolute risk reduction of 17%. The use of prokinetic agents did not significantly increase mortality (RR, 0.97; 95% CI, 0.81–1.1; low-quality evidence); however, the incidence of fatal or nonfatal cardiac arrhythmias was not consistently reported across studies. There was no significant effect on the risk of pneumonia or vomiting. The majority of trials examined the effect of metoclopramide or erythromycin; subgroup analysis by drug class was underpowered to detect important subgroup differences ([606]). We considered the desirable consequences (lower risk of feeding intolerance) and the low quality of evidence showing no difference in mortality or pneumonia, and issued a weak recommendation for using prokinetic agents (metoclopramide or erythromycin) to treat feeding intolerance in patients with sepsis. Future large comparative trials are needed to determine the relative efficacy and safety of different agents.

Monitoring the QT interval with serial electrocardiograms is required when these agents are used in the ICU, especially if concomitantly used with other agents that could prolong the QT interval ([607]). The need for prokinetic agents should be assessed daily, and they should be stopped when clinically not indicated.

Feeding intolerance is defined as vomiting, abdominal distention, or high GRVs that result in interruption of enteral nutrition. Critically ill patients are at risk of gastroparesis and feeding intolerance; evidence of delayed gastric emptying can be found in approximately 50% of critically ill patients ([608]). The proportion of patients who will progress to develop clinical symptoms is less clear. Feeding intolerance can result in interruption of nutritional support, vomiting, aspiration of gastric contents, or pneumonia ([609]). The pathophysiology is not completely understood and is likely to be multifactorial. Gastroparesis can be caused by pharmacologic agents that are frequently used in the ICU (e.g., sedatives, opioids, or NMBAs), gastric hypoperfusion in the context of shock, hyperglycaemia, or vasopressor use ([610–612]).

Post-pyloric tubes have the theoretical advantage of improving feeding intolerance in patients with gastroparesis, consequently improving the delivery of nutrition into the gut. Post-pyloric feeding tubes, although safe, are not always available, and require technical skill for successful insertion. Gastric air insufflation and prokinetic agents are both effective strategies to facilitate the insertion of post-pyloric tubes in critically ill patients ([613]). Endoscopy and an external magnet device can also be used to guide post-pyloric tube insertion, but are not always available, are expensive, and require a higher level of expertise.

We conducted a systematic review and meta-analysis of randomized trials to examine the effect of post-pyloric (compared to gastric) feeding on patient-important outcomes. We identified 21 eligible RCTs enrolling 1,579 patients. Feeding via post-pyloric tube reduced the risk of pneumonia compared to gastric tube feeding (RR, 0.75; 95% CI, 0.59–0.94; low-quality evidence). This translates into a 2.5% (95% CI, 0.6%–4.1%) absolute reduction in pneumonia risk. However, there was no significant effect on the risk of death, aspiration, or vomiting (Supplemental Digital Content 16, http://links.lww.com/CCM/C337). This is consistent with the results of older meta-analyses ([614], [615]). Although the use of post-pyloric tubes reduced risk of pneumonia, the quality of evidence was low, the magnitude of benefit was small, and there was uncertainty about the effect on other patient-important outcomes. Cost-effectiveness studies that describe the economic consequences of using post-pyloric feeding tubes are lacking. Therefore, we decided that the balance between desirable and undesirable consequences was unclear in low-risk patients; however, the use of post-pyloric feeding tubes may be justified in patients at high risk of aspiration (i.e., patients with history of recurrent aspiration, severe gastroparesis, feeding intolerance, or refractory medical treatment).

Selenium was administered in the hope that it could correct the known reduction of selenium concentration in sepsis patients and provide a pharmacologic effect through an antioxidant defence. Although some RCTs are available, the evidence for the use of IV selenium is not convincing. Two recent meta-analyses suggest, with weak findings, a potential benefit of selenium supplementation in sepsis ([616], [617]). However, a recent large RCT also examined the effect on mortality rates ([618]). Overall pooled odds ratio (0.94; CI,

0.77–1.15) suggests no significant impact on mortality with sepsis. Also, no differences in secondary outcomes of development of nosocomial pneumonia or ICU LOS were found. When updating our meta-analysis to include the results of this recent study, there was no difference in mortality between both groups (**Supplemental Digital Content 17, http://links.lww.com/CCM/C338**).

Arginine availability is reduced in sepsis, which can lead to reduced nitric oxide synthesis, loss of microcirculatory regulation, and enhanced production of superoxide and peroxynitrite. However, arginine supplementation could lead to unwanted vasodilation and hypotension ([619], [620]). Human trials of L-arginine supplementation have generally been small and reported variable effects on mortality ([621–624]). The only study in septic patients showed improved survival, but had limitations in study design ([623]). Other studies suggested no benefit or possible harm in the subgroup of septic patients ([621], [624], [625]). Some authors found improvement in secondary outcomes in septic patients, such as reduced infectious complications) and hospital LOS, but the relevance of these findings in the face of potential harm is unclear.

Glutamine levels are also reduced during critical illness. Exogenous supplementation can improve gut mucosal atrophy and permeability, possibly leading to reduced bacterial translocation. Other potential benefits are enhanced immune cell function, decreased proinflammatory cytokine production, and higher levels of glutathione and antioxidative capacity ([619], [620]). However, the clinical significance of these findings is not clearly established.

Although a previous meta-analysis showed mortality reduction ([626]), several other meta-analyses did not ([627–630]) Four recent well-designed studies also failed to show a mortality benefit in the primary analyses, although none focused specifically on septic patients ([631–634]). Two small studies on septic patients showed no benefit in mortality rates ([635], [636]), but showed a significant reduction in infectious complications ([636]) and a faster recovery of organ dysfunction.

Massive disruption in energy metabolism contributes to sepsis severity and end organ failure. The magnitude of the energy shift, and, possibly more importantly, the host's metabolic adaptiveness to the shift in energy demand, likely influence patient survival. Carnitine, endogenously manufactured from lysine and methionine, is required for the transport of long-chain fatty acids into the mitochondria and the generation of energy. As such, carnitine utilization is essential for enabling the switch from glucose to long-chain fatty acid metabolism during the sepsis energy crisis. This is the basis for the rationale of employing L-carnitine as a therapeutic in sepsis. One small randomized trial in patients with sepsis reported a 28-day mortality decrease in septic shock patients treated with IV L-carnitine therapy within 24 hours of shock onset; however, the trial was underpowered to detect such a difference ([637]). Larger, ongoing trials should provide more evidence of the usefulness of carnitine supplementation.

Recommendation 79. (SSCG Section T, Recommendation 1).

We recommend against the administration of early parenteral nutrition alone or parenteral nutrition in combination with enteral feedings (but rather initiate early enteral nutrition) in critically ill patients with sepsis or septic shock who can be fed enterally.
Quality/level of evidence: Moderate + Strength of recommendation: Strong

Recommendation 80. (SSCG Section T, Recommendation 2).
We recommend against the administration of parenteral nutrition alone or in combination with enteral feeds (but rather to initiate IV glucose and advance enteral feeds as tolerated) over the first 7 days in critically ill patients with sepsis or septic shock for whom early enteral feeding is not is not feasible.
Quality/level of evidence: Moderate + Strength of recommendation: Strong

Recommendation 81. (SSCG Section T, Recommendation 3).
We suggest the early initiation of enteral feeding rather than a complete fast or only IV glucose in critically ill patients with sepsis or septic shock who can be fed enterally.
Quality/level of evidence: Low + Strength of recommendation: Weak

Recommendation 82. (SSCG Section T, Recommendation 4).
We suggest either early trophic/hypocaloric or early full enteral feeding in critically ill patients with sepsis or septic shock; if trophic/hypocaloric feeding is the initial strategy, then feeds should be advanced according to patient tolerance.
Quality/level of evidence: Moderate + Strength of recommendation: Weak

Recommendation 83. (SSCG Section T, Recommendation 5).
We recommend against the use of omega-3 fatty acids as an immune supplement in critically ill patients with sepsis or septic.
Quality/level of evidence: Low + Strength of recommendation: Strong

Recommendation 84. (SSCG Section T, Recommendation 6).
We suggest against routinely monitoring gastric residual volumes (GRVs) in critically ill patients with sepsis or septic shock (weak recommendation, low quality of evidence). However, we suggest measurement of gastric residuals in patients with feeding intolerance or who are considered to be at high risk of aspiration.
Quality/level of evidence: Very low + Strength of recommendation: Weak

Remarks: *This recommendation refers to nonsurgical critically ill patients with sepsis or septic shock.*

Recommendation 85. (SSCG Section T, Recommendation 7).
We suggest the use of prokinetic agents in critically ill patients with sepsis or septic shock and feeding intolerance.
Quality/level of evidence: Low + Strength of recommendation: Weak

Recommendation 86. (SSCG Section T, Recommendation 8).
We suggest placement of post-pyloric feeding tubes in critically ill patients with sepsis or septic shock with feeding intolerance or who are considered to be at high risk of aspiration.
Quality/level of evidence: Low + Strength of recommendation: Weak

Recommendation 87. (SSCG Section T, Recommendation 9).
We recommend against the use of IV selenium to treat sepsis and septic shock.
Quality/level of evidence: Moderate + Strength of recommendation: Strong

Recommendation 88. (SSCG Section T, Recommendation 10).
We suggest against the use of arginine to treat sepsis and septic shock.

Quality/level of evidence: Low **+ Strength of recommendation: Weak**

Recommendation 89. (SSCG Section T, Recommendation 11).
We recommend against the use of glutamine to treat sepsis and septic shock.
Quality/level of evidence: Moderate **+ Strength of recommendation: Strong**

Recommendation 90. (SSCG Section T, Recommendation 12).
We make no recommendation about the use of carnitine for sepsis and septic shock.
Quality/level of evidence: N/A **+ Strength of recommendation: N/A**

Implementation Points for Nutrition Support Provision in ICU Patients with Sepsis were provided by a *subgroup of the ICU Dietitians Group of INDI (Irish Nutrition and Dietetic Institute)*

Overall implementation point

Critically ill patients including those with sepsis have complex nutritional needs and require intensive nutritional input. The importance of recognising different phases of critical illness when considering route, timing and dose of nutrition support is an essential component of managing nutrition support in individual ICU patients. For implementation and further details on nutritional care of critically ill patients, see the Critical Care Programme Intensive Care Nutrition Support Algorithm 2019 update.

Implementation point (Recommendation 79)

All patients should be screened on admission to ICU to assess their nutrition risk and the need for nutrition support (Singer *et al*., 2018, McClave *et al*., 2016). This should be followed by a nutritional assessment. See Tables 6 and 7 from the Critical Care Programme Intensive Care Nutrition Support Algorithm 2019 update for general principles around early enteral nutrition and guidance on delaying, commencing low dose or commencing early progressive enteral nutrition.

Implementation point (Recommendation 80)

Optimal timing of initiation of parenteral nutrition in ICU patients remains unclear. In light of conflicting evidence, a pragmatic approach to commencing Parenteral Nutrition (PN) in ICU patients would be to start on day 3-4 when enteral feeding has failed or is contraindicated. Malnourished patients are not represented in available RCTs, as highlighted above. Consideration should be given to commencing PN earlier than day 7 in patients at high nutrition risk or severely malnourished, where EN is contraindicated (Singer *et al*., 2018).

Implementation Point (Recommendation 84)

Traditionally in the ICU setting, a measurement of Enteral Nutrition (EN) tolerance using Gastric Residual Volume (GRV) monitoring is carried out at regular intervals and feed rate is reduced or suspended if levels are above an agreed cut-off. Abandoning this practice as routine care has been suggested in recent nutrition support guidelines (Mc Clave *et al*., 2016). GRV measurement correlates poorly with gastric emptying, as well as incidence of regurgitation and aspiration and has been shown to contribute to reduce EN delivery.

However, evidence for omission of GRV measurement is largely based on one trial where difficult to feed patients, such as those with multi-organ failure, and surgical patients were under-represented. For this reason, Canadian (2015) and European (Singer *et al.,* 2018) guidelines still recommend a GRV cut off level between 250-500ml and that measurement is done at 4-8 hourly intervals. When EN is established continued monitoring of GRVs may not be necessary.

3.1.19 Setting goals of care

Key questions

- *In patients with sepsis, should we recommend discussion of goals of care and prognosis with family?*
- *In patients with sepsis, should we recommend incorporating palliative and end-of-life care?*
- *Should we recommend addressing goals of care early (within 72 hours) during ICU stay?*

SSCG Rationale

Patients with sepsis and multiple organ system failure have a high mortality rate; some will not survive or will have a poor quality of life. Although the outcome of intensive care treatment in critically ill patients may be difficult to prognosticate accurately, establishing realistic ICU treatment goals is paramount (638), especially because inaccurate expectations about prognosis are common among surrogates (639). Nonbeneficial ICU advanced life-prolonging treatment is not consistent with setting goals of care (640, 641). Models for structuring initiatives to enhance care in the ICU highlight the importance of incorporating goals of care, along with prognosis, into treatment plans (642). The use of proactive family care conferences to identify advance directives and treatment goals within 72 hours of ICU admission has been demonstrated to promote communication and understanding between the patient's family and the treating team; improve family satisfaction; decrease stress, anxiety, and depression in surviving relatives; facilitate end-of-life decision-making; and shorten ICU LOS for patients who die in the ICU (643, 644). Promoting shared-decision-making with patients and families is beneficial in ensuring appropriate care in the ICU and that futile care is avoided (641, 645, 646).

Palliative care is increasingly accepted as an essential component of comprehensive care for critically ill patients regardless of diagnosis or prognosis (642, 647). Use of palliative care in the ICU enhances the ability to recognize pain and distress; establish the patient's wishes, beliefs, and values, and their impact on decision-making; develop flexible communication strategies; conduct family meetings and establish goals of care; provide family support during the dying process; help resolve team conflicts; and establish reasonable goals for life support and resuscitation (648).

A recent systematic review of the effect of palliative care interventions and advanced care planning on ICU utilization identified that, despite wide variation in study type and quality among nine randomized control trials and 13 nonrandomized controlled trials, patients who received advance care planning or palliative care interventions consistently showed a pattern toward decreased ICU admissions and reduced ICU LOS (649).

However, significant inter-hospital variation in ratings and delivery of palliative care is consistent with prior studies showing variation in intensity of care at the end of life (650). Despite differences in geographic location, legal system, religion, and culture, there is worldwide professional consensus for key end-of-life practices in the ICU (651).

Promoting patient- and family-centered care in the ICU has emerged as a priority and includes implementation of early and repeated care conferencing to reduce family stress and improve consistency in communication; open flexible visitation; family presence during clinical rounds, resuscitation, and invasive procedures; and attention to cultural and spiritual support (652–655).

Recommendation 91. (SSCG Section U, Recommendation 1).
We recommend that goals of care and prognosis be discussed with patients and families.
Quality/level of evidence: Low + Strength of recommendation: BPS

Recommendation 92. (SSCG Section U, Recommendation 2).
We recommend that goals of care be incorporated into treatment and end-of-life care planning, utilizing palliative care principles where appropriate.
Quality/level of evidence: Moderate + Strength of recommendation: Strong

Recommendation 93. (SSCG Section U, Recommendation 3).
We suggest that goals of care be addressed as early as feasible, but no later than within 72 hours of ICU admission.
Quality/level of evidence: Low + Strength of recommendation: Weak

3.2 Rehabilitation and post-discharge care

The evidence base behind the benefits of structured rehabilitation for post sepsis patients is still evolving and further research is on-going. A summary of the findings to date with suggested good practice points are outlined below. These good practice points are divided in hospital practices aimed at preventing long-term morbidity, and post-hospital discharge strategies designed to screen, evaluate and manage clinical conditions among sepsis survivors.

HOSPITAL PRACTICES FOR PREVENTING LONG-TERM MORBIDITY:

The GDG recognises that the good practice points for hospital practices below are already current practice and anticipates that no additional funding will be required for implementing in a more standardised way.

- Awareness of the long-term sequelae of sepsis and septic shock should be promoted amongst healthcare providers, patients and/or next of kin.
- Mobilisation and physical rehabilitation should start as early as clinically possible during hospital stay, basing rehabilitation goals on the clinical assessment of healthcare professionals experienced in critical care and rehabilitation.

- The approach to sepsis patients admitted to the ICU should align with international practice guidelines for the management of pain, agitation, delirium and sleep disruption.
- Sepsis information booklets[21] should be made available to the relatives and friends of patients admitted to a critical care area with sepsis.
- The option of starting a diary should be considered.
- Pre-discharge assessment of sepsis patients should include checking for ongoing dietetics, physiotherapy and psychosocial requirements and referral for community follow-up based on their clinical need.
- Pre-discharge medication reconciliation.
- The discharge letter provided to Primary Care Physicians should include ongoing dietetic, physiotherapy and psychosocial requirements as well as hospital diagnoses, treatment and ongoing medication.

POST-HOSPITAL DISCHARGE STRATEGIES FOR ASSESSMENT AND MANAGEMENT OF CLINICAL SEQUELAE

The GDG recognises that additional funding will be required to implement the good practice points for post-hospital discharge outlined below. However, these good practice points support the Government policy direction for Ireland's healthcare system - Slaintecare (Government of Ireland 2017) and should be considered as part of the expansion of capacity to deliver healthcare closer to the patient in the community.

- The utilisation of a structured clinical evaluation method such as the 'Framework for evaluating and treating patients in the 90 days after hospitalization for sepsis'(REF), (Appendix 10), aimed at screening for common mental and physical impairments after sepsis at outpatient clinic review post discharge or by GP's.
- Individualising protocols of physical rehabilitation aimed at improving function in activities of daily living (ADL), functional exercise capacity, aerobic capacity, and skeletal muscle strength, with focus on respiratory muscles.
- Self-management practices and peer-support as valuable resources to mitigate mental health impairments.

Rationale:

A recent meta-analysis of epidemiological studies estimated yearly worldwide hospital survival after sepsis to be as high as 73%[61]. A considerable proportion of sepsis survivors, however, manifest an increased likelihood of long-term morbidity when compared to matched cohorts[62, 63, 64, 65, 66, 67]. Common long-term sequelae after sepsis include the following: cognitive impairment with decline in cognitive functions such as verbal fluency, memory and attention, and executive functioning[68]; deterioration of mental health status related to depression[69, 70], anxiety[71], and post-traumatic stress disorder[72, 73]; physical disabilities that result in swallowing difficulties[65] and functional limitations of activities of daily living (ADLs)[62]; increased predisposition to recurrent infections[66, 74]; progression and

aggravation of chronic medical conditions such as congestive heart failure, chronic kidney disease, and chronic obstructive pulmonary disease[66]; and occurrence of acute or acute-on-chronic events such as myocardial infarction, stroke, ventricular arrhythmias and sudden death[65, 67]. Overall, a combination of long-term sequelae often results in a reduction of physical and psychological quality of life among sepsis survivors[75, 76]. Importantly, performance in the workplace may decrease, and social interactions may be subtly undermined[69].

Given these considerable human and socioeconomic implications, it is necessary to define a conceptual framework of practices aimed at reducing long-term morbidity in septic patients[78]. As a general paradigm, recovery after sepsis could be enhanced by adopting both hospital practices aimed at preventing long-term morbidity, and post-hospital discharge strategies designed to screen, evaluate and manage clinical conditions among sepsis survivors[78, 79].

Among the hospital practices for preventing long-term morbidity, we recognise the importance of adhering to international practice guidelines for the management of pain, agitation and delirium in ICU, and to perform early mobilisation and physical rehabilitation as early as clinically possible.
Pain, agitation and delirium are common complications among sepsis patients admitted to the ICU and are associated with extended ICU length of stay and increased risk of developing neuropathic pain, cognitive impairment, and post-traumatic stress disorder [Crit Care Med. 2018 Sep;46(9):e825-e873]. Implementation of care bundles recommended by clinical practice guidelines could improve clinical outcomes in this domain [J Crit Care. 2013 Dec;28(6):918-22 / Crit Care. 2015 Apr 9;19:157].
A recent Cochrane review on the effects of early mobilisation for critically ill adults concluded that the evidence for the effectiveness of such practices for short-term clinical outcomes is inconsistent and uncertain[80]. Despite the majority of published RCTs showed improvement in short-term physical and neurological outcomes, their quality of evidence is low to moderate due to small sample sizes, lack of blinding of participants and personnel, variation in the interventions and outcomes used to measure their effect and inadequate descriptions of the interventions delivered as usual care[80]. Moreover, no RCTs provide high quality evidence on the effectiveness of early mobilisation during ICU stay in reducing the long-term risk of acquiring physical and mental disabilities after hospital discharge. Nevertheless, given the positive results of most studies and the strong theoretical rationale for benefit, we recommend performing mobilisation and physical rehabilitation as early as clinically possible. In agreement with the National Institute for Health and Care Excellence guidelines, rehabilitation goals should be patient-specific, and based on the clinical assessment of healthcare professionals experienced in critical care and rehabilitation[81, 82].

Among the post-hospital discharge strategies for assessment and management of clinical sequelae we recognise the importance of clinical follow-up of sepsis survivors, including the adoption of a structured clinical evaluation method aimed at screening for common mental and physical impairments after sepsis. We also recognise the role of individualised protocols of physical rehabilitation and self-management practices and peer-support as valuable resources to mitigate mental health impairments.
To date, very little research has focused on strategies to improve rehabilitation after hospital discharge specifically among sepsis survivors. One retrospective propensity score-

matched cohort study of sepsis survivors showed that engaging in rehabilitation within 90 days of hospital discharge was associated with a significantly lower risk of 10-year mortality[83]. In that study, rehabilitation consisted of individualised protocols constructed by physicians and psychiatrists, and delivered by a multidisciplinary team which included physical and/or occupational therapists, speech therapists, social workers, and/or athletic trainers. These protocols were patient-specific, and aimed at improving muscle strengthening and movement, activities of daily living, cardiovascular capacity, functional ability, and occupational and communication therapy[83]. Only one RCT was designed to examine the effects of specific primary care-based interventions on long-term mental quality of life after sepsis[84]. Such interventions included education for primary care physicians and patients about long-term disabilities after sepsis, case management provided by trained nurses, and clinical decision-making support for primary care physicians provided by consulting physicians. Of all the outcomes measured, marginal positive findings were noted on functional outcomes such as physical function and disability at 6 months, ADL limitations at 6 and 12 months, and quality of sleep at 12 months. Despite the paucity of high-quality evidence for rehabilitation among sepsis survivors, indirect evidence can be derived from the literature on rehabilitation from critical illness[85], as many of the clinical sequelae after sepsis have been associated to the ICU stay. In this field, interventions proposed in different low-quality RCTs have yielded inconsistent findings regarding a beneficial effect on functional exercise capacity, or on health-related quality of life, of an exercise-based intervention initiated after ICU discharge for survivors of critical illness[86].
Peer support groups for ICU survivors have been recently proposed as a strategy to relieve psychological distress[87], and ICU diaries have been shown to reduce PTSD symptoms among patients and caregivers[88, 89].

ICU Steps Dublin is a voluntary support group open to former intensive care patients, family and carers. Informal “drop-in” meetings facilitated by former patients, relatives and ICU nurses are held one evening every 8 weeks where people recovering from critical illness can share experiences and lend support to one another. (www.icusteps.ie).

3.3 Summary budget impact analysis

Overview
Each recommendation statement was systematically reviewed by the GDG to assess the potential budget impact. The analysis focused on the additional cost implications that may arise from implementation of this National Clinical Guideline update.

Key findings relating to costs
Only 1 of 93 recommendations was determined to have a potential budgetary impact. In addition, the GDG suggest that research be undertaken to determine the burden of chronic sequelae associated with sepsis survival.

Recommendation 1: Hospitals and hospital systems have a performance improvement programme for sepsis including sepsis screening for acutely ill high-risk patients.

Cost of the National Sepsis Programme:

1. Fixed costs due to salary contributed to over 95% of the programme’s costs.

TABLE 16. STAFFING OF THE NATIONAL SEPSIS PROGRAMME

	2014 Salary inclusive of PRSI, Pension, Overheads.	2015 Salary inclusive of PRSI, Pension, Overheads.	2016 Salary inclusive of PRSI, Pension, Overheads.	2017 Salary inclusive of PRSI, Pension, Overheads.	2018 Salary inclusive of PRSI, Pension, Overheads.
National Clinical Lead	0.5 WTE €63,677	0.5 WTE €63,677	0.5 WTE €63,677	0.5 WTE €63,677	0.5 WTE €63,677
Project Manager		1 WTE €85,587	1 WTE €61,243	1 WTE €61,243	1 WTE (Jan-Aug) €40,828
Hospital Groups Assistant Directors of Nursing			6 WTE €90,238(x6) €541,428	6 WTE €90,238(x6) €541,428	6 WTE €90,238(x6) €541,428
Team WTE	0.5	1.5	7.5	7.5	7.5
Total Cost	**€63,677**	**€149,264**	**€666,348**	**€666,348**	**€645,933**

Staff costs 2014 -2018 = €2,191,570.00

Future annual staff costs 0.5 WTE Clinical Lead, 0.5 WTE Programme Manager, 7 Assistant Directors of Nursing **€747,136**

Variable costs:
These included the sepsis summits, design and printing, the e-learning programme, the annual outcome reports, conference expenses and national travel expenses for the team who attend all the acute hospitals nationally and are estimated at approximately €180,000 per annum.

Future variable costs include VAT.

- Education update: eLearning Approximately €54,000
  Cost applies to updating existing eLearning programme on HSEland.
- NQAIS sepsis
  Cost applies to initial construction of the platform year 1 €38,000 and on-going annual maintenance cost approx. €50,000
- Annual outcome report design and printing costs €4,000

- Data extraction for HIPE, interpretation and analysis. Cost associated with QIT time resource €3983.
- Annual sepsis summit €15,000
  Costs include catering, international speakers (flights and accommodation), Audio Visual and promotion
- Public awareness
  Costs include social media interface for information materials including leaflets/posters/videos €30,000

Total future variable costs (when one off costs removed) €60,983

Deliverables:

- Ongoing Sepsis education
- Sepsis updates and clinical advice as per International Benchmarking
- Clinical decision tool development & PDSA testing
- Management algorithm development
- Performance improvement audit and feedback
- Annual Sepsis summits
- E-learning
- Annual National Sepsis Outcome Report
- National Sepsis Guideline & updated Guideline

Key findings relating to benefits - Value achieved by the National Sepsis Programme

Table 17. Improved documentation of sepsis consequent to the programme

Year	Projected number of cases of SIRS of Infectious Origin, Sepsis & Septic Shock Based on an annual 7% increase*	Documented number of cases of SIRS of Infectious Origin, Sepsis & Septic Shock
2016	**9,510**	**14,804**
2017	**10,175**	**17,106**
2018	**10,887**	**16,578****
Total	**30,572**	**48,488**

*Prior to the education and awareness programme the number of cases documented was increasing by on average 7% per annum[5]

**In 2018, the sepsis-3 definition was implemented, identifying a more unwell cohort of patients which impacted the number of SIRS of infectious origin cases that were documented in the notes as this no longer constitutes a sepsis case.

- An additional 17,916 cases of SIRS of Infectious origin, Sepsis & Septic Shock were recognised and documented consequent to the education and awareness programme
- 302 lives saved and €10.6million saved in direct costs from the cohort of patients with a SIRS of Infectious Origin, Sepsis or Septic Shock diagnosis and an admission to Critical Care alone.

The cost of the programme per additional sepsis case recognised and documented was approximately €122.

Additional benefits:

- Updating the education programme ensures that relevant staff have the tools and knowledge to comply with the updated guideline
- The NQAIS sepsis mortality prediction model and scoring system will facilitate comparison of age and co-morbidity adjusted hospital sepsis-associated mortality rates nationally and internationally and will provide real time data to the system.
- The Annual Outcome Report describes the burden of sepsis, in terms of the number of cases and the associated mortality, to our healthcare system.
- The annual Sepsis Summit provides a platform to share information/updates on the recognition and management of sepsis and septic shock
- The Centre for Disease Control identifies that up to 70% of sepsis cases arise in the community. Therefore, the public awareness campaign aims to provide the general public with the tools to recognise the signs of sepsis and seek early medical interventation.

Conclusion

The budget impact analysis considers the additional resources required to implement the updated Sepsis Management National Clinical Guideline No 6. Over the life of the guideline the budget impact of the guideline recommendations is estimated to be €366,500 excluding VAT. The GDG recognises that there is ongoing research into rehabilitation and support for patients following a sepsis diagnosis. Horizon scanning for new evidence supporting interventions that reduce the burden of sequelae in survivors is a key function of the National Sepsis Programme. The GDG would be keen that such interventions be assessed for implementation in Ireland as soon as practicable.

Section 4: Appendices

Appendix 1: Guideline Development Group Terms of Reference

Note the names of GDG membership is shown at the intro pages. This appendix is for their terms of reference.

Guideline Development Group
Terms of Reference

1. Purpose

The purpose of this Adult Guideline Development Group (GDG) is to update the existing NCG No.6 (SEPSIS MANAGEMENT) (NOV 2014) to reflect current best evidence.

2. Objectives

The objectives of the GDG are to:

- Ensure adherence to the NCEC methodology in drafting the revised clinical guideline
- Include a budget impact analysis in the updated guideline
- Review current guidelines in peer reviewed journals since 2015 with a view to adopting or adapting a guideline
- Include an implementation strategy in the revised guideline
- Prepare a draft updated guideline
- Circulate draft guideline for consultation and external review
- Finalise and approve the updated clinical guideline
- Submit to National Sepsis Steering Group for review and approval
- Submit finalised updated guideline to NPSO/NCEC, DOH for appraisal, endorsement and ministerial launch

3. Scope

The scope of the GDG is to revise and update the existing NCG No.6 (Sepsis Management Guideline) (2014) to reflect current best practice utilising Irish national data. The GDG will be cognisant of this throughout the guideline revision process and will consider adapting, adopting current guidelines or making recommendations based on a current literature review.

4. Membership

Membership nominations were sought from a wide range of experts so as to be as representative of all the relevant key stakeholders. The GDG may on occasion co-opt expertise from relevant sources as required.

5. Working Arrangements

a) A schedule of meetings will be agreed with the Chair for the year. Work will be undertaken between meetings and members will contribute to, and approve work, via e-mail correspondence (and teleconference when available).

b) The Chair and Deputy Chair will be responsible for circulating papers and minutes of meetings. Papers for meetings will be circulated no later than 3 working days before meetings and minutes will be circulated no later than 2 weeks after meetings.
c) The group will be quorate if a third of total membership (8) are present.
d) Apologies should be sent in advance of meetings. If a group member does not attend more than three consecutive meetings the Chair or Deputy Chair will contact him/her to seek confirmation of continued participation or if they would like to nominate a replacement.
e) Members of the GDG will reflect the views of the specialist groups and individual organisations they represent and will communicate through the relevant organisation's governance structures.
f) Decision-making: the agenda will identify items that require important decisions to be made at the meeting. Where group members are unable to attend they may submit comments to the Chair / Deputy, by e-mail, by 5pm on the day prior to the meeting. The Chair/ Deputy will bring forward all comments received for consideration by the group in attendance. Decisions will be made by the group attending the meeting. Meeting notes will detail such decisions to group members who are not in attendance.
g) There may be a requirement to establish various working groups to advance actions as guideline development progresses. The Chair of the working group will report to the GDG on progress and outputs and seek further advice or decisions where appropriate.

Roles and Responsibilities *(based on NCEC guidance and National SEPSIS Steering group TOR)*

GDG Chairperson/Deputy Chairperson Role and Responsibility

- Develop and agree terms of reference
- Ensure guideline is developed using NCEC methodology
- Set and agree timelines (using a standard project management approach where possible)
- Set and circulate the agenda of each meeting to members
- Encourage broad participation from members in discussion
- Identify and assign tasks
- Agree a process for dealing with conflicts of interest
- Identify and oversee the progress of specific sub-groups
- End each meeting with a summary of decisions and actions
- Act as a point of contact for GDG members

GDG Member Roles and Responsibilities

- Review and agree group membership to reflect all key stakeholders
- Agree timelines for meetings and the clinical guideline development process
- Convene as required
- Give consideration to each of the stages of the clinical guideline path
- Review existing policies, guidelines, national and international evidence of best practice, relevant scientific and clinical expert opinion pertaining to the clinical guideline area
- Determine whether to adapt, adopt or develop a new clinical guideline
- Draft clinical guideline using NCEC methodology
- Consult with relevant interested parties and the public
- Review and incorporate feedback from consultation process as appropriate

- Finalise and approve clinical guideline for submission to Steering Group

GDG Service user Roles and Responsibilities (in addition to above)

- Ensure that key questions are informed by issues that matter to the service user
- Identify outcome measures they think are important for each key question
- Assist the GDG with the collection of service user views e.g. by helping to prepare questions for focus groups
- Help the GDG with consultation arrangements
- Identify areas where service users' preferences and choices may need to be acknowledged in the clinical guideline
- Help write the information for the service users section of the clinical guideline including identifying sources of further information
- Help ensure that the clinical guideline is clearly and sensitively worded

Conflict of Interest

- Each participant on the group will be asked to sign the relevant form in relation to conflict of interest. This is necessary to participate on the GDG.

External Reviewers

- Prof. Kevin Rooney, National Clinical Lead on Sepsis, Healthcare Improvement Scotland and Professor of Care Improvement, University of the West of Scotland

- Dr. John Bates from the Joint Faculty of Intensive Care Medicine in Ireland

Appendix 2: Sepsis Steering Committee / Working Group Membership

National Sepsis Steering Committee membership – 2019 to be finalised

Name	Job title and affiliation
Dr Fidelma Fitzpatrick	Chair
Dr Martina Healy	Clinical Lead for Sepsis
Ciara Hughes	National Sepsis Programme Manager
Celine Conroy	Group Sepsis ADONS - Ireland East
Dr Karn Cliffe	Group Sepsis ADONS - Dublin Midlands
Fidelma Gallagher	Group Sepsis ADONS - Saolta
Mary Bedding	Group Sepsis ADONS - RCSI Group
Yvonne Young	Group Sepsis ADONS - UHL Group
Kay O'Mahony	Group Sepsis ADONS - Sepsis – South / Southwest
TBC	Representative from Integrated Care
TBC	Representative from Clinical Design and Innovation
TBC	Representative from Quality Improvement Division
Elaine Brown	Representative from Acute Hospitals Division
Dr Vida Hamilton	Representative from NCAGL office
Ger Shaw	Representative from ONMSD
Jacqui Curley	Representative from Health Pricing Office
TBC	Representative from HSE Health Intelligence Unit
TBC	Representative from National Office Clinical Audit
TBC	Representative for HCAI – HPSC representative
Dr Gerry McCarthy / Fiona McDaid	Representative for Emergency Medicine
TBC	Representative for Acute Medicine
TBC	Representative for Critical Care
Dr Omar Tujjar	Representative for Anaesthesia
Dr Debbie McNamara / Jamie Logan	Representative for Surgery
Dr David O'Hanlon	Representative for Primary Care
TBC	Representative for Women and Children's Health
TBC	Representative for Older Person
TBC	Representative for Paediatrics
Ms Avilene Casey	Representative for Deteriorating Patient
TBC	Representative for General Practitioner
Barbara Egan	Patient representatives x2
Mr Brian Power	Representative Pre-Hospital Emergency Care Council
Ms Anne McCabe	Representative for NASCCRS (National Ambulance Service and critical care and retrieval services)
TBC	Representative for National Ambulance Service

National Sepsis Programme Working Group – 2019

Name	Job Title and Affiliation
Vida Hamilton Martina Healy	National Sepsis Clinical Lead (2013 – 2018) National Sepsis Clinical Lead (2018 onwards)
Christina Doyle Ciara Hughes	Programme Manager National Sepsis (2013 – 2018) Programme Manager National Sepsis (2019 onwards)
Mary Bedding	Sepsis ADON RCSI Hospital Group
Karn Cliffe	Sepsis ADON/M Dublin Midlands Hospital Group
Celine Conroy	Sepsis ADON Ireland East Hospital Group
Yvonne Young	Group ADON University Limerick Hospital Group
Fidelma Gallagher	Group ADON Saolta Hospital Group
Kay O'Mahony	Group ADON South / South West Hospital Group

Appendix 3: Literature search strategy

The methodology applied to the search strategy is outlined in the Guideline Methodology Page 28)

The full details of the literature search strategy will be included before submission to NCEC

Appendix 4: ISBAR Communication Tool

ISBAR Communication Tool	
I	**IDENTIFY** *You* *Recipient of handover information* *Patient*
S	**SITUATION** Why are you calling? (identify your concerns)
B	**BACKGROUND** What is the relevant background?
A	**ASSESSMENT** What do you think is the problem?
R	**RECOMMENDATION** What do you want them to do?

Reproduced and adopted from Dr S. Marshall, Monash University, Australia. (Awaiting permission)

Appendix 5: Consultation report

Date	11th December 2019
Patients groups	Patients Focus Irish Patients Association
External review	Prof. Kevin Rooney, National Clinical Lead on Sepsis, Healthcare Improvement Scotland and Professor of Care Improvement, University of the West of Scotland and the validators Dr. John Bates from the Joint Faculty of Intensive Care Medicine in Ireland
Clinical Programmes and healthcare divisions	Department of Health ONMSD (N and M) CNO office DOH Divisions Patient Advocacy Unit Quality Improvement Division National Quality Assurance and Verification Division Quality and Patient Safety, Acute Hospitals Division Office of the Nursing and Midwifery Services Hospital Group Clinical Directors Hospital Group CDONM's Hospital Directors of Nursing, Acute Division Hospital Chief Executive Officers and General Managers, Acute Division Hospital Clinical Directors, Acute Division National Director for Clinical Design and Innovation Nurse Leads, Clinical Design and Innovation Clinical Leads, Clinical Strategy and Programmes Division Programme Managers, Clinical Design and Innovation Directorate National Clinical Advisor and Group Lead for Acute Hospitals HSE National Director of Acute Hospitals HSE Deputy National Director of Acute Hospitals Hospital Group Directors of Nursing Hospital Group Chief Executive Officers NWIP NAS National Office of Clinical Audit PHECC HPSC HSPC AMRIC – Antimicrobial Resistance Infection Prevention and Control
Academic Bodies	Royal College of Surgeons Royal College of Physicians in Ireland Irish College of General Practitioners
Professional groups	Surving Sepsis Campaign Guidline Committee Intensive Care Society of Ireland Irish Association of Emergency Medicine Irish Association of Advanced Nurse Midwife Practitioners Irish Association of Direcotrs of Nursign and Midwifery

Appendix 6: Economic assessment

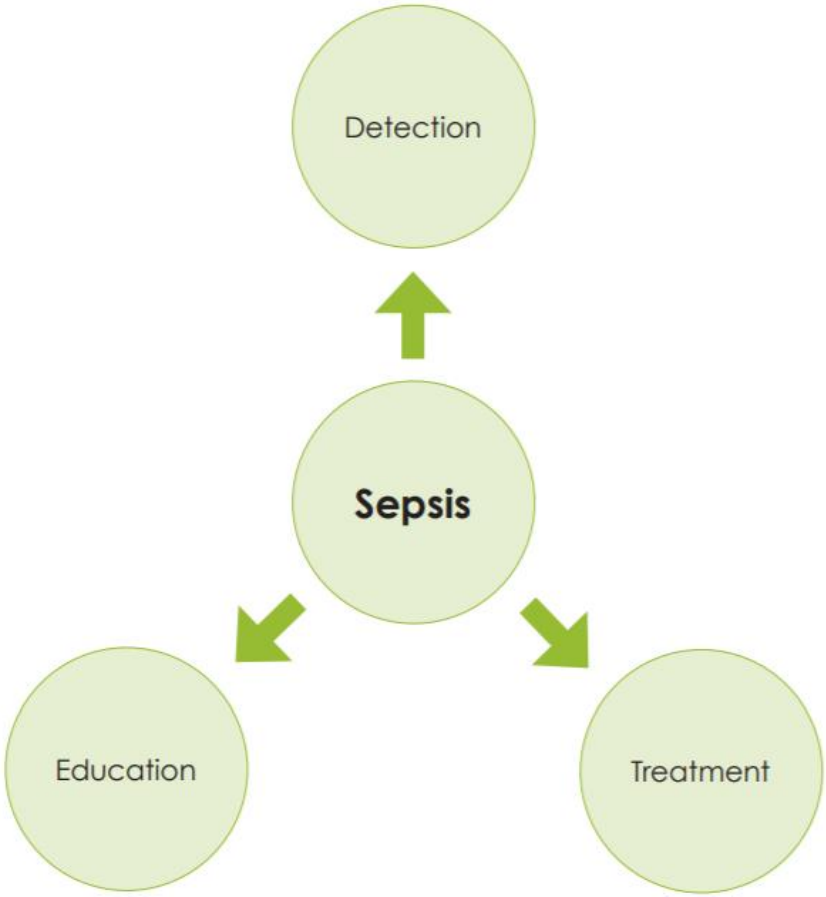
Part A: Economic evidence summary

Report completed by Gethin White, Clinical Librarian.

Introduction

The search strategy is based on the developed PICOS (population, interventions, comparisons and outcomes) and a schema of concepts as outlined in Figure 1.

Figure 14. Concepts for systematic review of economic impact report of sepsis management



PICOS Search Terms

Intervention 1: Sepsis detection

Population: All patients who may be at risk of or may have sepsis in acute hospitals including obstetrics.
Intervention: Sepsis detection options
Comparison: Between sepsis detection techniques and no sepsis detection techniques; between different options applied
Outcomes: Resources and costs

Concepts and key words
1. Early recognition of Sepsis
    a. Deteriorating
    b. SIRS criteria (Systemic Inflammatory Response criteria)
    c. Suspected infection, blood stream infection
    d. Septic shock, Septicaemia

2. Sepsis screening
3. Electronic Early Warning Score (EWS) generation

4. Point of care lactate
    a. POC LAC
    b. POC lactate
    c. Emergency department triage, ED triage
    d. Acute medical unit (AMU)
    e. Critical Care Units; Intensive Care Unit (ICU), High Dependency Unit(HDU), Coronary Care Unit (CCU), Maternity Unit, Acute wards.

5. Sepsis Six, Sepsis 6

6. Surviving Sepsis
    a. One hour bundle

7. Acute hospitals
    a. Acute Care
    b. Secondary Care
    c. Tertiary Care
    d. Inpatients

Intervention 2: Sepsis education

Population: All patients who may be at risk of or may have sepsis in acute hospitals including obstetrics.
Intervention: Sepsis education techniques
Comparison: Sepsis education interventions applied to target population compared with no sepsis education intervention applied
Outcomes: Resources and costs

Concepts and key words
1. Sepsis education programmes:
    a. Suspected infection; sepsis; septic shock; septicaemia, blood stream infection, SIRS criteria
    b. techniques; programmes

c. Surviving Sepsis Campaign
d. ESICM (European Society of Intensive Care Medicine) PACT (Patient Centred Acute Care Training) modular learning programmes.

2. Specialist sepsis education coordinator:
    a. audit
    b. implementation.

3. Electronic learning tools for Sepsis
4. Smart phone applications for Sepsis
5. Undergraduate and post graduate sepsis training programmes
6. Acute hospitals
    a. Acute Care
    b. Secondary Care
    c. Tertiary Care
    d. Inpatients

Intervention 3: Sepsis treatment

Population: All patients who may be at risk of or may have sepsis in acute hospitals including obstetrics.
Intervention: Care options for Sepsis
Comparison: Between care options and no care options;
Outcomes: Resources and costs

Concepts and key words

1. Sepsis; infection, blood stream infection, septicaemia

2. Early recognition of Sepsis
    a. Deteriorating
    b. SIRS criteria (Systemic Inflammatory Response criteria)
    c. Suspected infection
    d. Septic shock

3. Early intervention
    a. Sepsis Six: Cultures; lactate; oxygen; fluids; crystalloids; Urine output; antibiotics; antimicrobials, antibacterial
    b. One- hour bundle
    c. Vasopressin, Central Venous Oxygen (SCVO2), Corticosteroids, Haemoglobin transfusion, PEEP (Positive End Expiratory Pressure)

4. Critical Care; Intensive Care Unit (ICU), High Dependency Unit(HDU),
    a. Intensive Care Unit (ICU), Coronary Care Unit (CCU),
    b. Ventilator
    c. Dopamine

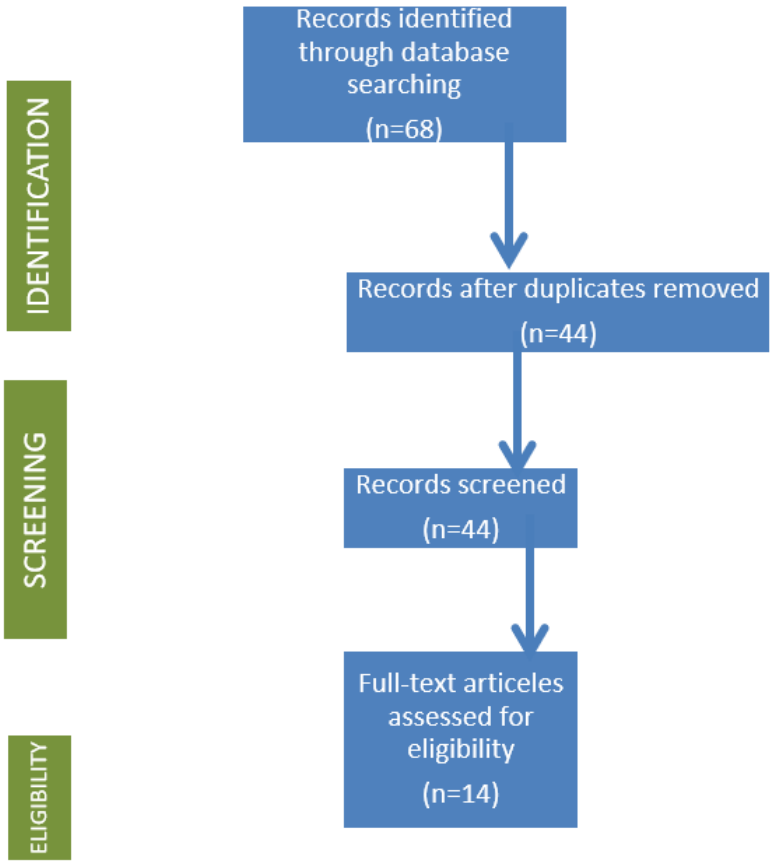
Information sources

1. (With economic filter (Glanville *et al*. 2009))
    • EmbaseClassic+Embase June 2014 to August 2018
    • Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) June 2014 to present, run through OVID on August 2018

2. Without economic filter (built into database type))

- Database of abstracts of Reviews of Effects
- NHS Economic Evaluation Database
- Health Technology Assessment Database
- Cochrane Central Register of Controlled Trials
- Cochrane Database of Systematic Reviews
- Grey literature websites: www.eunethta.eu/
www.inahta.org/
www.htai.org/
www.euroscan.org.uk

Figure 15. Flow chart of included and excluded studies for economic literature review



Method (To be inserted)

Part B: Budget impact analysis

Overview

Each recommendation statement was systematically reviewed by the GDG to assess the potential budget impact. The analysis focused on the additional cost implications that may arise from implementation of this National Clinical Guideline update.

Key findings relating to costs

Only 1 of 93 recommendations was determined to have a potential budgetary impact. In addition, the GDG suggest that research be undertaken to determine the burden of chronic sequelae associated with sepsis survival.

Table 18. Budget Impact Analysis Summary

Resource Category	Description & Issues	Assumptions	Cost Estimate (€)
Education	• Education update: eLearning	• existing eLearning programme on HSEland requires update in line with NCG update	• Approx €54,000
	• Annual sepsis summit	• platform to share updated information for sepsis recognition and management	• €15, 000 include speakers, catering, accommodation, printing, AV.
	• Public awareness	• Lack of public awareness of sepsis	• €30,000 to be determined in collaboration with HSE Comms
Evaluation & Audit	• NQAIS sepsis Cost applies to	• Currently no mechanism to compare age and co-morbidity adjusted hospital sepsis-associated mortality rates nationally and internationally	• Construction of the platform €38,000 ongoing annual maintenance cost approx. €50,000
	• Annual outcome report	• Ongoing design & publishing cost	• €5,000
Research	***Rehab***		*To be determined*

Appendix 7: Implementation plan

These guidelines are divided into sections with each one pertaining to a different aspect of patient care. Implementation points are included to guide implementation of the SSCG recommendations in Ireland, particularly in the non-critical care environment.

While the implementation plan is specific to the individual recommendations in the guideline, some actions will assist with guideline implementation as a whole. These include the role of the Sepsis ADONS and engagement with hospital sepsis committees to ensure dissemination and communication of the updated guideline. The National Sepsis Programme will work with HSE communications both internally and externally to inform key stakeholders of the Sepsis Management – National Clinical Guideline No. 6 update and to provide support as appropriate. The Annual Sepsis Summit will also be used as a platform to disseminate the updated guideline. The sepsis e-learning module update further supports the updated National Clinical Guideline and will continue to be available through HSELand.

The implementation of the Sepsis Management National Clinical Guideline No. 6 (2020) is dependent on various factors. The following table identifies the enablers and barriers to implementing the recommendations along with the responsibilities and timelines. See also the Logic model illustrated in Figure

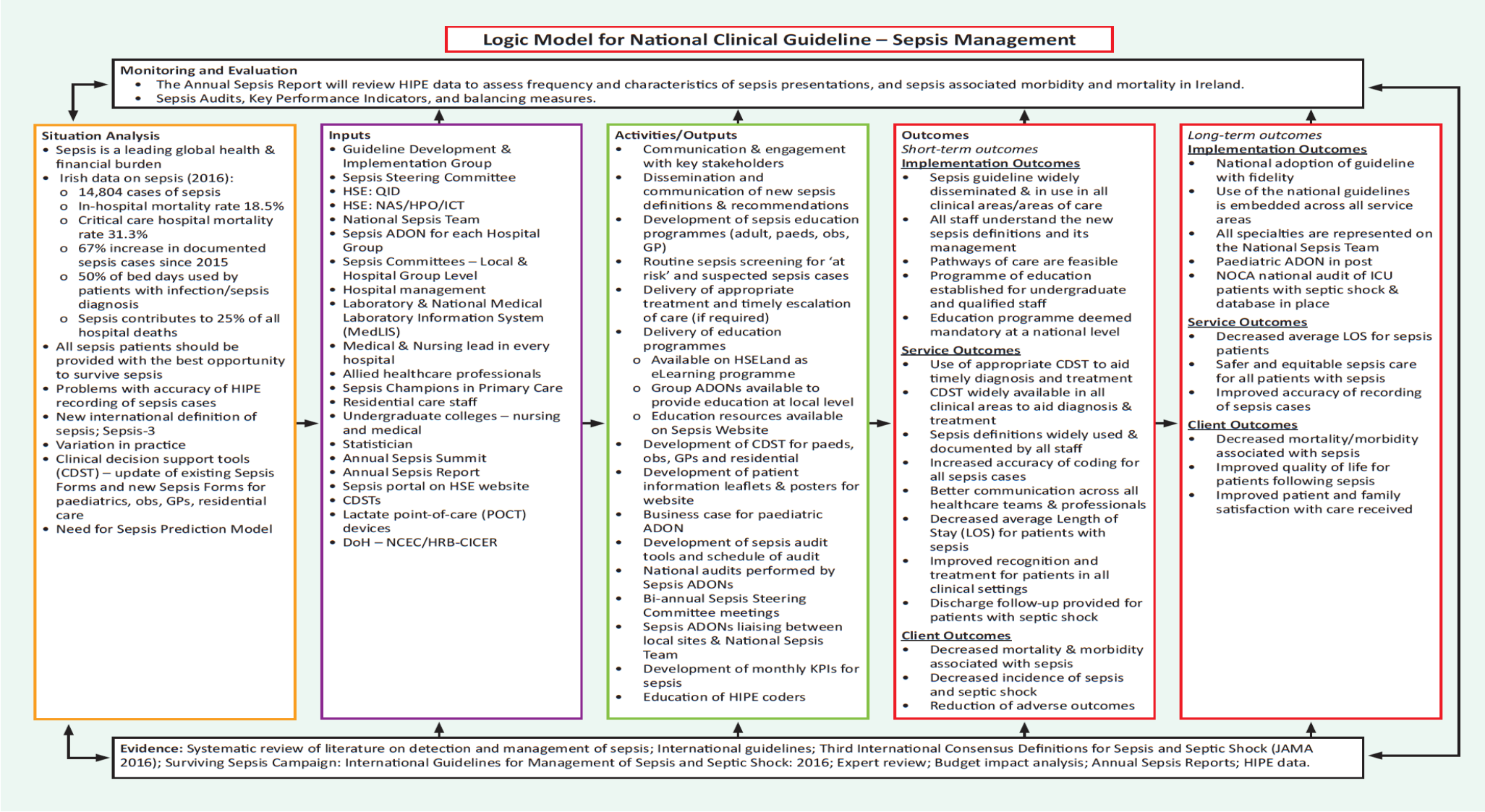
Table 19. (Draft) Implementation Plan for National Clinical Guideline (NCG) on: Sepsis Management

Guideline recomm-endation or number(s)	Implementation barriers / enablers / gaps	Action / intervention / task to implement recommendation	Lead responsibility for delivery of the action	Timeframe for completion			Expected outcome and verification
				Year 1	Year 2	Yea r 3	
GENERAL	**Enablers** • Current good compliance with a lot of the recommendations • Sepsis Summit **Barrier** • Lack of knowledge	Develop communication, dissemination and stakeholder engagement plan, including annual Sepsis Summit.	• Sepsis National Clinical Programme	X			**Outcome** Improved awareness and knowledge of sepsis guideline **Verification** Acknowledgement from hospital leads upon receipt of guideline. Monitoring and Audit feedback
SCREENING FOR SEPSIS AND PERFORMANCE IMPROVEMENT **Recommendation 1**	**Enablers** • Audit and feedback • Champions • Support from Hospital Senior Management • Local Sepsis Committees • Sepsis ADONs • NQAIS Sepsis currently being tested **Barrier** • Lack of hospital senior management engagement • Lack of medical/nursing champions • No Group paediatric ADON	Develop role description for Clinical Leads Development of network of champions – medical and nursing Develop and use audit tools and audit schedules Dissemination of audit findings with hospital management Link with NQAIS Sepsis team re: building of mortality prediction model for sepsis Advocate for permanent allocation of paediatric ADON	• National Sepsis Team • Sepsis ADONs • Hospital Sepsis Committees	X	X	X	**Outcomes** Greater clarity for role of Clinical Leads More champions Improved focus on sepsis by management Improved compliance with guideline, leading to improved outcomes for patients Improved support from hospital management Improved access to sepsis data and hospital comparisons of mortality data **Verification** Audit and annual reports Reporting from Sepsis ADONs Feedback from Hospital Sepsis Committees Feedback from hospital group

							management Paediatric ADON in place on permanent
INITIAL RESUSCITATION Recommendations (2 – 14)	**Enabler** • CDST (Sepsis Forms and Algorithms) for early recognition & treatment **Barriers:** • Reluctance to use CDSTs • Lack of knowledge	Ongoing review and update of CDSTs Promote value and importance of CDSTs (use champions) Targeted education on use of clinical decision-making tools – develop scenarios and video/animation	• National Sepsis Team • Hospital Nursing and Clinical Leads • National Sepsis Team	X	X	X	**Outcome** Improved knowledge of recognising sepsis **Verification** Audit and Annual report
	Enablers • Sepsis e-learning programme • Mandatory training **Barriers** • Lack of knowledge • Challenges in recognising sepsis early – complex and evolving	Update e-learning sepsis education programme to include the new sepsis definitions and review every three years Advocate for making sepsis e-learning mandatory in all hospital groups Delivery of local education, as required (by ADONs, ANPs, Clinical leads, National Clinical Lead)	• Sepsis National Clinical Programme • Sepsis ADONs • Local Sepsis Committees	X X	 X		**Outcome** **Verification** HSEland e-learning reports
	Barriers • Lack of IT systems to capture information • Lack of integration across IT systems	Identify requirements from IT systems (EHR and MN-CNS) and advocate for their inclusion Liaise with national groups overseeing development of IT systems to ensure requirements are put in place	• National Sepsis Team • National Sepsis Team		X	 X	**Outcome** IT systems more fit for purpose – earlier recognition, supporting more effective treatment, monitoring **Verification** IT systems in place
ANTI MICROBIAL THERAPY Recommendations (15-33)	**Enabler** • Local Sepsis Committees • CDSTs • Local antimicrobial guidelines • Consultant Microbiologists • Antimicrobial stewardship **Barriers**	Conduct gap analysis on equipment for point-of-care lactates	• Sepsis ADONs • Hospital Sepsis Committees	X	X		**Outcome** Improved access to equipment Improved adherence to local antimicrobial guidelines **Verification** Review of Hospital Antimicrobial Consumption

	• Lack of laboratory equipment to measure procalcitonin levels • Lack of equipment to measure lactate • Lack of knowledge	Secure resources through service planning processes, where needed, for equipment for point-of-care lactates (ED and AMU already have)					
SOURCE CONTROL Recommendation (34-35) **VASOACTIVE MEDICATION Recommendations (36-41)** **CORTICOSTEROIDS (Recommendation 42)** **BLOOD PRODUCTS (Recommendation 43)** **IMMUNOGLOBULINS (Recommendation 44)** **BLOOD PURIFICATION (Recommendation 45)** **ANTICOAGULANTS (Recommendation 46-47)** **MECHANICAL VENTILATION (Recommendation 48-62)** **SEDATION AND ANALGESIA (Recommendation 63)** **GLUCOSE CONTROL (Recommendation 64-67)** **RENAL REPLACEMENT THERAPY (Recommendation 68-70)** **BICARBONATE THERAPY (Recommendation 71)** **VENOUS THROMBOEEMBOLISM PROPHYLAXIS (Recommendation 72-75)** **STRESS ULCER PROPHYLAXIS (Recommendation 76-78)** **NUTRITION (Recommendation 79-90)** **SETTING GOALS OF CARE (Recommendation 91-93)**	The GDG have provided implementation points after each recommendation or group of recommendations, to guide implementation of the SSCG recommendations in Ireland						

Table 20: Logic model for National Clinical Guideline - Sepsis Management



Appendix 8: Supporting tools

To be completed

Appendix 9: Glossary of terms and abbreviations

The following abbreviations are used in this document: (Needs further additions)

AMR: Antimicrobial resistance

CCU: Coronary care unit

CDI: Clinical Design and Innovation

CNS: Central Nervous System

CVP: Central Venous Pressure

DoH: Department of Health

ED: Emergency department

ESRI: The Economic and Social Research Institute

GDG: Guideine Development Group

GDH: Glutamate dehydrogenase

GP: General practitioner

HCAI: Healthcare-associated infection

HCW: Healthcare worker/healthcare staff

HDU: High dependency unit

HIPE: Hospital Inpatient Enquiry Scheme

HPA: Health Protection Agency

HPSC: Health Protection Surveillance Centre

HIQA: Health Information and Quality Authority

HSE: Health Services Executive

IDSA: Infectious Disease Society of America (IDSA)

ICU: Intensive care unit

IMEWS: Irish Maternity Early Warning System

IV: Intravenous

IPC(T): Infection prevention and control (team)

LOS: Length of stay

MAP: Mean arterial pressure

NCEC: National Clinical Effectiveness Committee

NEWS: National Early Warning Score

NEWS: National Early Warning Score

NCP: National Clinical Programme

PPIs: Proton pump inhibitors

RCT: Randomised controlled trial

SAC: Scientific advisory committee

SCC: Surviving Sepsis Campaign

ScvO2: Central Venous Oxygen Saturation

SPHM: Specialist in Public Health Medicine

US: United States

UFH: Unfractionated heparin

UK: United Kingdom

WHO: World Health Organisation

Appendix 10: Box framework for Evaluating and treating Patients in the 90 days after hospitalization for Sepsis. *(Reproduced with permission from Prescott & Angus, 2018)*

Box Framework for Evaluation and Treating Patients in the 90 days after Hospitalisation for Sepsis*		
Screen for Common, treatable Impairments after Sepsis	**Group**	**Implementation Points**
Functional Disability	Patients aged 65 years or older develop an average of 1 to 2 new functional limitations[6]	For patients with newly reduced exercise capacity, consider enrollment in a clinical trial of rehabilitation. If a trial is not available, consider referral to physical therapy, referral to pulmonary or cardiac rehabilitation, or prescribe a structured exercise program, depending on the severity of impairments and motivation of the patients
		For patients with new limitations of activities or instrumental activities of daily living, consider referral to occupational therapy
		If sepsis has occurred in the setting of long-standing comorbidity and declining health, discuss whether transition to palliative focus is appropriate
Swallowing Impairment	Of patients aged 65 years or older, 1.8% (95% CI, 1.3%-2.3%) are readmitted within 90 days for principal diagnosis of aspiration pneumonitis[37]	For patients with evidence of swallowing impairment (dysphagia, weak voice, or cough), consider referral to speech therapy for further evaluation (e.g., fluoroscopic swallow evaluation) and treatment (e.g., swallow strengthening exercises, modified diet)
Mental Health Impairments	Point prevalence for clinically significant anxiety is 32% (95% CI, 27%-38%) at 2 to 3 months[41]; for depression, 29% (range, 22%-36%) at 2 to 3 months[42]; and for PTSD, 44% (range, 36%-52%) at 1 to 6 months[43]	Review the details of the hospital course with interested patients because ICU diaries are associated with decreased PTSD
		Consider screening for depression and anxiety with validated surveys
		Consider referring patients and caregivers to peer support programs or mental health services
Review and Adjust Long-term Medications	**Group**	**Implementation Points**
Medication Errors	Errors of omission occur in 10% to 25% of patients,	Confirm that long-term medications should remain on list

	depending on medication class.[25] Errors of commission occur in 1% to 25%, depending on medication class [26,27]	
		Discontinue hospital medications without on-going indication (e.g., inhalers, atypical antipsychotics, gastric acid suppressants)
		Assess whether any doses should be adjusted based on changes in body mass, renal, or cardiac function, focusing on diuretics, anti-hypertensives, and renally cleared medications
Anticipate and Mitigate Risk for Common and Preventable Causes of Health Deterioration	**Group**	**Implementation Points**
Infection	Of patients aged 65 years or older, 11.9% (95% CI, 10.6%-13.1%) are readmitted within 90 days for principal diagnosis of infection (sepsis, pneumonia, urinary tract, and skin or soft tissue infection), 6.4% are readmitted for a principal diagnosis of sepsis[37]	Counsel patients about their risk of infection and recurrent sepsis
		Ensure receipt of vaccines appropriate for the patient
		Encourage patients to seek medical care for infectious signs and symptoms
		Counsel patients on signs and symptoms that infection has progressed to sepsis (eg, decreased urine output, confusion, cyanosis, mottled skin), indicating that immediate evaluation is needed
		For patients presenting with signs or symptoms of infection, consider chest x-ray, complete blood cell count, urinalysis, or cultures to confirm or rule out suspected infection
		Schedule in-person or telephone follow-up to monitor for symptomatic improvement in patients with suspected infection
Heart Failure Exacerbation	Of patients aged 65 years or older, 5.5% (95% CI, 4.6%-6.4%) are readmitted within 90 days for principal diagnosis of congestive heart failure37	Reassess need and dosage for diuretics, β-blockers, and ACE-inhibitors because dosage requirements may change after sepsis due to changes in body weight, renal function, or cardiac function
		Monitor volume status and weight at each visit, recognizing that dry weight may have declined due to lost muscle mass
Acute Renal Failure	Of patients aged 65 years or older, 3.3% (range, 2.6%-4.0%) were readmitted within 90 days for principal diagnosis of acute renal failure[37]	For patients with acute renal injury during sepsis, consider surveillance laboratory testing to ensure that renal function improves or stabilizes (e.g., check chemistry panel once a week for 3 weeks, then monitor less frequently once blood work

		is stable)
		Reassess need and dosages for renally cleared and nephrotoxic agents (e.g., ACE-inhibitors, NSAIDS, statins, ranitidine, opiates, benzodiazepines)
COPD Exacerbation	Of patients aged 65 years or older, 1.9% (95% CI, 1.4%-2.4%) are readmitted within 90 days for principal diagnosis of COPD exacerbation[37]	Confirm and initiate appropriate controller inhalers Ensure receipt of vaccines appropriate for the patient Review and consider stopping or reducing dosages of medications that may suppress respiration such as benzodiazepines and opiates

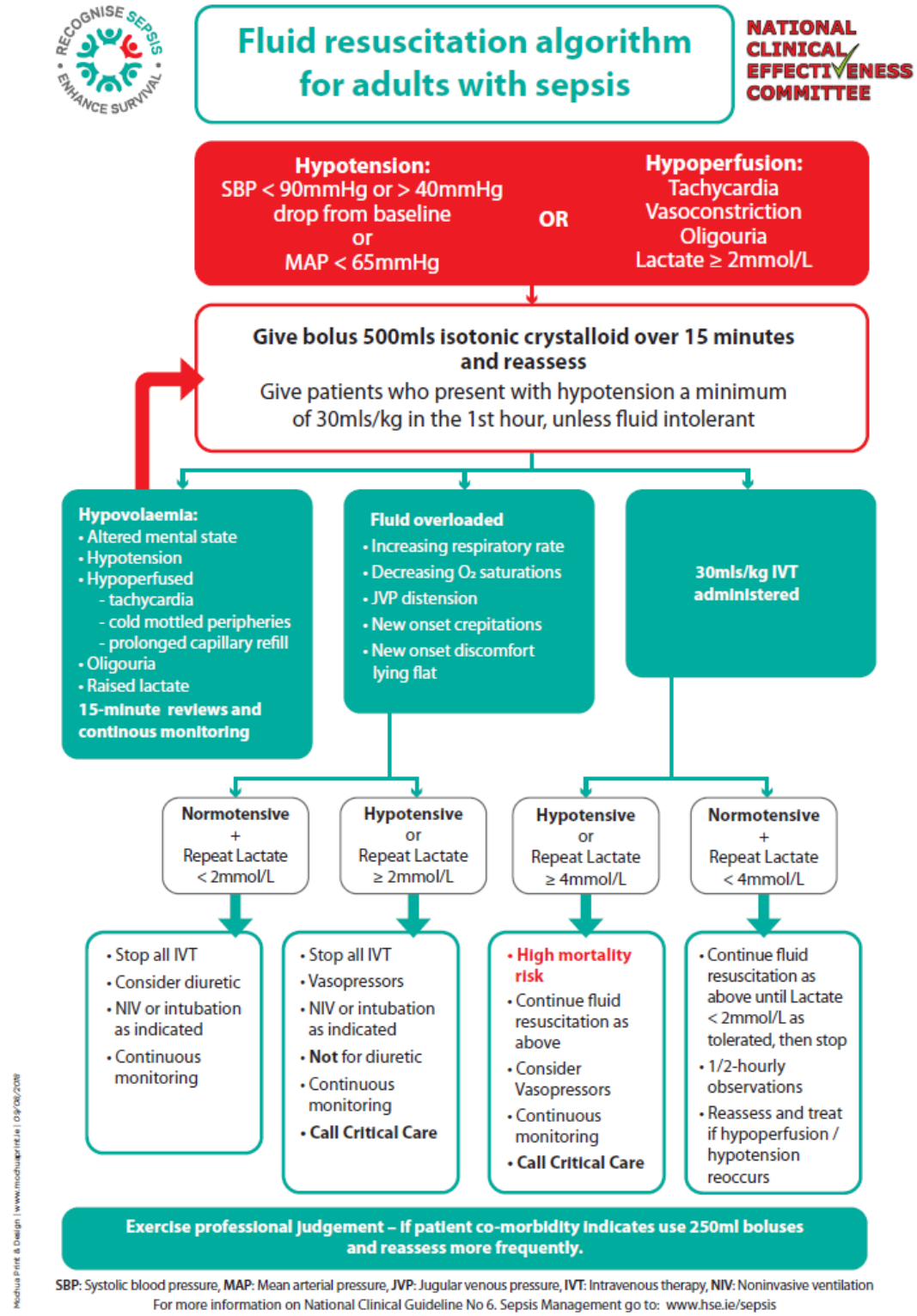
*This Box provides a framework to approach medical evaluation and treatment of patients who have recently survived sepsis hospitalization. Post-hospital care should focus on screening for new impairments; reviewing and adjusting long-term medications; and screening for common, preventable causes for medical deterioration

**Abbreviations: ACE, angiotensin-converting enzyme inhibitor; COPD, chronic obstructive pulmonary disease; NSAIDS, non-steroidal anti-inflammatory drugs; PTSD, posttraumatic stress disorder.

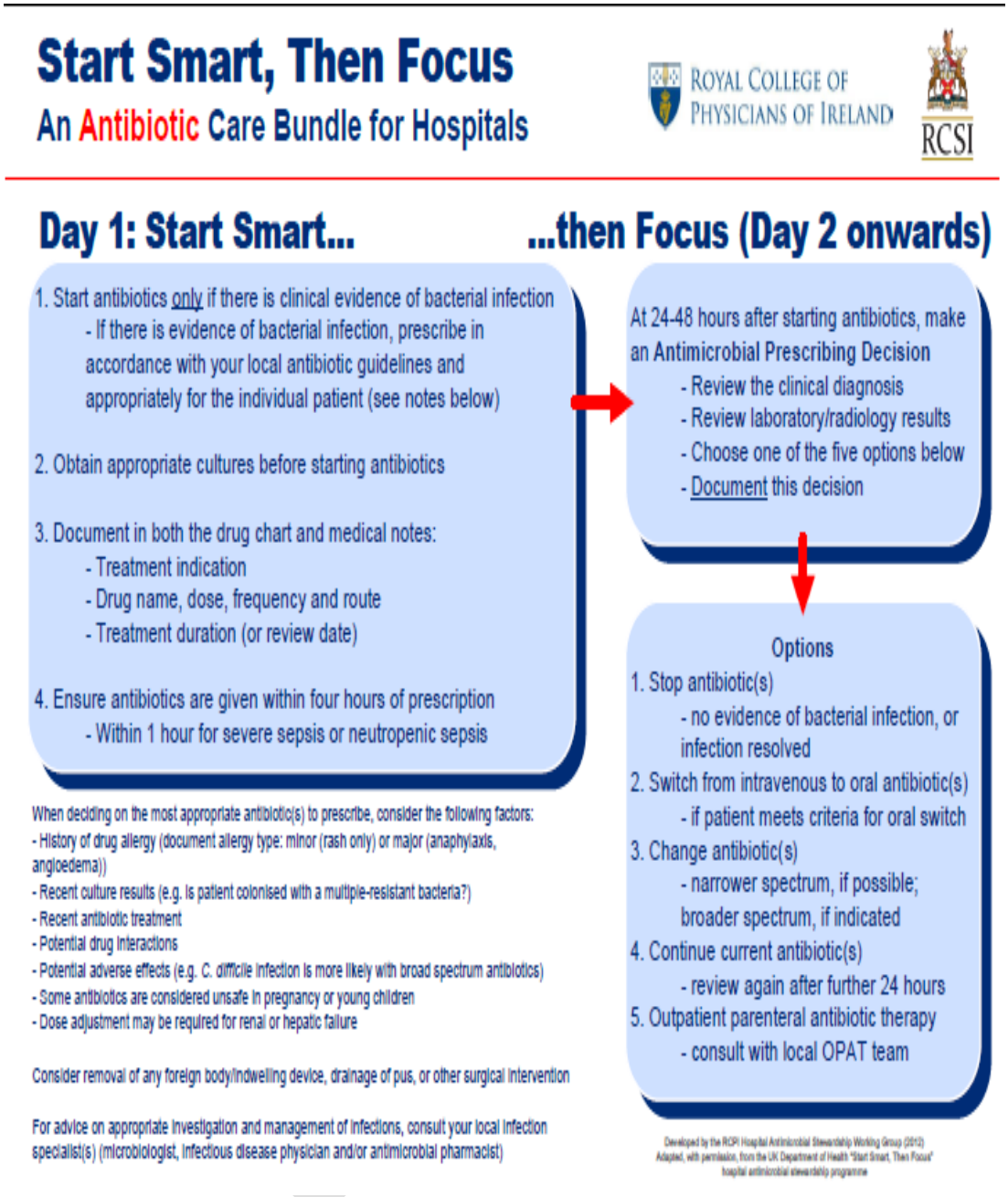
Appendix 11. In-patient Sepsis Form

To be inserted

Appendix 12: Fluid resuscitation algorithm for adults with sepsis



Appendix 13: Start Smart and then Focus' approach for antimicrobial therapy.



Start Smart, Then Focus

An Antibiotic Care Bundle for Hospitals

Royal College of Physicians of Ireland

RCSI

Day 1: Start Smart...

1. Start antibiotics only if there is clinical evidence of bacterial infection
   - If there is evidence of bacterial infection, prescribe in accordance with your local antibiotic guidelines and appropriately for the individual patient (see notes below)

2. Obtain appropriate cultures before starting antibiotics

3. Document in both the drug chart and medical notes:
   - Treatment indication
   - Drug name, dose, frequency and route
   - Treatment duration (or review date)

4. Ensure antibiotics are given within four hours of prescription
   - Within 1 hour for severe sepsis or neutropenic sepsis

When deciding on the most appropriate antibiotic(s) to prescribe, consider the following factors:
- History of drug allergy (document allergy type: minor (rash only) or major (anaphylaxis, angioedema))
- Recent culture results (e.g. Is patient colonised with a multiple-resistant bacteria?)
- Recent antibiotic treatment
- Potential drug interactions
- Potential adverse effects (e.g. *C. difficile* infection is more likely with broad spectrum antibiotics)
- Some antibiotics are considered unsafe in pregnancy or young children
- Dose adjustment may be required for renal or hepatic failure

Consider removal of any foreign body/indwelling device, drainage of pus, or other surgical intervention

For advice on appropriate investigation and management of infections, consult your local infection specialist(s) (microbiologist, infectious disease physician and/or antimicrobial pharmacist)

...then Focus (Day 2 onwards)

At 24-48 hours after starting antibiotics, make an Antimicrobial Prescribing Decision
- Review the clinical diagnosis
- Review laboratory/radiology results
- Choose one of the five options below
- Document this decision

Options

1. Stop antibiotic(s)
   - no evidence of bacterial infection, or infection resolved
2. Switch from intravenous to oral antibiotic(s)
   - if patient meets criteria for oral switch
3. Change antibiotic(s)
   - narrower spectrum, if possible; broader spectrum, if indicated
4. Continue current antibiotic(s)
   - review again after further 24 hours
5. Outpatient parenteral antibiotic therapy
   - consult with local OPAT team

Developed by the RCPI Hospital Antimicrobial Stewardship Working Group (2012)
Adapted, with permission, from the UK Department of Health "Start Smart, Then Focus" hospital antimicrobial stewardship programme

Appendix 14.Sepsis Predisposition and Recognition in the Community

Sepsis Predisposition & Recognition in the Community

Maternal Sepsis is a life-threatening condition defined as organ dysfunction resulting from infection during pregnancy, childbirth, post-abortion or postpartum period (WHO 2017).

Clinical suspicion of infection?

Yes

Are you concerned that the woman could have infection	
☐ History of fevers or rigors ☐ Cough/sputum/breathlessness ☐ Flu like symptoms ☐ Unexplained abdominal pain/distension ☐ Pelvic pain ☐ Vomiting and/or diarrhoea ☐Skin Breakage/IV Cannulation/Epidural puncture site any infection/ redness/swelling/pain	☐ Possible intrauterine infection ☐ Myalgia/back pain/general malaise/headache ☐ New onset of confusion ☐ Cellulitis/wound infection/perineal infection ☐ Possible breast infection ☐ Multiple presentation with non-specific malaise ☐ Others

Have a lower index of suspicion for infection or sepsis in the unwell women with risk factors.
THINK SEPSIS

RECOGNISE SEPSIS • ENHANCE SURVIVAL •

Feidhmeannacht na Seirbhíse Sláinte
Health Service Executive

Risk Factors

Pregnancy Related
- Pre-term/prolonged rupture of membranes
- Retained products
- History pelvic infection
- Group A Strep. – young children unwell at home
- Recent amniocentesis

Non Pregnancy Related
- Age > 35 years
- Minority ethnic group
- Vulnerable socio-economic background
- Obesity
- Diabetes, including gestational diabetes
- Recent surgery
- Symptoms of infection in the past week
- Immunocompromised e.g. Systemic Lupus
- Chronic renal failure
- Chronic liver failure
- Chronic heart failure

Deciding if for medical review

Screen for Sepsis Always Exercise Clinical Judgement

Obstetric History	
Gestation: _____ Pregnancy related complaints: Days post-natal:_____	Delivery: ☐ Spontaneous vaginal delivery (SVD) ☐ Vacuum assisted delivery ☐ Forceps assisted delivery ☐ Caesarean section

Assessment

Heart rate:_____ Resp rate:_____ Temperature: _____ BP: _____

Post natal blood loss: _____ (? Foul smelling)

Infection Plus any one of the following:

Any 1 of the following signs of acute organ dysfunction:

- Altered Mental State
- RR > 30 rpm
- HR >130 bpm
- SBP < 90mmHg
- Oligo or anuria
- Pallor/Mottled or ashen appearance with prolonged capillary refill
- Non-blanching rash
- Other organ dysfunction

Sustained SIRS Response, i.e. ≥ 2 modified SIRS criteria listed below.

- Respiratory rate ≥ 20 bpm
- Heart rate ≥100 bpm
- Temperature <36°C or ≥38.3°C
- Acutely altered mental status

At risk of neutropenia (bone marrow failure, autoimmune disorder or treatment including but not limited to, **chemotherapy and radiotherapy** and unwell

Yes

Requires hospital medical review

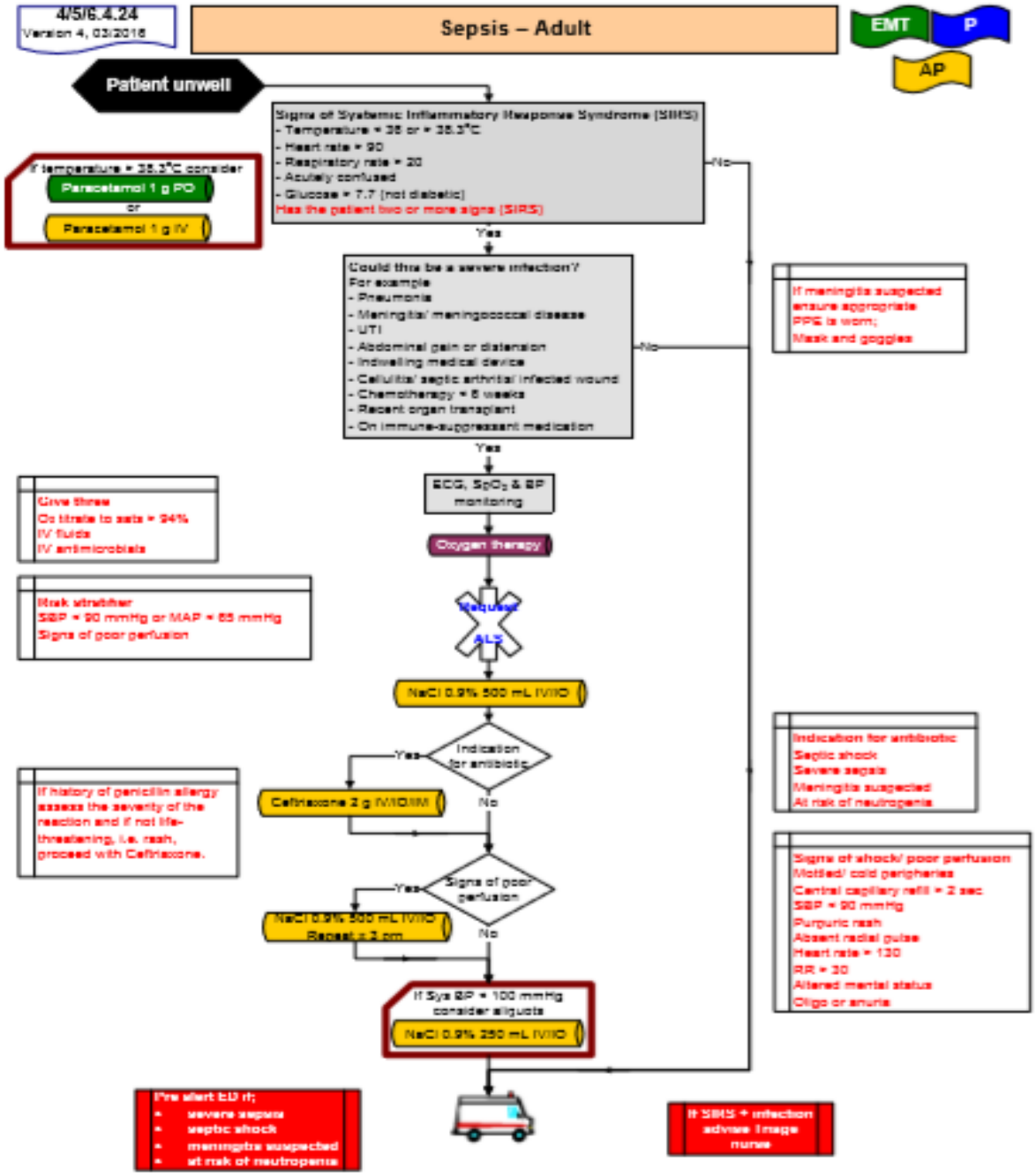
No

Follow usual pathway for uncomplicated infection.

Give safety net advice and the Sepsis Information leaflet. If condition deteriorates advise to contact PHN or GP.

Appendix 15. PHECC practitioner screening and treatment CPG for Sepsis.

This algorithm applies to patients with clinical signs of tissue hypoperfusion where infection is suspected to be the cause. The focus of care is to 'give three'; oxygen, IV fluids and antimicrobials, however the latter two are within the scope of practice of advanced paramedics only. The EMT and paramedic therefore will request advanced paramedic back-up to maximise the care of patients presenting with suspected sepsis.



Appendix 16: The Coding Process

The source document for coding in Ireland for HIPE is the medical record or chart. The clinical coder uses the entire chart to extract the conditions and procedures to provide a complete record of the patient and their health care encounter. The clinical coder, the person who translates medical terminology into alphanumeric code, performs an essential function in providing quality, accurate, and uniform medical information and greatly contributes to the continuous growth of medical knowledge. In addition to the discharge summary or letter, additional documentation referenced for coding a case include; nursing notes, consultation reports, progress notes, operative reports, pre- and post-operative reports, pathology reports and more recently the sepsis screening form.

The classification used is ICD-10-AM/ACHI/ACS 8th Edition (International Classification of Diseases, 10th Revision, Australian Modification/ Australian Classification of Health Interventions/Australian Coding Standards). The Australian Coding Standards have to be adhered to by clinical coders in their work. These are complemented by the Irish Coding Standards (ICS). The ICS are developed to complement the Australian Coding Standards (ACS) and are revised regularly to reflect changing clinical practice.

ACS 0010 General Abstraction Guidelines states that coders cannot infer diagnoses from laboratory results and that "The listing of diagnoses on the front sheet and/or the discharge summary of the clinical record is the responsibility of the clinician". It further states, "Unless a clinician can indicate that a test result is significant and/or indicates the relationship between an unclear test result and a condition, such test results should not be coded".

All HIPE data are keyed in at the hospital using the HIPE Portal data entry system that runs an extensive number of validation edit checks to ensure the quality of the data. Other data quality activities and data quality tools are in use at local and national HPO level.

Appendix 17: Glucose Measurement Conversion Chart

DiabetesChart

Convert Glucose (mg/dl) to Glucose (mmol/L)

mg/dl	40	42	44	46	48	50	52	54	56	58
mmol/L	2.2	2.3	2.4	2.6	2.7	2.8	2.9	3.0	3.1	3.2
mg/dl	60	62	64	66	68	70	72	74	76	78
mmol/L	3.3	3.4	3.6	3.7	3.8	3.9	4.0	4.1	4.2	4.3
mg/dl	80	82	84	86	88	90	92	94	96	98
mmol/L	4.4	4.6	4.7	4.8	4.9	5.0	5.1	5.2	5.3	5.4
mg/dl	100	102	104	106	108	110	112	114	116	118
mmol/L	5.6	5.7	5.8	5.9	6.0	6.1	6.2	6.3	6.4	6.5
mg/dl	120	122	124	126	128	130	132	134	136	138
mmol/L	6.7	6.8	6.9	7.0	7.1	7.2	7.3	7.4	7.5	7.7
mg/dl	140	142	144	146	148	150	152	154	156	158
mmol/L	7.8	7.9	8.0	8.1	8.2	8.3	8.4	8.5	8.7	8.8
mg/dl	160	162	164	166	168	170	172	174	176	178
mmol/L	8.9	9.0	9.1	9.2	9.3	9.4	9.5	9.7	9.8	9.9
mg/dl	180	182	184	186	188	190	192	194	196	198
mmol/L	10.0	10.1	10.2	10.3	10.4	10.5	10.7	10.8	10.9	11.0
mg/dl	200	202	204	206	208	210	212	214	216	218
mmol/L	11.1	11.2	11.3	11.4	11.5	11.7	11.8	11.9	12.0	12.1
mg/dl	220	222	224	226	228	230	232	234	236	238
mmol/L	12.2	12.3	12.4	12.5	12.7	12.8	12.9	13.0	13.1	13.2
mg/dl	240	242	244	246	248	250	252	254	256	258
mmol/L	13.3	13.4	13.5	13.7	13.8	13.9	14.0	14.1	14.2	14.3
mg/dl	260	262	264	266	268	270	272	274	276	278
mmol/L	14.4	14.5	14.7	14.8	14.9	15.0	15.1	15.2	15.3	15.4

Appendix 18: Subgroup of ICU Dietitians Group of INDI (Irish Nutrition and Dietetic Institute).

Jennifer Caffrey	Senior Dietitian	SVUH
Aine Kelly	Senior Dietitian	TUH
Carmel O'Hanlon	Clinical Specialist Dietitian	Beaumont
Marcella Richardson	Senior Dietitian	UHL
Geraldine Sexton	Senior Dietitian	Midland Regional Tullamore
Lisa Shanahan	Clinical Specialist Dietitian	Mater
Marie Sheahan	Senior Dietitian	CUH
Clare Twomey	Senior Dietitian	CUH

References – SSCG

1. Singer M, Deutschman CS, Seymour CW, et al: The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* 2016; 315:801–810
2. Shankar-Hari M, Phillips GS, Levy ML, et al; Sepsis Definitions Task Force: Developing a New Definition and Assessing New Clini- cal Criteria for Septic Shock: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* 2016; 315:775–787
3. Seymour CW, Liu VX, Iwashyna TJ, et al: Assessment of Clinical Criteria for Sepsis: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* 2016; 315:762–774
4. Angus DC, Linde-Zwirble WT, Lidicker J, et al: Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. *Crit Care Med* 2001; 29:1303–1310
5. Dellinger RP: Cardiovascular management of septic shock. *Crit Care Med* 2003; 31:946–955
6. Martin GS, Mannino DM, Eaton S, et al: The epidemiology of sepsis in the United States from 1979 through 2000. *N Engl J Med* 2003; 348:1546–1554
7. Levy MM, Fink MP, Marshall JC, et al: 2001 SCCM/ESICM/ACCP/ ATS/SIS International Sepsis Definitions Conference. *Crit Care Med*. 2003;31(4):1250–1256
8. Dellinger RP, Levy MM, Rhodes A, et al; Surviving Sepsis Campaign Guidelines Committee including The Pediatric Subgroup: Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. *Intensive Care Med* 2013; 39:165– 228
9. Dellinger RP, Levy MM, Rhodes A, et al; Surviving Sepsis Campaign Guidelines Committee including the Pediatric Subgroup: Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med* 2013; 41:580–637
10. Dellinger RP, Carlet JM, Masur H, et al; Surviving Sepsis Campaign Management Guidelines Committee: Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. *Crit Care Med* 2004; 32:858–873
11. Dellinger RP, Levy MM, Carlet JM, et al; International Surviving Sep- sis Campaign Guidelines Committee; American Association of Crit- ical-Care Nurses; American College of Chest Physicians; American College of Emergency Physicians; Canadian Critical Care Society; European Society of Clinical Microbiology and Infectious Diseases; European Society of Intensive Care Medicine; European Respiratory Society; International Sepsis Forum; Japanese Association for Acute Medicine; Japanese Society of Intensive Care Medicine; Society of Critical Care Medicine; Society of Hospital Medicine; Surgical Infection Society; World Federation of Societies of Intensive and Critical Care Medicine: Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. *Crit Care Med* 2008; 36:296–327
12. Dellinger RP, Levy MM, Carlet JM, et al; International Surviving Sep- sis Campaign Guidelines Committee; American Association of Critical-Care Nurses; American College of Chest Physicians; American College of Emergency Physicians; Canadian Critical Care Society; European Society of Clinical Microbiology and Infectious Diseases; European Society of Intensive Care Medicine; European Respiratory Society; International Sepsis Forum; Japanese Association for Acute Medicine; Japanese Society of Intensive Care Medicine; Society of Critical Care Medicine; Society of Hospital Medicine; Surgical Infection Society; World Federation of Societies of Intensive and Critical Care Medicine: Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. *Crit Care Med* 2008; 36:296–327
13. Guyatt GH, Oxman AD, Kunz R, et al: GRADE guidelines: 2. Framing the question and deciding on important outcomes. *J Clin Epidemiol* 2011; 64:395–400
14. Guyatt GH, Oxman AD, Vist GE, et al; GRADE Working Group: GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008; 336:924–926
15. Guyatt GH, Schünemann HJ, Djulbegovic B, et al: Guideline panels should not GRADE good practice statements. *J Clin Epidemiol* 2015; 68:597–600
16. Rivers E, Nguyen B, Havstad S, et al; Early Goal-Directed Therapy Collaborative Group: Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001; 345:1368– 1377
17. Peake SL, Delaney A, Bailey M, et al: Goal-directed resuscitation for patients with early septic shock. *N Engl J Med*. 2014;371(16): 1496–1506
18. Yealy DM, Kellum JA, Huang DT, et al: A randomized trial of proto- col-based care for early septic shock. *N Engl J Med*. 2014;370(18): 1683–1693
19. Mouncey PR, Osborn TM, Power GS, et al; ProMISe Trial Investigators: Trial of early, goal-directed resuscitation for septic shock. *N Engl J Med* 2015; 372:1301–1311
20. Levy MM, Dellinger RP, Townsend SR, et al; Surviving Sepsis Campaign: The Surviving Sepsis Campaign: results of an international guideline-based performance improvement program targeting severe sepsis. *Crit Care Med* 2010; 38:367–374
21. Levy MM, Rhodes A, Phillips GS, et al: Surviving Sepsis Campaign: association between performance metrics and outcomes in a 7.5-year study. *Crit Care Med* 2015; 43:3–12
22. Cecconi M, De Backer D, Antonelli M, et al: Consensus on circulatory shock and hemodynamic monitoring. Task force of the European

Society of Intensive Care Medicine. *Intensive Care Med* 2014; 40:1795–1815

23. Eskesen TG, Wetterslev M, Perner A: Systematic review including re-analyses of 1148 individual data sets of central venous pressure as a predictor of fluid responsiveness. *Intensive Care Med* 2016; 42:324–332
24. Monnet X, Marik P, Teboul JL: Passive leg raising for predicting fluid responsiveness: a systematic review and meta-analysis. *Intensive Care Med* 2016; 42:1935–1947
25. Cecconi M, Hofer C, Teboul JL, et al; FENICE Investigators; ESICM Trial Group: Fluid challenges in intensive care: the FENICE study: A global inception cohort study. *Intensive Care Med* 2015; 41: 1529–1537
26. LeDoux D, Astiz ME, Carpati CM, et al: Effects of perfusion pressure on tissue perfusion in septic shock. *Crit Care Med* 2000; 28: 2729–2732
27. Bourgoin A, Leone M, Delmas A, et al: Increasing mean arterial pressure in patients with septic shock: effects on oxygen variables and renal function. *Crit Care Med* 2005; 33:780–786
28. Thooft A, Favory R, Salgado DR, et al: Effects of changes in arterial pressure on organ perfusion during septic shock. *Crit Care* 2011; 15:R222
29. Asfar P, Meziani F, Hamel JF, et al; SEPSISPAM Investigators: High versus low blood-pressure target in patients with septic shock. *N Engl J Med* 2014; 370:1583–1593
30. Lamontagne F, Meade MO, Hébert PC, et al; Canadian Critical Care Trials Group: Higher versus lower blood pressure targets for vasopressor therapy in shock: a multicentre pilot randomized controlled trial. *Intensive Care Med* 2016; 42:542–550
31. Levy B: Lactate and shock state: the metabolic view. *Curr Opin Crit Care* 2006; 12:315–321
32. Casserly B, Phillips GS, Schorr C, et al: Lactate measurements in sepsis-induced tissue hypoperfusion: results from the Surviving Sep- sis Campaign database. *Crit Care Med* 2015; 43:567–573
33. Jansen TC, van Bommel J, Schoonderbeek FJ, et al; LACTATE study group: Early lactate-guided therapy in intensive care unit patients: a multicenter, open-label, randomized controlled trial. *Am J Respir Crit Care Med* 2010; 182:752–761
34. Jones AE, Shapiro NI, Trzeciak S, et al; Emergency Medicine Shock Research Network (EMShockNet) Investigators: Lactate clearance vs central venous oxygen saturation as goals of early sepsis therapy: a randomized clinical trial. *JAMA* 2010; 303:739–746
35. Lyu X, Xu Q, Cai G, et al: [Efficacies of fluid resuscitation as guided by lactate clearance rate and central venous oxygen saturation in patients with septic shock]. *Zhonghua Yi Xue Za Zhi* 2015; 95:496– 500
36. Tian HH, Han SS, Lv CJ, et al: [The effect of early goal lactate clearance rate on the outcome of septic shock patients with severe pneumonia]. *Zhongguo Wei Zhong Bing Ji Jiu Yi Xue* 2012; 24:42–45
37. Yu B, Tian HY, Hu ZJ, et al: [Comparison of the effect of fluid resuscitation as guided either by lactate clearance rate or by central venous oxygen saturation in patients with sepsis]. *Zhonghua Wei Zhong Bing Ji Jiu Yi Xue* 2013; 25:578–583
38. Gu WJ, Zhang Z, Bakker J: Early lactate clearance-guided therapy in patients with sepsis: a meta-analysis with trial sequential analysis of randomized controlled trials. *Intensive Care Med* 2015; 41:1862– 1863
39. Simpson SQ, Gaines M, Hussein Y, et al: Early goal-directed therapy for severe sepsis and septic shock: A living systematic review. *J Crit Care* 2016; 36:43–48
40. Dellinger RP: Foreword. The Future of Sepsis Performance Improve- ment. *Crit Care Med* 2015; 43:1787–1789
41. Murphy DJ, Ogbu OC, Coopersmith CM: ICU director data: using data to assess value, inform local change, and relate to the external world. *Chest* 2015; 147:1168–1178
42. Black MD, Schorr C, Levy MM: Knowledge translation and the multi- faceted intervention in the intensive care unit. *Crit Care Med* 2012; 40:1324–1328
43. Gatewood MO, Wemple M, Greco S, et al: A quality improvement project to improve early sepsis care in the emergency department. *BMJ Qual Saf* 2015; 24:787–795
44. Hayden GE, Tuuri RE, Scott R, et al: Triage sepsis alert and sepsis protocol lower times to fluids and antibiotics in the ED. *Am J Emerg Med*. 2016;34(1):1–9
45. Jones SL, Ashton CM, Kiehne L, et al: Reductions in Sepsis Mortality and Costs After Design and Implementation of a Nurse-Based Early Recognition and Response Program. *Jt Comm J Qual Patient Saf* 2015; 41:483–491
46. Levy MM, Pronovost PJ, Dellinger RP, et al: Sepsis change bundles: converting guidelines into meaningful change in behavior and clinical outcome. *Crit Care Med* 2004; 32:S595–S597
47. Damiani E, Donati A, Serafini G, et al: Effect of performance improve- ment programs on compliance with sepsis bundles and mortality: a systematic review and meta-analysis of observational studies. *PLoS One* 2015; 10:e0125827
48. Rhodes A, Phillips G, Beale R, et al: The Surviving Sepsis Campaign bundles and outcome: results from the International Multicentre Prev- alence Study on Sepsis (the IMPreSS study). *Intensive Care Med* 2015; 41:1620–1628
49. Zadroga R, Williams DN, Gottschall R, et al: Comparison of 2 blood culture media shows significant differences in bacterial recovery for patients on antimicrobial therapy. *Clin Infect Dis* 2013; 56:790–797
50. Kanegaye JT, Soliemanzadeh P, Bradley JS: Lumbar puncture in pedi- atric bacterial meningitis: defining the time interval for recovery of cerebrospinal fluid pathogens after parenteral antibiotic pretreatment. *Pediatrics* 2001; 108:1169–1174
51. Pollack LA, van Santen KL, Weiner LM, et al: Antibiotic Stewardship Programs in U.S. Acute Care Hospitals: Findings From the 2014 National Healthcare Safety Network Annual Hospital Survey. *Clin Infect Dis* 2016; 63:443–449
52. Cardoso T, Carneiro AH, Ribeiro O, et al: Reducing mortality in severe sepsis with the implementation of a core 6-hour bundle: results from

the Portuguese community-acquired sepsis study (SACiUCI study). *Crit Care* 2010; 14:R83

53. De Sousa AG, Fernandes Junior CJ, Santos GPD, et al: The impact of each action in the Surviving Sepsis Campaign measures on hos- pital mortality of patients with severe sepsis/septic shock. *Einstein*. 2008;6(3):323–327
54. Garnacho-Montero J, Gutiérrez-Pizarraya A, Escoresca-Ortega A, et al: De-escalation of empirical therapy is associated with lower mortal- ity in patients with severe sepsis and septic shock. *Intensive Care Med*. 2013:1–9
55. Weiss CH, Persell SD, Wunderink RG, et al: Empiric antibiotic, mechanical ventilation, and central venous catheter duration as poten- tial factors mediating the effect of a checklist prompting intervention on mortality: an exploratory analysis. *BMC Health Serv Res* 2012; 12:198
56. Ferrer R, Artigas A, Suarez D, et al; Edusepsis Study Group: Effectiveness of treatments for severe sepsis: a prospective, multi- center, observational study. *Am J Respir Crit Care Med* 2009; 180: 861–866
57. Kumar A, Roberts D, Wood KE, et al: Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med* 2006; 34:1589–1596
58. Vaughn VM, Chopra V: Revisiting the panculture. *BMJ Qual Saf*. 2016 Feb 19. doi:10.1136/bmjqs-2015–004821 [Epub ahead of print]
59. Weinstein MP, Reller LB, Murphy JR, et al: The clinical significance of positive blood cultures: a comprehensive analysis of 500 episodes of bacteremia and fungemia in adults. I. Laboratory and epidemiologic observations. *Rev Infect Dis* 1983; 5:35–53
60. Li J, Plorde JJ, Carlson LG: Effects of volume and periodicity on blood cultures. *J Clin Microbiol* 1994; 32:2829–2831
61. Baron EJ, Miller JM, Weinstein MP, et al: A guide to utilization of the microbiology laboratory for diagnosis of infectious diseases: 2013 recommendations by the Infectious Diseases Society of America (IDSA) and the American Society for Microbiology (ASM)(a). *Clin Infect Dis* 2013; 57:e22–e121
62. O'Grady NP, Alexander M, Burns LA, et al; Healthcare Infection Control Practices Advisory Committee (HICPAC): Guidelines for the prevention of intravascular catheter-related infections. *Clin Infect Dis* 2011; 52:e162–e193
63. Blot F, Schmidt E, Nitenberg G, et al: Earlier positivity of central- venous- versus peripheral-blood cultures is highly predictive of cathe- ter-related sepsis. *J Clin Microbiol* 1998; 36:105–109
64. Kaasch AJ, Rieg S, Hellmich M, et al: Differential time to positivity is not predictive for central line-related Staphylococcus aureus blood- stream infection in routine clinical care. *J Infect* 2014; 68:58–61
65. Malgrange VB, Escande MC, Theobald S: Validity of earlier positiv- ity of central venous blood cultures in comparison with peripheral blood cultures for diagnosing catheter-related bacteremia in cancer patients. *J Clin Microbiol* 2001; 39:274–278
66. O'Grady NP, Barie PS, Bartlett JG, et al; American College of Critical Care Medicine; Infectious Diseases Society of America: Guidelines for evaluation of new fever in critically ill adult patients: 2008 update from the American College of Critical Care Medicine and the Infectious Dis- eases Society of America. *Crit Care Med* 2008; 36:1330–1349
67. Mermel LA, Allon M, Bouza E, et al: Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 Update by the Infectious Diseases Society of America. *Clin Infect Dis* 2009; 49:1–45
68. Boyce JM, Nadeau J, Dumigan D, et al: Obtaining blood cultures by venipuncture versus from central lines: impact on blood culture con- tamination rates and potential effect on central line-associated blood- stream infection reporting. *Infect Control Hosp Epidemiol* 2013; 34:1042–1047
69. Beekmann SE, Diekema DJ, Huskins WC, et al; Infectious Diseases Society of America Emerging Infections Network: Diagnosing and reporting of central line-associated bloodstream infections. *Infect Control Hosp Epidemiol* 2012; 33:875–882
70. Garcia RA, Spitzer ED, Beaudry J, et al: Multidisciplinary team review of best practices for collection and handling of blood cultures to determine effective interventions for increasing the yield of true- positive bacteremias, reducing contamination, and eliminating false- positive central line-associated bloodstream infections. *Am J Infect Control*. 2015;43(11):1222–1237
71. Vincent JL, Brealey D, Libert N, et al; Rapid Diagnosis of Infections in the Critically Ill Team: Rapid Diagnosis of Infection in the Critically Ill, a Multicenter Study of Molecular Detection in Bloodstream Infec- tions, Pneumonia, and Sterile Site Infections. *Crit Care Med* 2015; 43:2283–2291
72. Makristathis A, Riss S, Hirschl AM: A novel fluorescence in situ hybridization test for rapid pathogen identification in positive blood cultures. *Clin Microbiol Infect* 2014; 20:O760–O763
73. Tissari P, Zumla A, Tarkka E, et al: Accurate and rapid identification of bacterial species from positive blood cultures with a DNA-based microarray platform: an observational study. *Lancet* 2010; 375: 224–230
74. Ferrer R, Martin-Loeches I, Phillips G, et al: Empiric antibiotic treat- ment reduces mortality in severe sepsis and septic shock from the first hour: results from a guideline-based performance improvement program. *Crit Care Med* 2014; 42:1749–1755
75. Zhang D, Micek ST, Kollef MH: Time to Appropriate Antibiotic Ther- apy Is an Independent Determinant of Postinfection ICU and Hospi- tal Lengths of Stay in Patients With Sepsis. *Crit Care Med* 2015; 43:2133–2140
76. Bagshaw SM, Lapinsky S, Dial S, et al; Cooperative Antimicrobial Therapy of Septic Shock (CATSS) Database Research Group: Acute kidney injury in septic shock: clinical outcomes and impact of dura- tion of hypotension prior to initiation of antimicrobial therapy. *Intensive Care Med* 2009; 35:871–881
77. Iscimen R, Cartin-Ceba R, Yilmaz M, et al: Risk factors for the devel- opment of acute lung injury in patients with septic shock: an observa- tional cohort study. *Crit Care Med* 2008; 36:1518–1522

78. Garnacho-Montero J, Aldabo-Pallas T, Garnacho-Montero C, et al: Timing of adequate antibiotic therapy is a greater determinant of outcome than are TNF and IL-10 polymorphisms in patients with sepsis. *Crit Care* 2006; 10:R111
79. Barie PS, Hydo LJ, Shou J, et al: Influence of antibiotic therapy on mortality of critical surgical illness caused or complicated by infection. *Surg Infect (Larchmt)* 2005; 6:41–54
80. Barochia AV, Cui X, Vitberg D, et al: Bundled care for septic shock: an analysis of clinical trials. *Crit Care Med* 2010; 38:668–678
81. Gaieski DF, Mikkelsen ME, Band RA, et al: Impact of time to antibiot- ics on survival in patients with severe sepsis or septic shock in whom early goal-directed therapy was initiated in the emergency depart- ment. *Crit Care Med* 2010; 38:1045–1053
82. Kumar A: Systematic Bias in Meta-Analyses of Time to Antimicrobial in Sepsis Studies. *Crit Care Med* 2016; 44:e234–e235
83. Shirakura Y, Kuriyama A: Timing of Antibiotic Administration in Sepsis and Septic Shock: The Impact That a Meta-Analysis Does Not Depict. *Crit Care Med* 2016; 44:e1004
84. Kaasch AJ, Rieg S, Kuetscher J, et al; preSABATO study group: Delay in the administration of appropriate antimicrobial therapy in Staphylococcus aureus bloodstream infection: a prospective multicenter hospital-based cohort study. *Infection* 2013; 41:979–985
85. Corona A, Bertolini G, Lipman J, et al: Antibiotic use and impact on outcome from bacteraemic critical illness: the BActeraemia Study in Intensive Care (BASIC). *J Antimicrob Chemother* 2010; 65:1276– 1285
86. Giner AM, Kuster SP, Zbinden R, et al: Initial management of and outcome in patients with pneumococcal bacteremia: a retrospec- tive study at a Swiss university hospital, 2003-2009. *Infection* 2011; 39:519–526
87. Lin MY, Weinstein RA, Hota B: Delay of active antimicrobial therapy and mortality among patients with bacteremia: impact of severe neutropenia. *Antimicrob Agents Chemother* 2008; 52:3188–3194
88. Amaral AC, Fowler RA, Pinto R, et al; Cooperative Antimicrobial Ther- apy of Septic Shock Database Research Group: Patient and Organizational Factors Associated With Delays in Antimicrobial Therapy for Septic Shock. *Crit Care Med* 2016; 44:2145–2153
89. Funk DJ, Kumar A: Antimicrobial therapy for life-threatening infections: speed is life. *Crit Care Clin* 2011; 27:53–76
90. Petitpas F, Guenezan J, Vendeuvre T, et al: Use of intra-osseous access in adults: a systematic review. *Crit Care* 2016; 20:102
91. Buck ML, Wiggins BS, Sesler JM: Intraosseous drug administration in children and adults during cardiopulmonary resuscitation. *Ann Pharmacother* 2007; 41:1679–1686
92. Romanelli G, Cravarezza P: Intramuscular meropenem in the treat- ment of bacterial infections of the urinary and lower respiratory tracts. Italian Intramuscular Meropenem Study Group. *J Antimicrob Che- mother* 1995; 36 Suppl A:109–119
93. Cormio L, Berardi B, Callea A, et al: Antimicrobial prophylaxis for transrectal prostatic biopsy: a prospective study of ciprofloxacin vs piperacillin/tazobactam. *BJU Int* 2002; 90:700–702
94. Barbhaiya RH, Knupp CA, Tenney J, et al: Safety, tolerance, and phar- macokinetics of cefepime administered intramuscularly to healthy subjects. *J Clin Pharmacol* 1990; 30:900–910
95. Kumar A, Ellis P, Arabi Y, et al; Cooperative Antimicrobial Therapy of Septic Shock Database Research Group: Initiation of inappropri- ate antimicrobial therapy results in a fivefold reduction of survival in human septic shock. *Chest* 2009; 136:1237–1248
96. Ibrahim EH, Sherman G, Ward S, et al: The influence of inadequate antimicrobial treatment of bloodstream infections on patient out- comes in the ICU setting. *Chest* 2000; 118:146–155
97. Paul M, Shani V, Muchtar E, et al: Systematic review and meta-analysis of the efficacy of appropriate empiric antibiotic therapy for sepsis. *Antimicrob Agents Chemother* 2010; 54:4851–4863
98. Kreger BE, Craven DE, McCabe WR: Gram-negative bacteremia. IV. Re-evaluation of clinical features and treatment in 612 patients. *Am J Med* 1980; 68:344–355
99. Mermel LA, Maki DG: Detection of bacteremia in adults: conse- quences of culturing an inadequate volume of blood. *Ann Intern Med* 1993; 119:270–272
100. Bow EJ, Evans G, Fuller J, et al: Canadian clinical practice guidelines for invasive candidiasis in adults. *Can J Infect Dis Med Microbiol* 2010; 21:e122–e150
101. Connolly S: *Clinical Practice Guidelines: Burn Patient Management*. ACI Statewide Burn Injury Service. Chatswood, NSW, Australia: NSW Agency for Clinical Innovation; 2011
102. Cornely OA, Bassetti M, Calandra T, et al; ESCMID Fungal Infection Study Group: ESCMID* guideline for the diagnosis and manage- ment of Candida diseases 2012: non-neutropenic adult patients. *Clin Microbiol Infect* 2012; 18 Suppl 7:19–37
103. Kalil AC, Metersky ML, Klompas M, et al: Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society. *Clin Infect Dis* 2016; 63:e61–e111
104. Liu C, Bayer A, Cosgrove SE, et al; Infectious Diseases Society of America: Clinical practice guidelines by the infectious dis- eases society of america for the treatment of methicillin-resistant Staphylococcus aureus infections in adults and children. *Clin Infect Dis* 2011; 52:e18–e55
105. Pappas PG, Kauffman CA, Andes DR, et al: Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America. *Clin Infect Dis* 2016; 62:e1–50
106. Penack O, Becker C, Buchheidt D, et al: Management of sepsis in neutropenic patients: 2014 updated guidelines from the Infectious Diseases Working Party of the German Society of Hematology and Medical Oncology (AGIHO). *Ann Hematol* 2014; 93:1083–1095
107. Penack O, Buchheidt D, Christopeit M, et al; German Society of Hematology and Oncology: Management of sepsis in neutropenic patients: guidelines from the infectious diseases working party of the German Society of Hematology and Oncology. *Ann Oncol* 2011; 22:1019–1029

108. Solomkin JS, Mazuski JE, Bradley JS, et al: Diagnosis and management of complicated intra-abdominal infection in adults and children: guide- lines by the Surgical Infection Society and the Infectious Diseases Society of America. *Surg Infect (Larchmt)* 2010; 11:79–109
109. Stevens DL, Bisno AL, Chambers HF, et al: Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the infectious diseases society of America. *Clin Infect Dis* 2014; 59:147–159
110. Micek ST, Welch EC, Khan J, et al: Empiric combination antibiotic therapy is associated with improved outcome against sepsis due to Gram-negative bacteria: a retrospective analysis. *Antimicrob Agents Chemother* 2010; 54:1742–1748
111. Pittet D, Monod M, Suter PM, et al: Candida colonization and sub- sequent infections in critically ill surgical patients. *Ann Surg* 1994; 220:751–758
112. Blumberg HM, Jarvis WR, Soucie JM, et al; National Epidemiology of Mycoses Survey (NEMIS) Study Group: Risk factors for candidal bloodstream infections in surgical intensive care unit patients: the NEMIS prospective multicenter study. The National Epidemiology of Mycosis Survey. *Clin Infect Dis* 2001; 33:177–186
113. Green DL: Selection of an empiric antibiotic regimen for hospital- acquired pneumonia using a unit and culture-type specific antibio- gram. *J Intensive Care Med* 2005; 20:296–301
114. Kaufman D, Haas CE, Edinger R, et al: Antibiotic susceptibility in the surgical intensive care unit compared with the hospital-wide antibio- gram. *Arch Surg* 1998; 133:1041–1045
115. Kerremans JJ, Verbrugh HA, Vos MC: Frequency of microbio- logically correct antibiotic therapy increased by infectious disease consultations and microbiological results. *J Clin Microbiol* 2012; 50:2066–2068
116. Raineri E, Pan A, Mondello P, et al: Role of the infectious diseases specialist consultant on the appropriateness of antimicrobial therapy prescription in an intensive care unit. *Am J Infect Control* 2008; 36:283–290
117. Bai AD, Showler A, Burry L, et al: Impact of Infectious Disease Consultation on Quality of Care, Mortality, and Length of Stay in Staphylococcus aureus Bacteremia: Results From a Large Multicenter Cohort Study. *Clin Infect Dis* 2015; 60:1451–1461
118. Guo Y, Gao W, Yang H, et al: De-escalation of empiric antibiotics in patients with severe sepsis or septic shock: A meta-analysis. *Heart Lung* 2016; 45:454–459
119. Bernard GR, Vincent JL, Laterre PF, et al; Recombinant human pro- tein C Worldwide Evaluation in Severe Sepsis (PROWESS) study group: Efficacy and safety of recombinant human activated protein C for severe sepsis. *N Engl J Med* 2001; 344:699–709
120. Klein Klouwenberg PM, Cremer OL, van Vught LA, et al: Likelihood of infection in patients with presumed sepsis at the time of intensive care unit admission: a cohort study. *Crit Care* 2015; 19:319
121. Working Gropu IAP/APA Acute Pancreatitis Guidelines: IAP/APA evidence-based guidelines for the management of acute pancreati- tis. *Pancreatology*. 2013;13(4):e1–e15
122. Wittau M, Mayer B, Scheele J, et al: Systematic review and meta- analysis of antibiotic prophylaxis in severe acute pancreatitis. *Scand J Gastroenterol* 2011; 46:261–270
123. Avni T, Levcovich A, Ad-El DD, et al: Prophylactic antibiotics for burns patients: systematic review and meta-analysis. *BMJ* 2010; 340:c241
124. Barajas-Nava LA, López-Alcalde J, Roqué i Figuls M, Solà I, Bonfill Cosp X: Antibiotic prophylaxis for preventing burn wound infection. *Cochrane Database Syst Rev*. 2013;(6):CD008738
125. Chelluri L, Jastremski MS: Inadequacy of standard aminoglycoside load- ing doses in acutely ill patients. *Crit Care Med* 1987; 15:1143–1145
126. Pletz MW, Bloos F, Burkhardt O, et al: Pharmacokinetics of moxiflox- acin in patients with severe sepsis or septic shock. *Intensive Care Med* 2010; 36:979–983
127. van Zanten AR, Polderman KH, van Geijlswijk IM, et al: Ciprofloxacin pharmacokinetics in critically ill patients: a prospective cohort study. *J Crit Care* 2008; 23:422–430
128. Blot S, Koulenti D, Akova M, et al: Does contemporary vancomy- cin dosing achieve therapeutic targets in a heterogeneous clinical cohort of critically ill patients? Data from the multinational DALI study. *Crit Care* 2014; 18:R99
129. Moore RD, Smith CR, Lietman PS: Association of aminoglycoside plasma levels with therapeutic outcome in gram-negative pneumo- nia. *Am J Med* 1984; 77:657–662
130. Men P, Li HB, Zhai SD, et al: Association between the AUC0-24/ MIC Ratio of Vancomycin and Its Clinical Effectiveness: A Systematic Review and Meta-Analysis. *PLoS One* 2016; 11:e0146224
131. Moise-Broder PA, Forrest A, Birmingham MC, et al: Pharmacodynamics of vancomycin and other antimicrobials in patients with Staphylococcus aureus lower respiratory tract infections. *Clin Pharmacokinet* 2004; 43:925–942
132. Zelenitsky S, Rubinstein E, Ariano R, et al; Cooperative Antimicrobial Therapy of Septic Shock-CATSS Database Research Group: Vancomycin pharmacodynamics and survival in patients with meth- icillin-resistant Staphylococcus aureus-associated septic shock. *Int J Antimicrob Agents* 2013; 41:255–260
133. Forrest A, Nix DE, Ballow CH, et al: Pharmacodynamics of intra- venous ciprofloxacin in seriously ill patients. *Antimicrob Agents Chemother* 1993; 37:1073–1081
134. Preston SL, Drusano GL, Berman AL, et al: Pharmacodynamics of levofloxacin: a new paradigm for early clinical trials. *JAMA* 1998; 279:125–129
135. Drusano GL, Preston SL, Fowler C, et al: Relationship between fluoroquinolone area under the curve: minimum inhibitory con- centration ratio and the probability of eradication of the infecting pathogen in patients with nosocomial pneumonia J Infect Dis 2004; 189:1590-1597

136. AD, Nafziger AN, Drusano GL, et al: Optimizing aminogly- coside therapy for nosocomial pneumonia caused by gram-negative bacteria. *Antimicrob Agents Chemother* 1999; 43:623–629

137. Schentag JJ, Smith IL, Swanson DJ, et al: Role for dual individualiza- tion with cefmenoxime. *Am J Med* 1984; 77:43–50

138. Crandon JL, Bulik CC, Kuti JL, et al: Clinical pharmacodynamics of cefepime in patients infected with Pseudomonas aeruginosa. *Antimicrob Agents Chemother* 2010; 54:1111–1116

139. McKinnon PS, Paladino JA, Schentag JJ: Evaluation of area under the inhibitory curve (AUIC) and time above the minimum inhibitory concentration (T>MIC) as predictors of outcome for cefepime and ceftazidime in serious bacterial infections. *Int J Antimicrob Agents* 2008; 31:345–351

140. Roberts JA, Abdul-Aziz MH, Davis JS, et al: Continuous versus Intermittent β-Lactam Infusion in Severe Sepsis. A Meta-analysis of Individual Patient Data from Randomized Trials. *Am J Respir Crit Care Med* 2016; 194:681–691

141. Barza M, Ioannidis JP, Cappelleri JC, et al: Single or multiple daily doses of aminoglycosides: a meta-analysis. *BMJ* 1996; 312:338–345

142. Hatala R, Dinh T, Cook DJ: Once-daily aminoglycoside dosing in immunocompetent adults: a meta-analysis. *Ann Intern Med* 1996; 124:717–725

143. Zelenitsky SA, Ariano RE: Support for higher ciprofloxacin AUC 24/ MIC targets in treating Enterobacteriaceae bloodstream infection. *J Antimicrob Chemother* 2010; 65:1725–1732

144. Dunbar LM, Wunderink RG, Habib MP, et al: High-dose, short- course levofloxacin for community-acquired pneumonia: a new treat- ment paradigm. *Clin Infect Dis* 2003; 37:752–760

145. Rybak MJ, Lomaestro BM, Rotschafer JC, et al: Vancomycin thera- peutic guidelines: a summary of consensus recommendations from the infectious diseases Society of America, the American Society of Health-System Pharmacists, and the Society of Infectious Diseases Pharmacists. *Clin Infect Dis* 2009; 49:325–327

146. Matsumoto K, Takesue Y, Ohmagari N, et al: Practice guidelines for therapeutic drug monitoring of vancomycin: a consensus review of the Japanese Society of Chemotherapy and the Japanese Society of Therapeutic Drug Monitoring. *J Infect Chemother* 2013; 19:365–380

147. Steinmetz T, Eliakim-Raz N, Goldberg E, et al: Association of van- comycin serum concentrations with efficacy in patients with MRSA infections: a systematic review and meta-analysis. *Clin Microbiol Infect* 2015; 21:665–673

148. Mohamed AF, Karaiskos I, Plachouras D, et al: Application of a load- ing dose of colistin methanesulfonate in critically ill patients: popula- tion pharmacokinetics, protein binding, and prediction of bacterial kill. *Antimicrob Agents Chemother* 2012; 56:4241–4249

149. Pea F, Brollo L, Viale P, et al: Teicoplanin therapeutic drug moni- toring in critically ill patients: a retrospective study emphasizing the importance of a loading dose. *J Antimicrob Chemother* 2003; 51:971–975

150. Pea F, Viale P: Bench-to-bedside review: Appropriate antibiotic ther- apy in severe sepsis and septic shock–does the dose matter? *Crit Care* 2009; 13:214

151. Wang JT, Fang CT, Chen YC, et al: Necessity of a loading dose when using vancomycin in critically ill patients. *J Antimicrob Chemother* 2001; 47:246

152. Kumar A: An alternate pathophysiologic paradigm of sepsis and sep- tic shock: implications for optimizing antimicrobial therapy. *Virulence* 2014; 5:80–97

153. Rhodes NJ, MacVane SH, Kuti JL, et al: Impact of loading doses on the time to adequate predicted beta-lactam concentrations in prolonged and continuous infusion dosing schemes. *Clin Infect Dis* 2014; 59:905–907

154. Lodise TP Jr, Lomaestro B, Drusano GL: Piperacillin-tazobactam for Pseudomonas aeruginosa infection: clinical implications of an extended-infusion dosing strategy. *Clin Infect Dis* 2007; 44:357–363

155. Yost RJ, Cappelletty DM; RECEIPT Study group: The Retrospective Cohort of Extended-Infusion Piperacillin-Tazobactam (RECEIPT) study: a multicenter study. *Pharmacotherapy* 2011; 31:767–775

156. Falagas ME, Tansarli GS, Ikawa K, et al: Clinical outcomes with extended or continuous versus short-term intravenous infusion of carbapenems and piperacillin/tazobactam: a systematic review and meta-analysis. *Clin Infect Dis* 2013; 56:272–282

157. Yusuf E, Spapen H, Piérard D: Prolonged vs intermittent infusion of piperacillin/tazobactam in critically ill patients: a narrative and sys- tematic review. *J Crit Care* 2014; 29:1089–1095

158. Mah GT, Mabasa VH, Chow I, et al: Evaluating outcomes associated with alternative dosing strategies for piperacillin/tazobactam: a quali- tative systematic review. *Ann Pharmacother* 2012; 46:265–275

159. Roberts JA, Abdul-Aziz MH, Lipman J, et al; International Society of Anti-Infective Pharmacology and the Pharmacokinetics and Pharmacodynamics Study Group of the European Society of Clinical Microbiology and Infectious Diseases: Individualised antibiotic dos- ing for patients who are critically ill: challenges and potential solu- tions. *Lancet Infect Dis* 2014; 14:498–509

160. Baptista JP, Sousa E, Martins PJ, et al: Augmented renal clearance in septic patients and implications for vancomycin optimisation. *Int J Antimicrob Agents* 2012; 39:420–423

161. Hobbs AL, Shea KM, Roberts KM, et al: Implications of Augmented Renal Clearance on Drug Dosing in Critically Ill Patients: A Focus on Antibiotics. *Pharmacotherapy* 2015; 35:1063–1075

162. Udy AA, Varghese JM, Altukroni M, et al: Subtherapeutic initial β-lactam concentrations in select critically ill patients: association between augmented renal clearance and low trough drug concen- trations. *Chest* 2012; 142:30–39

163. Blot S, Koulenti D, Akova M, et al: Does contemporary vancomy- cin dosing achieve therapeutic targets in a heterogeneous clinical cohort

of critically ill patients? Data from the multinational DALI study. *Crit Care* 2014; 18:R99

164. Roberts JA, Paul SK, Akova M, et al; DALI Study: DALI: defining antibiotic levels in intensive care unit patients: are current β-lactam antibiotic doses sufficient for critically ill patients? *Clin Infect Dis* 2014; 58:1072–1083
165. Taccone FS, Laterre PF, Spapen H, et al: Revisiting the loading dose of amikacin for patients with severe sepsis and septic shock. *Crit Care* 2010; 14:R53
166. Rea RS, Capitano B, Bies R, et al: Suboptimal aminoglycoside dos- ing in critically ill patients. *Ther Drug Monit* 2008; 30:674–681
167. Kumar A, Safdar N, Kethireddy S, et al: A survival benefit of combina- tion antibiotic therapy for serious infections associated with sepsis and septic shock is contingent only on the risk of death: a meta-ana- lytic/meta-regression study. *Crit Care Med* 2010; 38:1651–1664
168. Kumar A, Zarychanski R, Light B, et al; Cooperative Antimicrobial Therapy of Septic Shock (CATSS) Database Research Group: Early combination antibiotic therapy yields improved survival compared with monotherapy in septic shock: a propensity-matched analysis. *Crit Care Med* 2010; 38:1773–1785
169. Al-Hasan MN, Wilson JW, Lahr BD, et al: Beta-lactam and fluoro- quinolone combination antibiotic therapy for bacteremia caused by gram-negative bacilli. *Antimicrob Agents Chemother* 2009; 53:1386–1394
170. Delannoy PY, Boussekey N, Devos P, et al: Impact of combination therapy with aminoglycosides on the outcome of ICU-acquired bacteraemias. *Eur J Clin Microbiol Infect Dis* 2012; 31:2293–2299
171. Díaz-Martín A, Martínez-González ML, Ferrer R, et al; Edusepsis Study Group: Antibiotic prescription patterns in the empiric therapy of severe sepsis: combination of antimicrobials with different mecha- nisms of action reduces mortality. *Crit Care* 2012; 16:R223
172. Martin-Loeches I, Lisboa T, Rodriguez A, et al: Combination antibi- otic therapy with macrolides improves survival in intubated patients with community-acquired pneumonia. *Intensive Care Med* 2010; 36:612–620
173. Brunkhorst FM, Oppert M, Marx G, et al; German Study Group Competence Network Sepsis (SepNet): Effect of empirical treatment with moxifloxacin and meropenem vs meropenem on sepsis-related organ dysfunction in patients with severe sepsis: a randomized trial. *JAMA* 2012; 307:2390–2399
174. Safdar N, Handelsman J, Maki DG: Does combination antimicrobial therapy reduce mortality in Gram-negative bacteraemia? A meta-analysis. *Lancet Infect Dis* 2004; 4:519–527
175. Paul M, Silbiger I, Grozinsky S, Soares-Weiser K, Leibovici L: Beta lactam antibiotic monotherapy versus beta lactam-aminoglycoside antibiotic combination therapy for sepsis. *Cochrane Database Syst Rev*. 2006;(1):CD003344
176. Rodríguez A, Mendia A, Sirvent JM, et al; CAPUCI Study Group: Combination antibiotic therapy improves survival in patients with community-acquired pneumonia and shock. *Crit Care Med* 2007; 35:1493–1498
177. Baddour LM, Yu VL, Klugman KP, et al; International Pneumococcal Study Group: Combination antibiotic therapy lowers mortality among severely ill patients with pneumococcal bacteremia. *Am J Respir Crit Care Med* 2004; 170:440–444
178. Hilf M, Yu VL, Sharp J, et al: Antibiotic therapy for Pseudomonas aeruginosa bacteremia: outcome correlations in a prospective study of 200 patients. *Am J Med* 1989; 87:540–546
179. Tumbarello M, Viale P, Viscoli C, et al: Predictors of mortality in bloodstream infections caused by Klebsiella pneumoniae carbapen- emase-producing K. pneumoniae: importance of combination ther- apy. *Clin Infect Dis* 2012; 55:943–950
180. Bass SN, Bauer SR, Neuner EA, et al: Impact of combination antimi- crobial therapy on mortality risk for critically ill patients with carbape- nem-resistant bacteremia. *Antimicrob Agents Chemother* 2015; 59:3748–3753
181. Poulikakos P, Tansarli GS, Falagas ME: Combination antibiotic treatment versus monotherapy for multidrug-resistant, exten- sively drug-resistant, and pandrug-resistant Acinetobacter infec- tions: a systematic review. *Eur J Clin Microbiol Infect Dis* 2014; 33:1675–1685
182. Falagas ME, Lourida P, Poulikakos P, et al: Antibiotic treatment of infections due to carbapenem-resistant Enterobacteriaceae: sys- tematic evaluation of the available evidence. *Antimicrob Agents Chemother* 2014; 58:654–663
183. Hu Y, Li L, Li W, et al: Combination antibiotic therapy versus mono- therapy for Pseudomonas aeruginosa bacteraemia: a meta-analysis of retrospective and prospective studies. *Int J Antimicrob Agents* 2013; 42:492–496
184. Vardakas KZ, Tansarli GS, Bliziotis IA, et al: β-Lactam plus amino- glycoside or fluoroquinolone combination versus β-lactam mono- therapy for Pseudomonas aeruginosa infections: a meta-analysis. *Int J Antimicrob Agents* 2013; 41:301–310
185. Stevens DL, Tanner MH, Winship J, et al: Severe group A strepto- coccal infections associated with a toxic shock-like syndrome and scarlet fever toxin A. *N Engl J Med* 1989; 321:1–7
186. Zimbelman J, Palmer A, Todd J: Improved outcome of clindamy- cin compared with beta-lactam antibiotic treatment for invasive Streptococcus pyogenes infection. *Pediatr Infect Dis J* 1999; 18:1096–1100
187. Paul M, Soares-Weiser K, Leibovici L: Beta lactam monotherapy versus beta lactam-aminoglycoside combination therapy for fever with neutropenia: systematic review and meta-analysis. *BMJ* 2003; 326:1111
188. Freifeld AG, Bow EJ, Sepkowitz KA, et al; Infectious Diseases Society of America: Clinical practice guideline for the use of anti- microbial agents in neutropenic patients with cancer: 2010 update by the infectious diseases society of america. *Clin Infect Dis* 2011; 52:e56–e93
189. Gomes Silva BN, Andriolo RB, Atallah AN, Salomão R: De-escalation of antimicrobial treatment for adults with sepsis, severe sepsis or septic shock. *Cochrane Database Syst Rev*. 2010;(12):CD007934
190. Morel J, Casoetto J, Jospé R, et al: De-escalation as part of a global strategy of empiric antibiotherapy management. A retrospective study in a medico-surgical intensive care unit. *Crit Care* 2010; 14:R225

191. Joung MK, Lee JA, Moon SY, et al: Impact of de-escalation therapy on clinical outcomes for intensive care unit-acquired pneumonia. *Crit Care* 2011; 15:R79

192. Leone M, Bechis C, Baumstarck K, et al; AZUREA Network Investigators: De-escalation versus continuation of empirical antimicrobial treatment in severe sepsis: a multicenter non-blinded randomized noninferiority trial. *Intensive Care Med* 2014; 40:1399–1408

193. Riccio LM, Popovsky KA, Hranjec T, et al: Association of excessive duration of antibiotic therapy for intra-abdominal infection with subsequent extra-abdominal infection and death: a study of 2,552 con- secutive infections. *Surg Infect (Larchmt)* 2014; 15:417–424

194. Aarts MA, Brun-Buisson C, Cook DJ, et al: Antibiotic management of suspected nosocomial ICU-acquired infection: does prolonged empiric therapy improve outcome? *Intensive Care Med* 2007; 33:1369–1378

195. Stevens V, Dumyati G, Fine LS, et al: Cumulative antibiotic expo- sures over time and the risk of Clostridium difficile infection. *Clin Infect Dis* 2011; 53:42–48

196. Goossens H: Antibiotic consumption and link to resistance. *Clin Microbiol Infect* 2009; 15 Suppl 3:12–15

197. Chastre J, Wolff M, Fagon JY, et al; Pneum A Trial Group: Comparison of 8 vs 15 days of antibiotic therapy for ventilator-associated pneu- monia in adults: a randomized trial. *JAMA* 2003; 290:2588–2598

198. Choudhury G, Mandal P, Singanayagam A, et al: Seven-day antibi- otic courses have similar efficacy to prolonged courses in severe community-acquired pneumonia–a propensity-adjusted analysis. *Clin Microbiol Infect* 2011; 17:1852–1858

199. Pugh R, Grant C, Cooke RP, Dempsey G: Short-course ver- sus prolonged-course antibiotic therapy for hospital-acquired pneumonia in critically ill adults. *Cochrane Database Syst Rev*. 2015;(8):CD007577

200. Sawyer RG, Claridge JA, Nathens AB, et al: Trial of short-course antimicrobial therapy for intraabdominal infection. *N Engl J Med* 2015; 372:1996–2005

201. Eliakim-Raz N, Yahav D, Paul M, et al: Duration of antibiotic treatment for acute pyelonephritis and septic urinary tract infection– 7 days or less versus longer treatment: systematic review and meta-analysis of randomized controlled trials. *J Antimicrob Chemother* 2013; 68:2183–2191

202. Rattan R, Allen CJ, Sawyer RG, et al: Patients with Complicated Intra-Abdominal Infection Presenting with Sepsis Do Not Require Longer Duration of Antimicrobial Therapy. *J Am Coll Surg* 2016; 222:440–446

203. Hepburn MJ, Dooley DP, Skidmore PJ, et al: Comparison of short- course (5 days) and standard (10 days) treatment for uncomplicated cellulitis. *Arch Intern Med* 2004; 164:1669–1674

204. Chaudhry ZI, Nisar S, Ahmed U, Ali M: Short course of antibiotic treatment in spontaneous bacterial peritonitis: a randomized con- trolled study. *J Coll Physicians Surg Pak*. 2000;10(8):284–288

205. Jack L, Bal AM, Harte S, et al: International guidelines: the need to standardize the management of candidaemia. *Infect Dis (Lond)* 2016; 48:779–781

206. Baddour LM, Wilson WR, Bayer AS, et al; American Heart Association Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease of the Council on Cardiovascular Disease in the Young, Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and Stroke Council: Infective Endocarditis in Adults: Diagnosis, Antimicrobial Therapy, and Management of Complications: A Scientific Statement for Healthcare Professionals From the American Heart Association. *Circulation* 2015; 132:1435–1486

207. Habib G, Lancellotti P, Antunes MJ, et al; Document Reviewers: 2015 ESC Guidelines for the management of infective endocardi- tis: The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). *Eur Heart J* 2015; 36:3075–3128

208. Weiss CH, Moazed F, McEvoy CA, et al: Prompting physicians to address a daily checklist and process of care and clinical outcomes: a single-site study. *Am J Respir Crit Care Med* 2011; 184:680–686

209. Aguado JM, Vázquez L, Fernández-Ruiz M, et al; PCRAGA Study Group; Spanish Stem Cell Transplantation Group; Study Group of Medical Mycology of the Spanish Society of Clinical Microbiology and Infectious Diseases; Spanish Network for Research in Infectious Diseases: Serum galactomannan versus a combination of galacto- mannan and polymerase chain reaction-based Aspergillus DNA detection for early therapy of invasive aspergillosis in high-risk hematological patients: a randomized controlled trial. *Clin Infect Dis* 2015; 60:405–414

210. Hou TY, Wang SH, Liang SX, et al: The Screening Performance of Serum 1,3-Beta-D-Glucan in Patients with Invasive Fungal Diseases: A Meta-Analysis of Prospective Cohort Studies. *PLoS One* 2015; 10:e0131602

211. Schuetz P, Briel M, Christ-Crain M, et al: Procalcitonin to guide ini- tiation and duration of antibiotic treatment in acute respiratory infections: an individual patient data meta-analysis. *Clin Infect Dis* 2012; 55:651–662

212. Matthaiou DK, Ntani G, Kontogiorgi M, et al: An ESICM systematic review and meta-analysis of procalcitonin-guided antibiotic therapy algorithms in adult critically ill patients. *Intensive Care Med* 2012; 38:940–949

213. Prkno A, Wacker C, Brunkhorst FM, et al: Procalcitonin-guided therapy in intensive care unit patients with severe sepsis and sep- tic shock–a systematic review and meta-analysis. *Crit Care* 2013; 17:R291

214. Westwood M, Ramaekers B, Whiting P, et al: Procalcitonin testing to guide antibiotic therapy for the treatment of sepsis in intensive care settings and for suspected bacterial infection in emergency depart- ment settings: a systematic review and cost-effectiveness analysis. *Health Technol Assess*. 2015;19(96):v–xxv, 1–236

215. Wacker C, Prkno A, Brunkhorst FM, et al: Procalcitonin as a diag- nostic marker for sepsis: a systematic review and meta-analysis. *Lancet Infect Dis* 2013; 13:426–435

216. Soni NJ, Samson DJ, Galaydick JL, et al: Procalcitonin-guided anti- biotic therapy: a systematic review and meta-analysis. *J Hosp Med* 2013;

8:530–540

217. de Jong E, van Oers JA, Beishuizen A, et al: Efficacy and safety of procalcitonin guidance in reducing the duration of antibiotic treat- ment in critically ill patients: a randomised, controlled, open-label trial. *Lancet Infect Dis* 2016; 16:819–827
218. Lesprit P, Landelle C, Girou E, et al: Reassessment of intrave- nous antibiotic therapy using a reminder or direct counselling. *J Antimicrob Chemother* 2010; 65:789–795
219. Paul M, Dickstein Y, Raz-Pasteur A: Antibiotic de-escalation for bloodstream infections and pneumonia: systematic review and meta- analysis. *Clin Microbiol Infect* 2016; 22:960–967
220. Schuetz P, Kutz A, Grolimund E, et al; ProHOSP Study Group: Excluding infection through procalcitonin testing improves outcomes of congestive heart failure patients presenting with acute respiratory symptoms: results from the randomized ProHOSP trial. *Int J Cardiol* 2014; 175:464–472
221. Hoeboer SH, van der Geest PJ, Nieboer D, et al: The diagnostic accuracy of procalcitonin for bacteraemia: a systematic review and meta-analysis. *Clin Microbiol Infect* 2015; 21:474–481
222. Jimenez MF, Marshall JC; International Sepsis Forum: Source control in the management of sepsis. *Intensive Care Med* 2001; 27 Suppl 1:S49–S62
223. Azuhata T, Kinoshita K, Kawano D, et al: Time from admission to initi- ation of surgery for source control is a critical determinant of survival in patients with gastrointestinal perforation with associated septic shock. *Crit Care* 2014; 18:R87
224. Bloos F, Thomas-Rüddel D, Rüddel H, et al; MEDUSA Study Group: Impact of compliance with infection management guidelines on out- come in patients with severe sepsis: a prospective observational multi-center study. *Crit Care* 2014; 18:R42
225. Moss RL, Musemeche CA, Kosloske AM: Necrotizing fasciitis in chil- dren: prompt recognition and aggressive therapy improve survival. *J Pediatr Surg* 1996; 31:1142–1146
226. Wong CH, Chang HC, Pasupathy S, et al: Necrotizing fasciitis: clini- cal presentation, microbiology, and determinants of mortality. *J Bone Joint Surg Am* 2003; 85-A:1454–1460
227. Chao WN, Tsai CF, Chang HR, et al: Impact of timing of surgery on outcome of Vibrio vulnificus-related necrotizing fasciitis. *Am J Surg* 2013; 206:32–39
228. Buck DL, Vester-Andersen M, Møller MH; Danish Clinical Register of Emergency Surgery: Surgical delay is a critical determinant of sur-vival in perforated peptic ulcer. *Br J Surg* 2013; 100:1045–1049
229. Karvellas CJ, Abraldes JG, Zepeda-Gomez S, et al; Cooperative Antimicrobial Therapy of Septic Shock (CATSS) Database Research Group: The impact of delayed biliary decompression and anti- microbial therapy in 260 patients with cholangitis-associated septic shock. *Aliment Pharmacol Ther* 2016; 44:755–766
230. Maitland K, Kiguli S, Opoka RO, et al; FEAST Trial Group: Mortality after fluid bolus in African children with severe infection. *N Engl J Med* 2011; 364:2483–2495
231. Acheampong A, Vincent JL: A positive fluid balance is an independent prognostic factor in patients with sepsis. *Crit Care* 2015; 19:251
232. Brotfain E, Koyfman L, Toledano R, et al: Positive fluid balance as a major predictor of clinical outcome of patients with sepsis/septic shock after ICU discharge. *Am J Emerg Med* 2016;34:2122–2126
233. Mitchell KH, Carlbom D, Caldwell E, et al: Volume Overload: Prevalence, Risk Factors, and Functional Outcome in Survivors of Septic Shock. *Ann Am Thorac Soc* 2015; 12:1837–1844
234. de Oliveira FS, Freitas FG, Ferreira EM, et al: Positive fluid balance as a prognostic factor for mortality and acute kidney injury in severe sepsis and septic shock. *J Crit Care* 2015; 30:97–101
235. Malbrain ML, Marik PE, Witters I, et al: Fluid overload, de-resusci- tation, and outcomes in critically ill or injured patients: a systematic review with suggestions for clinical practice. *Anaesthesiol Intensive Ther* 2014; 46:361–380
236. Yunos NM, Bellomo R, Hegarty C, et al: Association between a chloride-liberal vs chloride-restrictive intravenous fluid administra- tion strategy and kidney injury in critically ill adults. *JAMA* 2012; 308:1566–1572
237. Rochwerg B, Alhazzani W, Sindi A, et al; Fluids in Sepsis and Septic Shock Group: Fluid resuscitation in sepsis: a systematic review and network meta-analysis. *Ann Intern Med* 2014; 161:347–355
238. Young P, Bailey M, Beasley R, et al; SPLIT Investigators; ANZICS CTG: Effect of a Buffered Crystalloid Solution vs Saline on Acute Kidney Injury Among Patients in the Intensive Care Unit: The SPLIT Randomized Clinical Trial. *JAMA* 2015; 314:1701–1710
239. Finfer S, Norton R, Bellomo R, et al: The SAFE study: saline vs. albumin for fluid resuscitation in the critically ill. *Vox Sang* 2004; 87 Suppl 2:123–131
240. Delaney AP, Dan A, McCaffrey J, et al: The role of albumin as a resus- citation fluid for patients with sepsis: a systematic review and meta-analysis. *Crit Care Med* 2011; 39:386–391
241. Rochwerg B, Alhazzani W, Gibson A, et al; FISSH Group (Fluids in Sepsis and Septic Shock): Fluid type and the use of renal replace- ment therapy in sepsis: a systematic review and network meta-anal- ysis. *Intensive Care Med* 2015; 41:1561–1571
242. Xu JY, Chen QH, Xie JF, et al: Comparison of the effects of albumin and crystalloid on mortality in adult patients with severe sepsis and septic shock: a meta-analysis of randomized clinical trials. *Crit Care* 2014; 18:702
243. Uhlig C, Silva PL, Deckert S, et al: Albumin versus crystalloid solu- tions in patients with the acute respiratory distress syndrome: a sys-tematic review and meta-analysis. *Crit Care* 2014; 18:R10

244. Patel A, Laffan MA, Waheed U, et al: Randomised trials of human albumin for adults with sepsis: systematic review and meta-analy- sis with trial sequential analysis of all-cause mortality. *BMJ* 2014; 349:g4561

245. Jiang L, Jiang S, Zhang M, et al: Albumin versus other fluids for fluid resuscitation in patients with sepsis: a meta-analysis. *PLoS One* 2014; 9:e114666

246. Boldt J, Heesen M, Müller M, et al: The effects of albumin versus hydroxyethyl starch solution on cardiorespiratory and circulatory variables in critically ill patients. *Anesth Analg* 1996; 83:254–261

247. Boldt J, Heesen M, Welters I, et al: Does the type of volume therapy influence endothelial-related coagulation in the critically ill? *Br J Anaesth* 1995; 75:740–746

248. Boldt J, Müller M, Heesen M, et al: Influence of different volume therapies on platelet function in the critically ill. *Intensive Care Med* 1996; 22:1075–1081

249. Caironi P, Tognoni G, Masson S, et al; ALBIOS Study Investigators: Albumin replacement in patients with severe sepsis or septic shock. *N Engl J Med* 2014; 370:1412–1421

250. Haase N, Perner A, Hennings LI, et al: Hydroxyethyl starch 130/0.38-0.45 versus crystalloid or albumin in patients with sepsis: systematic review with meta-analysis and trial sequential analysis. *BMJ* 2013; 346:f839

251. Moeller C, Fleischmann C, Thomas-Rueddel D, et al: How safe is gela- tin? A systematic review and meta-analysis of gelatin-containing plasma expanders vs crystalloids and albumin. *J Crit Care* 2016; 35:75–83

252. Day NP, Phu NH, Bethell DP, et al: The effects of dopamine and adrenaline infusions on acid-base balance and systemic haemody- namics in severe infection. *Lancet* 1996; 348:219–223

253. De Backer D, Creteur J, Silva E, et al: Effects of dopamine, nor- epinephrine, and epinephrine on the splanchnic circulation in septic shock: which is best? *Crit Care Med* 2003; 31:1659–1667

254. Martin C, Papazian L, Perrin G, et al: Norepinephrine or dopamine for the treatment of hyperdynamic septic shock? *Chest* 1993; 103:1826–1831

255. Martin C, Viviand X, Leone M, et al: Effect of norepinephrine on the outcome of septic shock. *Crit Care Med* 2000; 28:2758–2765

256. Bollaert PE, Bauer P, Audibert G, et al: Effects of epinephrine on hemodynamics and oxygen metabolism in dopamine-resistant septic shock. *Chest* 1990; 98:949–953

257. Levy B, Bollaert PE, Charpentier C, et al: Comparison of norepi- nephrine and dobutamine to epinephrine for hemodynamics, lactate metabolism, and gastric tonometric variables in septic shock: a pro- spective, randomized study. *Intensive Care Med* 1997; 23:282–287

258. Zhou SX, Qiu HB, Huang YZ, et al: Effects of norepinephrine, epi- nephrine, and norepinephrine-dobutamine on systemic and gastric mucosal oxygenation in septic shock. *Acta Pharmacol Sin* 2002; 23:654–658

259. Mackenzie SJ, Kapadia F, Nimmo GR, et al: Adrenaline in treatment of septic shock: effects on haemodynamics and oxygen transport. *Intensive Care Med* 1991; 17:36–39

260. Moran JL, O'Fathartaigh MS, Peisach AR, et al: Epinephrine as an inotropic agent in septic shock: a dose-profile analysis. *Crit Care Med* 1993; 21:70–77

261. Yamazaki T, Shimada Y, Taenaka N, et al: Circulatory responses to afterloading with phenylephrine in hyperdynamic sepsis. *Crit Care Med* 1982; 10:432–435

262. Regnier B, Rapin M, Gory G, et al: Haemodynamic effects of dopa- mine in septic shock. *Intensive Care Med* 1977; 3:47–53

263. Beck GCh, Brinkkoetter P, Hanusch C, et al: Clinical review: immu- nomodulatory effects of dopamine in general inflammation. *Crit Care*. 2004;8(6):485–491

264. Avni T, Lador A, Lev S, et al: Vasopressors for the Treatment of Septic Shock: Systematic Review and Meta-Analysis. *PLoS One* 2015; 10:e0129305

265. Myburgh JA, Higgins A, Jovanovska A, et al; CAT Study investiga- tors: A comparison of epinephrine and norepinephrine in critically ill patients. *Intensive Care Med* 2008; 34:2226–2234

266. Landry DW, Levin HR, Gallant EM, et al: Vasopressin deficiency contributes to the vasodilation of septic shock. *Circulation* 1997; 95:1122–1125

267. Patel BM, Chittock DR, Russell JA, et al: Beneficial effects of short-term vasopressin infusion during severe septic shock. *Anesthesiology* 2002; 96:576–582

268. Dünser MW, Mayr AJ, Ulmer H, et al: Arginine vasopressin in advanced vasodilatory shock: a prospective, randomized, controlled study. *Circulation* 2003; 107:2313–2319

269. Lauzier F, Lévy B, Lamarre P, et al: Vasopressin or norepinephrine in early hyperdynamic septic shock: a randomized clinical trial. *Intensive Care Med* 2006; 32:1782–1789

270. Holmes CL, Walley KR, Chittock DR, et al: The effects of vasopres- sin on hemodynamics and renal function in severe septic shock: a case series. *Intensive Care Med* 2001; 27:1416–1421

271. Malay MB, Ashton RC Jr, Landry DW, et al: Low-dose vasopres- sin in the treatment of vasodilatory septic shock. *J Trauma* 1999; 47:699–703; discussion 703

272. O'Brien A, Clapp L, Singer M: Terlipressin for norepinephrine-resis- tant septic shock. *Lancet* 2002; 359:1209–1210

273. Sharshar T, Blanchard A, Paillard M, et al: Circulating vasopressin levels in septic shock. *Crit Care Med* 2003; 31:1752–1758
274. Russell JA, Walley KR, Singer J, et al; VASST Investigators: Vasopressin versus norepinephrine infusion in patients with septic shock. *N Engl J Med* 2008; 358:877–887
275. Dünser MW, Mayr AJ, Tür A, et al: Ischemic skin lesions as a compli- cation of continuous vasopressin infusion in catecholamine-resistant vasodilatory shock: incidence and risk factors. *Crit Care Med* 2003; 31:1394–1398
276. Gordon AC, Mason AJ, Thirunavukkarasu N, et al; VANISH Investigators: Effect of Early Vasopressin vs Norepinephrine on Kidney Failure in Patients With Septic Shock: The VANISH Randomized Clinical Trial. *JAMA* 2016; 316:509–518
277. Albanèse J, Leone M, Delmas A, et al: Terlipressin or norepinephrine in hyperdynamic septic shock: a prospective, randomized study. *Crit Care Med* 2005; 33:1897–1902
278. Morelli A, Ertmer C, Lange M, et al: Effects of short-term simultane- ous infusion of dobutamine and terlipressin in patients with septic shock: the DOBUPRESS study. *Br J Anaesth* 2008; 100:494–503
279. Morelli A, Ertmer C, Rehberg S, et al: Continuous terlipressin ver- sus vasopressin infusion in septic shock (TERLIVAP): a randomized, controlled pilot study. *Crit Care* 2009; 13:R130
280. Zhou F, Mao Z, Zeng X, et al: Vasopressors in septic shock: a sys- tematic review and network meta-analysis. *Ther Clin Risk Manag* 2015; 11:1047–1059
281. De Backer D, Aldecoa C, Njimi H, et al: Dopamine versus norepi- nephrine in the treatment of septic shock: a meta-analysis*. *Crit Care Med* 2012; 40:725–730
282. De Backer D, Biston P, Devriendt J, et al; SOAP II Investigators: Comparison of dopamine and norepinephrine in the treatment of shock. *N Engl J Med* 2010; 362:779–789
283. Parker MM, Shelhamer JH, Bacharach SL, et al: Profound but revers- ible myocardial depression in patients with septic shock. *Ann Intern Med* 1984; 100:483–490
284. Gattinoni L, Brazzi L, Pelosi P, et al: A trial of goal-oriented hemody- namic therapy in critically ill patients. SvO2 Collaborative Group. *NEngl J Med* 1995; 333:1025–1032
285. Hayes MA, Timmins AC, Yau EH, et al: Elevation of systemic oxygen delivery in the treatment of critically ill patients. *N Engl J Med* 1994; 330:1717–1722
286. Hollenberg SM, Ahrens TS, Annane D, et al: Practice parameters for hemodynamic support of sepsis in adult patients: 2004 update. *Crit Care Med* 2004; 32:1928–1948
287. Annane D, Vignon P, Renault A, et al; CATS Study Group: Norepinephrine plus dobutamine versus epinephrine alone for manage- ment of septic shock: a randomised trial. *Lancet* 2007; 370:676–684
288. ProCess Investigators, Yealy DM, Kellum JA, et al: A randomized trial of protocol-based care for early septic shock. *N Engl J Med*. 2014;370(18):1683–1693
289. ARISE Investigators, Anzics Clinical Trials Group, Peake SL, et al: Goal-directed resuscitation for patients with early septic shock. *N Engl J Med*. 2014;371(16):1496–1506
290. Barton P, Garcia J, Kouatli A, et al: Hemodynamic effects of i.v. mil- rinone lactate in pediatric patients with septic shock. A prospec- tive, double-blinded, randomized, placebo-controlled, interventional study. *Chest* 1996; 109:1302–1312
291. Morelli A, Teboul JL, Maggiore SM, et al: Effects of levosimendan on right ventricular afterload in patients with acute respiratory distress syndrome: a pilot study. *Crit Care Med* 2006; 34:2287–2293
292. Morelli A, De Castro S, Teboul JL, et al: Effects of levosimendan on systemic and regional hemodynamics in septic myocardial depres- sion. *Intensive Care Med* 2005; 31:638–644
293. Gordon AC, Perkins GD, Singer M, et al: Levosimendan for the pre- vention of acute organ dysfunction in sepsis. *N Engl J Med*. [Epub ahead of print]
294. Cohn JN: Blood pressure measurement in shock. Mechanism of inaccuracy in ausculatory and palpatory methods. *JAMA* 1967; 199:118–122
295. Hollenberg SM, Parrillo JE. Shock. *In*: Braunwald E, Isselbacher KJ, Wilson JD, et al. *Harrison's Principles of Internal Medicine*. 14th ed. New York: McGraw-Hill; 1997:214–222
296. Scheer B, Perel A, Pfeiffer UJ: Clinical review: complications and risk factors of peripheral arterial catheters used for haemodynamic monitoring in anaesthesia and intensive care medicine. *Crit Care* 2002; 6:199–204
297. Gu WJ, Wu XD, Wang F, et al: Ultrasound Guidance Facilitates Radial Artery Catheterization: A Meta-analysis With Trial Sequential Analysis of Randomized Controlled Trials. *Chest* 2016; 149:166–179
298. O'Horo JC, Maki DG, Krupp AE, et al: Arterial catheters as a source of bloodstream infection: a systematic review and meta-analysis. *Crit Care Med* 2014; 42:1334–1339
299. Annane D, Bellissant E, Bollaert PE, et al: Corticosteroids in the treatment of severe sepsis and septic shock in adults: a systematic review. *JAMA* 2009; 301:2362–2375
300. Bollaert PE, Charpentier C, Levy B, et al: Reversal of late septic shock with supraphysiologic doses of hydrocortisone. *Crit Care Med* 1998; 26:645–650
301. Briegel J, Forst H, Haller M, et al: Stress doses of hydrocortisone reverse hyperdynamic septic shock: a prospective, randomized, double-

blind, single-center study. *Crit Care Med* 1999; 27:723–732

302. Sprung CL, Annane D, Keh D, et al; CORTICUS Study Group: Hydrocortisone therapy for patients with septic shock. *N Engl J Med* 2008; 358:111–124
303. Sligl WI, Milner DA Jr, Sundar S, et al: Safety and efficacy of cortico- steroids for the treatment of septic shock: A systematic review and meta-analysis. *Clin Infect Dis* 2009; 49:93–101
304. Annane D, Bellissant E, Bollaert PE, Briegel J, Keh D, Kupfer Y: Corticosteroids for treating sepsis. *Cochrane Database Syst Rev*. 2015(12):CD002243
305. Volbeda M, Wetterslev J, Gluud C, et al: Glucocorticosteroids for sepsis: systematic review with meta-analysis and trial sequential analysis. *Intensive Care Med* 2015; 41:1220–1234
306. Annane D, Sébille V, Charpentier C, et al: Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *JAMA* 2002; 288:862–871
307. Briegel J, Sprung CL, Annane D, et al; CORTICUS Study Group: Multicenter comparison of cortisol as measured by different meth- ods in samples of patients with septic shock. *Intensive Care Med* 2009; 35:2151–2156
308. Allolio B, Dörr H, Stuttmann R, et al: Effect of a single bolus of etomi- date upon eight major corticosteroid hormones and plasma ACTH. *Clin Endocrinol (Oxf)* 1985; 22:281–286
309. Jabre P, Combes X, Lapostolle F, et al; KETASED Collaborative Study Group: Etomidate versus ketamine for rapid sequence intuba- tion in acutely ill patients: a multicentre randomised controlled trial. *Lancet* 2009; 374:293–300
310. Oppert M, Schindler R, Husung C, et al: Low-dose hydrocortisone improves shock reversal and reduces cytokine levels in early hyper-dynamic septic shock. *Crit Care Med* 2005; 33:2457–2464
311. Yildiz O, Doganay M, Aygen B, et al: Physiological-dose steroid therapy in sepsis [ISRCTN36253388]. *Crit Care* 2002; 6:251–259
312. Keh D, Boehnke T, Weber-Cartens S, et al: Immunologic and hemo- dynamic effects of "low-dose" hydrocortisone in septic shock: a double-blind, randomized, placebo-controlled, crossover study. *Am J Respir Crit Care Med* 2003; 167:512–520
313. Huh JW, Choi HS, Lim CM, et al: Low-dose hydrocortisone treat- ment for patients with septic shock: a pilot study comparing 3days with 7days. *Respirology* 2011; 16:1088–1095
314. Keh D, Trips E, Marx G, et al; SepNet–Critical Care Trials Group: Effect of Hydrocortisone on Development of Shock Among Patients With Severe Sepsis: The HYPRESS Randomized Clinical Trial. *JAMA* 2016; 316:1775–1785
315. Weber-Carstens S, Deja M, Bercker S, et al: Impact of bolus appli- cation of low-dose hydrocortisone on glycemic control in septic shock patients. *Intensive Care Med* 2007; 33:730–733
316. Holst LB, Haase N, Wetterslev J, et al; TRISS Trial Group; Scandinavian Critical Care Trials Group: Lower versus higher hemoglobin threshold for transfusion in septic shock. *N Engl J Med*2014; 371:1381–1391
317. Corwin HL, Gettinger A, Pearl RG, et al; EPO Critical Care Trials Group: Efficacy of recombinant human erythropoietin in critically ill patients: a randomized controlled trial. *JAMA* 2002; 288:2827–2835
318. Corwin HL, Gettinger A, Rodriguez RM, et al: Efficacy of recom- binant human erythropoietin in the critically ill patient: a random- ized, double-blind, placebo-controlled trial. *Crit Care Med* 1999; 27:2346–2350
319. Liumbruno G, Bennardello F, Lattanzio A, et al; Italian Society of Transfusion Medicine and Immunohaematology (SIMTI) Work Group: Recommendations for the transfusion of plasma andplate- lets. *Blood Transfus* 2009; 7:132–150
320. British Committee for Standards in Haematology, Blood Transfusion Task Force. Guidelines for the use of platelet transfusions. *Br J Haematol*. 2003;122(1):10–23
321. Diedrich B, Remberger M, Shanwell A, et al: A prospective random- ized trial of a prophylactic platelet transfusion trigger of 10 x 10(9) per L versus 30 x 10(9) per L in allogeneic hematopoietic progenitor cell transplant recipients. *Transfusion* 2005; 45:1064–1072
322. Kaufman RM, Djulbegovic B, Gernsheimer T, et al; AABB: Platelet transfusion: a clinical practice guideline from the AABB. *Ann Intern Med* 2015; 162:205–213
323. Schiffer CA, Anderson KC, Bennett CL, et al; American Society of Clinical Oncology: Platelet transfusion for patients with cancer: clini- cal practice guidelines of the American Society of Clinical Oncology. *J Clin Oncol* 2001; 19:1519–1538
324. Stanworth SJ, Estcourt LJ, Llewelyn CA, et al; TOPPS Study Investigators: Impact of prophylactic platelet transfusions on bleed- ing events in patients with hematologic malignancies: a subgroup analysis of a randomized trial. *Transfusion* 2014;54:2385–2393
325. Stanworth SJ, Estcourt LJ, Powter G, et al; TOPPS Investigators: A no-prophylaxisplatelet-transfusionstrategyforhematologiccancers. *N Engl J Med* 2013; 368:1771–1780
326. Wandt H, Schaefer-Eckart K, Wendelin K, et al; Study Alliance Leukemia: Therapeutic platelet transfusion versus routine pro- phylactic transfusion in patients with haematological malignan- cies: an open-label, multicentre, randomised study. *Lancet* 2012; 380:1309–1316
327. Zumberg MS, del Rosario ML, Nejame CF, et al: A prospective ran- domized trial of prophylactic platelet transfusion and bleeding inci-dence in hematopoietic stem cell transplant recipients: 10,000/L versus 20,000/microL trigger. *Biol Blood Marrow Transplant* 2002; 8:569–576
328. Werdan K, Pilz G, Bujdoso O, et al; Score-Based Immunoglobulin Therapy of Sepsis (SBITS) Study Group: Score-based immunoglob- ulin G therapy of patients with sepsis: the SBITS study. *Crit Care Med* 2007; 35:2693–2701
329. Alejandria MM, Lansang MA, Dans LF, Mantaring JB 3rd: Intravenous immunoglobulin for treating sepsis, severe sepsis and septic shock. *Cochrane Database Syst Rev*. 2013(9):CD001090

330. Soares MO, Welton NJ, Harrison DA, et al: An evaluation of the fea- sibility, cost and value of information of a multicentre randomised controlled trial of intravenous immunoglobulin for sepsis (severe sepsis and septic shock): incorporating a systematic review, meta-analysis and value of information analysis. *Health Technol Assess* 2012; 16:1–186
331. Laupland KB, Kirkpatrick AW, Delaney A: Polyclonal intravenous immunoglobulin for the treatment of severe sepsis and septic shock in critically ill adults: a systematic review and meta-analysis. *Crit Care Med* 2007; 35:2686–2692
332. Pildal J, Gøtzsche PC: Polyclonal immunoglobulin for treatment of bacterial sepsis: a systematic review. *Clin Infect Dis* 2004; 39:38–46
333. Kreymann KG, de Heer G, Nierhaus A, et al: Use of polyclonal immu- noglobulins as adjunctive therapy for sepsis or septic shock. *Crit Care Med* 2007; 35:2677–2685
334. Shankar-Hari M, Culshaw N, Post B, et al: Endogenous IgG hypogam- maglobulinaemia in critically ill adults with sepsis: systematic review and meta-analysis. *Intensive Care Med* 2015; 41:1393–1401
335. Turgeon AF, Hutton B, Fergusson DA, et al: Meta-analysis: intrave- nous immunoglobulin in critically ill adult patients with sepsis. *Ann Intern Med* 2007; 146:193–203
336. Zhou F, Peng Z, Murugan R, et al: Blood purification and mortality in sepsis: a meta-analysis of randomized trials. *Crit Care Med* 2013; 41:2209–2220
337. Payen DM, Guilhot J, Launey Y, et al; ABDOMIX Group: Early use of polymyxin B hemoperfusion in patients with septic shock due to peri- tonitis: a multicenter randomized control trial. *Intensive Care Med* 2015; 41:975–984
338. Klein DJ, Foster D, Schorr CA, et al: The EUPHRATES trial (Evaluating the Use of Polymyxin B Hemoperfusion in a Randomized controlled trial of Adults Treated for Endotoxemia and Septic shock): study protocol for a randomized controlled trial. *Trials* 2014; 15:218
339. Livigni S, Bertolini G, Rossi C, et al; GiViTI: Gruppo Italiano per la Valutazione degli Interventi in Terapia Intensiva (Italian Group for the Evaluation of Interventions in Intensive Care Medicine) is an independent collaboration network of Italian Intensive Care units: Efficacy of coupled plasma filtration adsorption (CPFA) in patients with septic shock: a multi- center randomised controlled clinical trial. *BMJ Open* 2014; 4:e003536
340. Allingstrup M, Wetterslev J, Ravn FB, et al: Antithrombin III for criti- cally ill patients. *Cochrane Database Syst Rev* 2016; 2:CD005370
341. Warren BL, Eid A, Singer P, et al; KyberSept Trial Study Group: Caring for the critically ill patient. High-dose antithrombin III in severe sepsis: a randomized controlled trial. *JAMA* 2001; 286:1869–1878
342. Vincent JL, Ramesh MK, Ernest D, et al: A randomized, double- blind, placebo-controlled, Phase 2b study to evaluate the safety and efficacy of recombinant human soluble thrombomodulin, ART-123, in patients with sepsis and suspected disseminated intravascular coagulation. *Crit Care Med* 2013; 41:2069–2079
343. Yamakawa K, Ogura H, Fujimi S, et al: Recombinant human soluble thrombomodulin in sepsis-induced disseminated intravascular coag- ulation: a multicenter propensity score analysis. *Intensive Care Med* 2013; 39:644–652
344. Zarychanski R, Abou-Setta AM, Kanji S, et al; Canadian Critical Care Trials Group: The efficacy and safety of heparin in patients with sepsis: a systematic review and metaanalysis. *Crit Care Med* 2015; 43:511–518
345. Ranieri VM, Thompson BT, Barie PS, et al; PROWESS-SHOCK Study Group: Drotrecogin alfa (activated) in adults with septic shock. *N Engl J Med* 2012; 366:2055–2064
346. Bernard GR, Artigas A, Brigham KL, et al: The American-European consensus conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical-trial coordination. *Am J Respir Crit Care Med*. 1994;149(3):818–824
347. Ranieri VM, Rubenfeld GD, Thompson BT, et al; ARDS Definition Task Force: Acute respiratory distress syndrome: the Berlin Definition. *JAMA* 2012; 307:2526–2533
348. Amato MB, Barbas CS, Medeiros DM, et al: Effect of a protective- ventilation strategy on mortality in the acute respiratory distress syndrome. *N Engl J Med* 1998; 338:347–354
349. Brochard L, Roudot-Thoraval F, Roupie E, et al: Tidal volume reduc- tion for prevention of ventilator-induced lung injury in acute respi- ratory distress syndrome. The Multicenter Trail Group on Tidal Volume reduction in ARDS. *Am J Respir Crit Care Med* 1998; 158:1831–1838
350. Brower RG, Matthay MA, Morris A, et al: Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med*. 2000;342(18):1301–1308
351. Brower RG, Shanholtz CB, Fessler HE, et al: Prospective, random- ized, controlled clinical trial comparing traditional versus reduced tidal volume ventilation in acute respiratory distress syndrome patients. *Crit Care Med* 1999; 27:1492–1498
352. Eichacker PQ, Gerstenberger EP, Banks SM, et al: Meta-analysis of acute lung injury and acute respiratory distress syndrome tri- als testing low tidal volumes. *Am J Respir Crit Care Med* 2002; 166:1510–1514
353. Burns KE, Adhikari NK, Slutsky AS, et al: Pressure and volume lim- ited ventilation for the ventilatory management of patients with acute lung injury: a systematic review and meta-analysis. *PLoS One* 2011; 6:e14623
354. Putensen C, Theuerkauf N, Zinserling J, et al: Meta-analysis: ventila- tion strategies and outcomes of the acute respiratory distress syn- drome and acute lung injury. *Ann Intern Med* 2009; 151:566–576
355. Marini JJ, Gattinoni L: Ventilatory management of acute respira- tory distress syndrome: a consensus of two. *Crit Care Med* 2004; 32:250–255
356. Tobin MJ: Culmination of an era in research on the acute respiratory distress syndrome. *N Engl J Med* 2000; 342:1360–1361
357. Hager DN, Krishnan JA, Hayden DL, et al; ARDS Clinical Trials Network: Tidal volume reduction in patients with acute lung injury when plateau pressures are not high. *Am J Respir Crit Care Med* 2005; 172:1241–1245

358. Checkley W, Brower R, Korpak A, et al; Acute Respiratory Distress Syndrome Network Investigators: Effects of a clinical trial on mechanical ventilation practices in patients with acute lung injury. *Am J Respir Crit Care Med* 2008; 177:1215–1222

359. Amato MB, Meade MO, Slutsky AS, et al: Driving pressure and sur- vival in the acute respiratory distress syndrome. *N Engl J Med* 2015; 372:747–755

360. Gattinoni L, Marcolin R, Caspani ML, et al: Constant mean airway pressure with different patterns of positive pressure breathing dur- ing the adult respiratory distress syndrome. *Bull Eur Physiopathol Respir* 1985; 21:275–279

361. Marini JJ, Ravenscraft SA: Mean airway pressure: physiologic deter- minants and clinical importance–Part 1: Physiologic determinants and measurements. *Crit Care Med* 1992; 20:1461–1472

362. Pesenti A, Marcolin R, Prato P, et al: Mean airway pressure vs. posi- tive end-expiratory pressure during mechanical ventilation. *Crit Care Med* 1985; 13:34–37

363. Brower RG, Lanken PN, MacIntyre N, et al; National Heart, Lung, and Blood Institute ARDS Clinical Trials Network: Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. *N Engl J Med* 2004; 351:327–336

364. Meade MO, Cook DJ, Guyatt GH, et al; Lung Open Ventilation Study Investigators: Ventilation strategy using low tidal volumes, recruit- ment maneuvers, and high positive end-expiratory pressure for acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. *JAMA* 2008; 299:637–645

365. Mercat A, Richard JC, Vielle B, et al; Expiratory Pressure (Express) Study Group: Positive end-expiratory pressure setting in adults with acute lung injury and acute respiratory distress syndrome: a random- ized controlled trial. *JAMA* 2008; 299:646–655

366. Villar J, Kacmarek RM, Pérez-Méndez L, et al: A high positive end- expiratory pressure, low tidal volume ventilatory strategy improves outcome in persistent acute respiratory distress syndrome: a ran- domized, controlled trial. *Crit Care Med* 2006; 34:1311–1318

367. Briel M, Meade M, Mercat A, et al: Higher vs lower positive end-expiratory pressure in patients with acute lung injury and acute respira- tory distress syndrome: systematic review and meta-analysis. *JAMA* 2010; 303:865–873

368. Goligher EC, Kavanagh BP, Rubenfeld GD, et al: Oxygenation response to positive end-expiratory pressure predicts mortality in acute respiratory distress syndrome. A secondary analysis of the LOVS and ExPress trials. *Am J Respir Crit Care Med* 2014; 190:70–76

369. Talmor D, Sarge T, Malhotra A, et al: Mechanical ventilation guided by esophageal pressure in acute lung injury. *N Engl J Med* 2008; 359:2095–2104

370. Amato MB, Barbas CS, Medeiros DM, et al: Beneficial effects of the "open lung approach" with low distending pressures in acute respiratory distress syndrome. A prospective randomized study on mechanical ventilation. *Am J Respir Crit Care Med* 1995; 152:1835–1846

371. Gattinoni L, Caironi P, Cressoni M, et al: Lung recruitment in patients with the acute respiratory distress syndrome. *N Engl J Med* 2006; 354:1775–1786

372. Pipeling MR, Fan E: Therapies for refractory hypoxemia in acute respiratory distress syndrome. *JAMA* 2010; 304:2521–2527

373. Fan E, Wilcox ME, Brower RG, et al: Recruitment maneuvers for acute lung injury: a systematic review. *Am J Respir Crit Care Med* 2008; 178:1156–1163

374. Guérin C, Reignier J, Richard JC, et al; PROSEVA Study Group: Prone positioning in severe acute respiratory distress syndrome. *N Engl J Med* 2013; 368:2159–2168

375. Beitler JR, Shaefi S, Montesi SB, et al: Prone positioning reduces mortality from acute respiratory distress syndrome in the low tidal volume era: a meta-analysis. *Intensive Care Med* 2014; 40:332–341

376. Jolliet P, Bulpa P, Chevrolet JC: Effects of the prone position on gas exchange and hemodynamics in severe acute respiratory distress syndrome. *Crit Care Med* 1998; 26:1977–1985

377. Lamm WJ, Graham MM, Albert RK: Mechanism by which the prone position improves oxygenation in acute lung injury. *Am J Respir Crit Care Med* 1994; 150:184–193

378. Stocker R, Neff T, Stein S, et al: Prone postioning and low-volume pressure-limited ventilation improve survival in patients with severe ARDS. *Chest* 1997; 111:1008–1017

379. Guerin C, Gaillard S, Lemasson S, et al: Effects of systematic prone positioning in hypoxemic acute respiratory failure: a randomized con- trolled trial. *JAMA* 2004; 292:2379–2387

380. Peek GJ, Mugford M, Tiruvoipati R, et al; CESAR trial collaboration: Efficacy and economic assessment of conventional ventilatory sup- port versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. *Lancet* 2009; 374:1351–1363

381. Sud S, Sud M, Friedrich JO, et al: High frequency oscillation in patients with acute lung injury and acute respiratory distress syndrome (ARDS): systematic review and meta-analysis. *BMJ* 2010; 340:c2327

382. Noah MA, Peek GJ, Finney SJ, et al: Referral to an extracorporeal membrane oxygenation center and mortality among patients with severe 2009 influenza A(H1N1). *JAMA* 2011; 306:1659–1668

383. Checkley W: Extracorporeal membrane oxygenation as a first-line treatment strategy for ARDS: is the evidence sufficiently strong? *JAMA* 2011; 306:1703–1704

384. Ferguson ND, Cook DJ, Guyatt GH, et al; OSCILLATE Trial Investigators; Canadian Critical Care Trials Group: High-frequency oscillation in early acute respiratory distress syndrome. *N Engl J Med* 2013; 368:795–805

385. Young D, Lamb SE, Shah S, et al; OSCAR Study Group: High- frequency oscillation for acute respiratory distress syndrome. *N Engl J Med* 2013; 368:806–813

386. Meade MO, Cook DJ, Guyatt GH, et al; Lung Open Ventilation Study Investigators: Ventilation strategy using low tidal volumes, recruit- ment maneuvers, and high positive end-expiratory pressure for acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. *JAMA* 2008; 299:637–645

387. Antonelli M, Conti G, Rocco M, et al: A comparison of noninvasive positive-pressure ventilation and conventional mechanical ventila- tion in patients with acute respiratory failure. *N Engl J Med* 1998; 339:429–435

388. Ferrer M, Esquinas A, Leon M, et al: Noninvasive ventilation in severe hypoxemic respiratory failure: a randomized clinical trial. *Am J Respir Crit Care Med* 2003; 168:1438–1444

389. Frat JP, Thille AW, Mercat A, et al; FLORALI Study Group; REVA Network: High-flow oxygen through nasal cannula in acute hypox- emic respiratory failure. *N Engl J Med* 2015; 372:2185–2196

390. Klessig HT, Geiger HJ, Murray MJ, et al: A national survey on the practice patterns of anesthesiologist intensivists in the use of muscle relaxants. *Crit Care Med* 1992; 20:1341–1345

391. Murray MJ, Cowen J, DeBlock H, et al; Task Force of the American College of Critical Care Medicine (ACCM) of the Society of Critical Care Medicine (SCCM), American Society of Health-System Pharmacists, American College of Chest Physicians: Clinical prac- tice guidelines for sustained neuromuscular blockade in the adult critically ill patient. *Crit Care Med* 2002; 30:142–156

392. Hansen-Flaschen JH, Brazinsky S, Basile C, et al: Use of sedat- ing drugs and neuromuscular blocking agents in patients requiring mechanical ventilation for respiratory failure. A national survey. *JAMA* 1991; 266:2870–2875

393. Freebairn RC, Derrick J, Gomersall CD, et al: Oxygen delivery, oxy- gen consumption, and gastric intramucosal pH are not improved by a computer-controlled, closed-loop, vecuronium infusion in severe sepsis and septic shock. *Crit Care Med* 1997; 25:72–77

394. Papazian L, Forel JM, Gacouin A, et al; ACURASYS Study Investigators: Neuromuscular blockers in early acute respiratory distress syndrome. *N Engl J Med* 2010; 363:1107–1116

395. Alhazzani W, Alshahrani M, Jaeschke R, et al: Neuromuscular block- ing agents in acute respiratory distress syndrome: a systematic review and meta-analysis of randomized controlled trials. *Crit Care* 2013; 17:R43

396. Forel JM, Roch A, Marin V, et al: Neuromuscular blocking agents decrease inflammatory response in patients presenting with acute respiratory distress syndrome. *Crit Care Med* 2006; 34:2749–2757

397. Shapiro BA, Warren J, Egol AB, et al: Practice parameters for sus- tained neuromuscular blockade in the adult critically ill patient: an executive summary. Society of Critical Care Medicine. *Crit Care Med* 1995; 23:1601–1605

398. Meyer KC, Prielipp RC, Grossman JE, et al: Prolonged weakness after infusion of atracurium in two intensive care unit patients. *Anesth Analg* 1994; 78:772–774

399. Lacomis D, Petrella JT, Giuliani MJ: Causes of neuromuscular weak- ness in the intensive care unit: a study of ninety-two patients. *Muscle Nerve* 1998; 21:610–617

400. Johnson KL, Cheung RB, Johnson SB, et al: Therapeutic paralysis of critically ill trauma patients: perceptions of patients and their family members. *Am J Crit Care* 1999; 8:490–498

401. Ballard N, Robley L, Barrett D, et al: Patients' recollections of thera- peutic paralysis in the intensive care unit. *Am J Crit Care* 2006; 15:86–94; quiz 95

402. Murray MJ, DeBlock H, Erstad B, et al: Clinical Practice Guidelines for Sustained Neuromuscular Blockade in the Adult Critically Ill Patient. *Crit Care Med* 2016; 44:2079–2103

403. Sibbald WJ, Short AK, Warshawski FJ, et al: Thermal dye measure- ments of extravascular lung water in critically ill patients. Intravascular Starling forces and extravascular lung water in the adult respiratory distress syndrome. *Chest* 1985; 87:585–592

404. Martin GS, Mangialardi RJ, Wheeler AP, et al: Albumin and furose- mide therapy in hypoproteinemic patients with acute lung injury. *Crit Care Med* 2002; 30:2175–2182

405. Mitchell JP, Schuller D, Calandrino FS, et al: Improved outcome based on fluid management in critically ill patients requiring pulmo- nary artery catheterization. *Am Rev Respir Dis* 1992; 145:990–998

406. Schuller D, Mitchell JP, Calandrino FS, et al: Fluid balance during pulmonary edema. Is fluid gain a marker or a cause of poor out- come? *Chest* 1991; 100:1068–1075

407. Wiedemann HP, Wheeler AP, Bernard GR, et al: Comparison of two fluid-management strategies in acute lung injury. *N Engl J Med*. 2006;354(24):2564–2575

408. Perkins GD, McAuley DF, Thickett DR, et al: The beta-agonist lung injury trial (BALTI): a randomized placebo-controlled clinical trial. *Am J Respir Crit Care Med* 2006; 173:281–287

409. Gao Smith F, Perkins GD, Gates S, et al; BALTI-2 study investiga- tors: Effect of intravenous β-2 agonist treatment on clinical outcomes in acute respiratory distress syndrome (BALTI-2): a multicentre, ran- domised controlled trial. *Lancet* 2012; 379:229–235

410. Matthay MA, Brower RG, Carson S, et al: Randomized, pla- cebo-controlled clinical trial of an aerosolized beta(2)-agonist for treatment of acute lung injury. *Am J Respir Crit Care Med*. 2011;184(5):561–568

411. Matthay MA, Brower RG, Carson S, et al: Randomized, placebo-con- trolled clinical trial of an aerosolized beta(2)-agonist for treatment of acute lung injury. *Am J Respir Crit Care Med*. 2011;184(5):561–568

412. Singh B, Tiwari AK, Singh K, et al: β2 agonist for the treatment of acute lung injury: a systematic review and meta-analysis. *Respir Care* 2014; 59:288–296

413. Connors AF Jr, Speroff T, Dawson NV, et al: The effectiveness of right heart catheterization in the initial care of critically ill patients. SUPPORT Investigators. *JAMA* 1996; 276:889–897

414. Iberti TJ, Fischer EP, Leibowitz AB, et al: A multicenter study of physi- cians' knowledge of the pulmonary artery catheter. Pulmonary Artery Catheter Study Group. *JAMA* 1990; 264:2928–2932

415. Osman D, Ridel C, Ray P, et al: Cardiac filling pressures are not appropriate to predict hemodynamic response to volume challenge. *Crit Care Med* 2007; 35:64–68

416. Richard C, Warszawski J, Anguel N, et al; French Pulmonary Artery Catheter Study Group: Early use of the pulmonary artery catheter and outcomes in patients with shock and acute respiratory distress syn- drome: a randomized controlled trial. *JAMA* 2003; 290:2713–2720

417. Wheeler AP, Bernard GR, Thompson BT, et al: Pulmonary artery ver- sus central venous catheter to guide treatment of acute lung injury. *N Engl J Med*. 2006;354(21):2213–2224

418. Harvey S, Harrison DA, Singer M, et al; PAC-Man study collabora- tion: Assessment of the clinical effectiveness of pulmonary artery catheters in management of patients in intensive care (PAC-Man): a randomised controlled trial. *Lancet* 2005; 366:472–477

419. Rhodes A, Cusack RJ, Newman PJ, Grounds RM, Bennett ED: A randomised, controlled trial of the pulmonary artery catheter in criti- cally ill patients. *Intensive Care Med*. 2002;28(3):256–264

420. Sandham JD, Hull RD, Brant RF, et al; Canadian Critical Care Clinical Trials Group: A randomized, controlled trial of the use of pulmonary-artery catheters in high-risk surgical patients. *N Engl JMed* 2003; 348:5–14

421. Shah MR, Hasselblad V, Stevenson LW, et al: Impact of the pulmo- nary artery catheter in critically ill patients: meta-analysis of random- ized clinical trials. *JAMA* 2005; 294:1664–1670

422. Petrucci N, De Feo C: Lung protective ventilation strategy for the acute respiratory distress syndrome. *Cochrane Database Syst Rev*. 2013(2):CD003844

423. Futier E, Constantin JM, Paugam-Burtz C, et al; IMPROVE Study Group: A trial of intraoperative low-tidal-volume ventilation in abdom- inal surgery. *N Engl J Med* 2013; 369:428–437

424. Pinheiro de Oliveira R, Hetzel MP, dos Anjos Silva M, Dallegrave D, Friedman G: Mechanical ventilation with high tidal volume induces inflammation in patients without lung disease. *Crit Care*. 2010;14(2):R39

425. Drakulovic MB, Torres A, Bauer TT, et al: Supine body position as a risk factor for nosocomial pneumonia in mechanically ventilated patients: a randomised trial. *Lancet* 1999; 354:1851–1858

426. van Nieuwenhoven CA, Vandenbroucke-Grauls C, van Tiel FH, et al: Feasibility and effects of the semirecumbent position to prevent ven- tilator-associated pneumonia: a randomized study. *Crit Care Med* 2006; 34:396–402

427. Ouellette DR, Patel S, Girard TD, et al: Liberation from mechani- cal ventilation: an official American College of Chest Physicians/ American Thoracic Society clinical practice guideline: inspiratory pressure augmentation during spontaneous breathing trials, proto- cols minimizing sedation, and non-invasive ventilation immediately after extubation. *Chest*. 2016 [Epub ahead of print]

428. Blackwood B, Burns KE, Cardwell CR, O'Halloran P: Protocolized versus non-protocolized weaning for reducing the duration of mechanical ventilation in critically ill adult patients. *Cochrane Database Syst Rev*. 2014(11):CD006904

429. Ely EW, Baker AM, Dunagan DP, et al: Effect on the duration of mechanical ventilation of identifying patients capable of breathing spontaneously. *N Engl J Med* 1996; 335:1864–1869

430. Kress JP, Pohlman AS, O'Connor MF, et al: Daily interruption of sed- ative infusions in critically ill patients undergoing mechanical ventila- tion. *N Engl J Med* 2000; 342:1471–1477

431. Girard TD, Kress JP, Fuchs BD, et al: Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. *Lancet* 2008; 371:126–134

432. Sevransky JE, Checkley W, Herrera P, et al; United States Critical Illness and Injury Trials Group-Critical Illness Outcomes Study Investigators: Protocols and Hospital Mortality in Critically Ill Patients: The United States Critical Illness and Injury Trials Group Critical Illness Outcomes Study. *Crit Care Med* 2015; 43:2076–2084

433. Schweickert WD, Pohlman MC, Pohlman AS, et al: Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. *Lancet* 2009; 373:1874–1882

434. Shehabi Y, Bellomo R, Reade MC, et al; Sedation Practice in Intensive Care Evaluation (SPICE) Study Investigators; ANZICS Clinical Trials Group: Early intensive care sedation predicts long- term mortality in ventilated critically ill patients. *Am J Respir Crit Care Med* 2012; 186:724–731

435. Brook AD, Ahrens TS, Schaiff R, et al: Effect of a nursing-imple- mented sedation protocol on the duration of mechanical ventilation. *Crit Care Med* 1999; 27:2609–2615

436. Bucknall TK, Manias E, Presneill JJ: A randomized trial of protocol- directed sedation management for mechanical ventilation in an Australian intensive care unit. *Crit Care Med* 2008; 36:1444–1450

437. Kollef MH, Levy NT, Ahrens TS, et al: The use of continuous i.v. seda- tion is associated with prolongation of mechanical ventilation. *Chest* 1998; 114:541–548

438. Carson SS, Kress JP, Rodgers JE, et al: A randomized trial of inter- mittent lorazepam versus propofol with daily interruption in mechani- cally

ventilated patients. *Crit Care Med* 2006; 34:1326–1332

439. Mehta S, Burry L, Cook D, et al; SLEAP Investigators; Canadian Critical Care Trials Group: Daily sedation interruption in mechani- cally ventilated critically ill patients cared for with a sedation proto- col: a randomized controlled trial. *JAMA* 2012; 308:1985–1992
440. Jansen JP, Naci H: Is network meta-analysis as valid as standard pairwise meta-analysis? It all depends on the distribution of effect modifiers. *BMC Med* 2013; 11:159
441. Strøm T, Martinussen T, Toft P: A protocol of no sedation for criti- cally ill patients receiving mechanical ventilation: a randomised trial. *Lancet* 2010; 375:475–480
442. Lonardo NW, Mone MC, Nirula R, et al: Propofol is associated with favor- able outcomes compared with benzodiazepines in ventilated intensive care unit patients. *Am J Respir Crit Care Med* 2014; 189:1383–1394
443. Fraser GL, Devlin JW, Worby CP, et al: Benzodiazepine versus non- benzodiazepine-based sedation for mechanically ventilated, critically ill adults: a systematic review and meta-analysis of randomized trials. *Crit Care Med* 2013; 41:S30–S38
444. Reade MC, Eastwood GM, Bellomo R, et al; DahLIA Investigators; Australian and New Zealand Intensive Care Society Clinical Trials Group: Effect of Dexmedetomidine Added to Standard Care on Ventilator-Free Time in Patients With Agitated Delirium: A Randomized Clinical Trial. *JAMA* 2016; 315:1460–1468
445. Barr J, Fraser GL, Puntillo K, et al; American College of Critical Care Medicine: Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. *Crit Care Med* 2013; 41:263–306
446. van den Berghe G, Wouters P, Weekers F, et al: Intensive insulin therapy in critically ill patients. *N Engl J Med* 2001; 345:1359–1367
447. Van den Berghe G, Wilmer A, Hermans G, et al: Intensive insulin therapy in the medical ICU. *N Engl J Med* 2006; 354:449–461
448. Arabi YM, Dabbagh OC, Tamim HM, et al: Intensive versus conven- tional insulin therapy: a randomized controlled trial in medical and surgical critically ill patients. *Crit Care Med* 2008; 36:3190–3197
449. Brunkhorst FM, Engel C, Bloos F, et al; German Competence Network Sepsis (SepNet): Intensive insulin therapy and pentastarch resuscitation in severe sepsis. *N Engl J Med* 2008; 358:125–139
450. De La Rosa Gdel C, Donado JH, Restrepo AH, et al: Strict gly- caemic control in patients hospitalised in a mixed medical and surgical intensive care unit: a randomised clinical trial. *Crit Care*. 2008;12(5):R120
451. Finfer S, Blair D, Bellomo R, et al: Intensive versus conven- tional glucose control in critically ill patients. *N Engl J Med*. 2009;360(13):1283–1297
452. Annane D, Cariou A, Maxime V, et al: Corticosteroid treatment and intensive insulin therapy for septic shock in adults: a randomized controlled trial. *JAMA*. 2010;303(4):341–348
453. Kalfon P, Giraudeau B, Ichai C, et al; CGAO-REA Study Group: Tight computerized versus conventional glucose control in the ICU: a ran- domized controlled trial. *Intensive Care Med* 2014; 40:171–181
454. Preiser JC, Devos P, Ruiz-Santana S, et al: A prospective ran- domised multi-centre controlled trial on tight glucose control by intensive insulin therapy in adult intensive care units: the Glucontrol study. *Intensive Care Med* 2009; 35:1738–1748
455. Zhang RH, W; Li, T et al: Evaluation of optimal goal of glucose con- trol in critically ill patients. *Chinese J Clin Nutr*. 2008;16:204–208
456. Friedrich JO, Chant C, Adhikari NK: Does intensive insulin therapy really reduce mortality in critically ill surgical patients? A reanalysis of meta-analytic data. *Crit Care* 2010; 14:324
457. Griesdale DE, de Souza RJ, van Dam RM, et al: Intensive insulin therapy and mortality among critically ill patients: a meta-analysis including NICE-SUGAR study data. *CMAJ* 2009; 180:821–827
458. Kansagara D, Fu R, Freeman M, et al: Intensive insulin therapy in hospitalized patients: a systematic review. *Ann Intern Med* 2011; 154:268–282
459. Marik PE, Preiser JC: Toward understanding tight glycemic control in the ICU: a systematic review and metaanalysis. *Chest* 2010; 137:544–551
460. Wiener RS, Wiener DC, Larson RJ: Benefits and risks of tight glu- cose control in critically ill adults: a meta-analysis. *JAMA* 2008; 300:933–944
461. Ling Y, Li X, Gao X: Intensive versus conventional glucose control in critically ill patients: a meta-analysis of randomized controlled trials. *Eur J Intern Med* 2012; 23:564–574
462. Song F, Zhong LJ, Han L, et al: Intensive insulin therapy for septic patients: a meta-analysis of randomized controlled trials. *Biomed Res Int* 2014; 2014:698265
463. American Diabetes Association: Standards of medical care in diabetes—2014. *Diabetes Care*. 2014;37 Suppl 1:S14–S80
464. Marvin MR, Inzucchi SE, Besterman BJ: Computerization of the Yale insulin infusion protocol and potential insights into causes of hypoglycemia with intravenous insulin. *Diabetes Technol Ther* 2013; 15:246–252
465. Qaseem A, Chou R, Humphrey LL, et al; Clinical Guidelines Committee of the American College of Physicians: Inpatient gly- cemic control: best practice advice from the Clinical Guidelines Committee of the American College of Physicians. *Am J Med Qual* 2014; 29:95–98
466. Siegelaar SE, Hermanides J, Oudemans-van Straaten HM, et al: Mean glucose during ICU admission is related to mortality by a U-shaped curve in surgical and medical patients: a retrospective cohort study. *Crit Care* 2010; 14:R224
467. Badawi O, Waite MD, Fuhrman SA, et al: Association between intensive care unit-acquired dysglycemia and in-hospital mortality. *Crit Care Med* 2012; 40:3180–3188

468. Finfer S, Liu B, Chittock DR, et al: Hypoglycemia and risk of death in critically ill patients. *N Engl J Med*. 2012;367(12):1108–1118

469. Kalfon P, Le Manach Y, Ichai C, et al; CGAO-REA Study Group: Severe and multiple hypoglycemic episodes are associated with increased risk of death in ICU patients. *Crit Care* 2015; 19:153

470. Krinsley JS: Glycemic variability: a strong independent predictor of mortality in critically ill patients. *Crit Care Med* 2008; 36:3008–3013

471. TodiS, Bhattacharya M: Glycemic variability and outcome in critically ill. *Indian J Crit Care Med* 2014; 18:285–290

472. Kauffmann RM, Hayes RM, Jenkins JM, et al: Provision of balanced nutrition protects against hypoglycemia in the critically ill surgical patient. *JPEN J Parenter Enteral Nutr* 2011; 35:686–694

473. Egi M, Bellomo R, Stachowski E, et al: Blood glucose concentration and outcome of critical illness: the impact of diabetes. *Crit Care Med* 2008; 36:2249–2255

474. Krinsley JS: Glycemic variability and mortality in critically ill patients: the impact of diabetes. *J Diabetes Sci Technol* 2009; 3:1292–1301

475. Krinsley JS, Preiser JC: Time in blood glucose range 70 to 140 mg/dl >80% is strongly associated with increased survival in non-diabetic critically ill adults. *Crit Care* 2015; 19:179

476. Egi M, Bellomo R, Stachowski E, et al: The interaction of chronic and acute glycemia with mortality in critically ill patients with diabetes. *Crit Care Med* 2011; 39:105–111

477. Sandler V, Misiasz MR, Jones J, et al: Reducing the risk of hypogly- cemia associated with intravenous insulin: experience with a computerized insulin infusion program in 4 adult intensive care units. *JDiabetes Sci Technol* 2014; 8:923–929

478. Pereira AJ, Corrêa TD, de Almeida FP, et al: Inaccuracy of Venous Point-of-Care Glucose Measurements in Critically Ill Patients: A Cross-Sectional Study. *PLoS One* 2015; 10:e0129568

479. Hoedemaekers CW, Klein Gunnewiek JM, Prinsen MA, et al: Accuracy of bedside glucose measurement from three glucometers in critically ill patients. *Crit Care Med* 2008; 36:3062–3066

480. Inoue S, Egi M, Kotani J, et al: Accuracy of blood-glucose measurements using glucose meters and arterial blood gas analyzers in critically ill adult patients: systematic review. *Crit Care* 2013; 17:R48

481. Kanji S, Buffie J, Hutton B, et al: Reliability of point-of-care testing for glucose measurement in critically ill adults. *Crit Care Med* 2005; 33:2778–2785

482. Khan AI, Vasquez Y, Gray J, et al: The variability of results between point-of-care testing glucose meters and the central laboratory analyzer. *Arch Pathol Lab Med* 2006; 130:1527–1532

483. RiceMJ, CoursinDB: GlucoseMeters: HereToday, GoneTomorrow? *Crit Care Med* 2016; 44:e97–100

484. Klonoff DC, Draznin B, Drincic A, et al: PRIDE Statement on the Need for a Moratorium on the CMS Plan to Cite Hospitals for Performing Point-of-Care Capillary Blood Glucose Monitoring on Critically Ill Patients. *J Clin Endocrinol Metab* 2015; 100:3607–3612

485. Wilson M, Weinreb J, Hoo GW: Intensive insulin therapy in critical care: a review of 12 protocols. *Diabetes Care* 2007; 30:1005–1011

486. Dortch MJ, Mowery NT, Ozdas A, et al: A computerized insulin infu- sion titration protocol improves glucose control with less hypoglycemia compared to a manual titration protocol in a trauma intensive care unit. *JPEN J Parenter Enteral Nutr* 2008; 32:18–27

487. Newton CA, Smiley D, Bode BW, et al: A comparison study of continuous insulin infusion protocols in the medical intensive care unit: computer-guided vs. standard column-based algorithms. *J Hosp Med* 2010; 5:432–437

488. Bartlett RH, Mault JR, Dechert RE, et al: Continuous arteriovenous hemofiltration: improved survival in surgical acute renal failure? *Surgery* 1986; 100:400–408

489. Bellomo R, Farmer M, Parkin G, et al: Severe acute renal failure: a comparison of acute continuous hemodiafiltration and conventional dialytic therapy. *Nephron* 1995; 71:59–64

490. Bellomo R, Mansfield D, Rumble S, et al: Acute renal failure in critical illness. Conventional dialysis versus acute continuous hemodiafiltra- tion. *ASAIO J* 1992; 38:M654–M657

491. Kierdorf H. Continuous versus intermittent treatment: clinical results in acute renal failure. *In*: Sieberth HG, Mann H, Stummvoll HK, eds. *Continuous Hemofiltration*. Basel: Karger; 1991:1–12

492. Mauritz W, Sporn P, Schindler I, et al: [Acute renal failure in abdominal infection. Comparison of hemodialysis and continuous arteriovenous hemofiltration]. *Anasth Intensivther Notfallmed* 1986; 21:212–217

493. Guérin C, Girard R, Selli JM, et al: Intermittent versus continuous renal replacement therapy for acute renal failure in intensive care units: results from a multicenter prospective epidemiological survey. *Intensive Care Med* 2002; 28:1411–1418

494. van Bommel E, Bouvy ND, So KL, et al: Acute dialytic support for the critically ill: intermittent hemodialysis versus continuous arterio-venous hemodiafiltration. *Am J Nephrol* 1995; 15:192–200

495. Kellum JA, Angus DC, Johnson JP, et al: Continuous versus intermit- tent renal replacement therapy: a meta-analysis. *Intensive Care Med* 2002; 28:29–37

496. Tonelli M, Manns B, Feller-Kopman D: Acute renal failure in the inten- sive care unit: a systematic review of the impact of dialytic modality on mortality and renal recovery. *Am J Kidney Dis* 2002; 40:875–885

497. Augustine JJ, Sandy D, Seifert TH, et al: A randomized controlled trial comparing intermittent with continuous dialysis in patients with ARF. *Am J Kidney Dis* 2004; 44:1000–1007

498. Gasparović V, Filipović-Grcić I, Merkler M, et al: Continuous renal replacement therapy (CRRT) or intermittent hemodialysis (IHD)– what

is the procedure of choice in critically ill patients? *Ren Fail* 2003; 25:855–862

499. Mehta RL, McDonald B, Gabbai FB, et al; Collaborative Group for Treatment of ARF in the ICU: A randomized clinical trial of continu- ous versus intermittent dialysis for acute renal failure. *Kidney Int* 2001; 60:1154–1163

500. Uehlinger DE, Jakob SM, Ferrari P, et al: Comparison of continuous and intermittent renal replacement therapy for acute renal failure. *Nephrol Dial Transplant* 2005; 20:1630–1637

501. Vinsonneau C, Camus C, Combes A, et al; Hemodiafe Study Group: Continuous venovenous haemodiafiltration versus intermittent hae- modialysis for acute renal failure in patients with multiple-organ dysfunction syndrome: a multicentre randomised trial. *Lancet* 2006; 368:379–385

502. John S, Griesbach D, Baumgärtel M, et al: Effects of continuous haemofiltration vs intermittent haemodialysis on systemic haemody- namics and splanchnic regional perfusion in septic shock patients: a prospective, randomized clinical trial. *Nephrol Dial Transplant* 2001; 16:320–327

503. Misset B, Timsit JF, Chevret S, et al: A randomized cross-over com- parison of the hemodynamic response to intermittent hemodialysis and continuous hemofiltration in ICU patients with acute renal fail- ure. *Intensive Care Med* 1996; 22:742–746

504. Bouman CS, Oudemans-Van Straaten HM, Tijssen JG, et al: Effects of early high-volume continuous venovenous hemofiltration on sur- vival and recovery of renal function in intensive care patients with acute renal failure: a prospective, randomized trial. *Crit Care Med* 2002; 30:2205–2211

505. Ronco C, Bellomo R, Homel P, et al: Effects of different doses in continuous veno-venous haemofiltration on outcomes of acute renal failure: a prospective randomised trial. *Lancet* 2000; 356:26–30

506. Bellomo R, Cass A, Cole L, et al: Intensity of continuous renal- replacement therapy in critically ill patients. *N Engl J Med*. 2009;361(17):1627–1638

507. Palevsky PM, Zhang JH, O'Connor TZ, et al: Intensity of renal sup- port in critically ill patients with acute kidney injury. *N Engl J Med*. 2008;359(1):7–20

508. Gaudry S, Hajage D, Schortgen F, et al; AKIKI Study Group: Initiation Strategies for Renal-Replacement Therapy in the Intensive Care Unit. *N Engl J Med* 2016; 375:122–133

509. Zarbock A, Kellum JA, Schmidt C, et al: Effect of Early vs Delayed Initiation of Renal Replacement Therapy on Mortality in Critically Ill Patients With Acute Kidney Injury: The ELAIN Randomized Clinical Trial. *JAMA* 2016; 315:2190–2199

510. Cooper DJ, Walley KR, Wiggs BR, et al: Bicarbonate does not improve hemodynamics in critically ill patients who have lactic acidosis. A pro- spective, controlled clinical study. *Ann Intern Med* 1990; 112:492–498

511. Mathieu D, Neviere R, Billard V, et al: Effects of bicarbonate therapy on hemodynamics and tissue oxygenation in patients with lactic aci- dosis: a prospective, controlled clinical study. *Crit Care Med* 1991; 19:1352–1356

512. Cook D, Crowther M, Meade M, et al: Deep venous thrombosis in medical-surgical critically ill patients: prevalence, incidence, and risk factors. *Crit Care Med* 2005; 33:1565–1571

513. Kahn SR, Lim W, Dunn AS, et al: Prevention of VTE in nonsurgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2012;141(2 Suppl):e195S–e226S

514. Alhazzani W, Lim W, Jaeschke RZ, et al: Heparin thromboprophy- laxis in medical-surgical critically ill patients: a systematic review and meta-analysis of randomized trials. *Crit Care Med* 2013; 41:2088–2098

515. Levi M, Levy M, Williams MD, et al; Xigris and Prophylactic HepaRin Evaluation in Severe Sepsis (XPRESS) Study Group: Prophylactic heparin in patients with severe sepsis treated with drotrecogin alfa (activated). *Am J Respir Crit Care Med* 2007; 176:483–490

516. Beitland S, Sandven I, Kjærvik LK, et al: Thromboprophylaxis with low molecular weight heparin versus unfractionated heparin in inten- sive care patients: a systematic review with meta-analysis and trial sequential analysis. *Intensive Care Med* 2015; 41:1209–1219

517. Phung OJ, Kahn SR, Cook DJ, et al: Dosing frequency of unfrac- tionated heparin thromboprophylaxis: a meta-analysis. *Chest* 2011; 140:374–381

518. Mahan CE, Pini M, Spyropoulos AC: Venous thromboembolism prophylaxis with unfractionated heparin in the hospitalized medi- cal patient: the case for thrice daily over twice daily dosing. *Intern Emerg Med* 2010; 5:299–306

519. Junqueira DR, Perini E, Penholati RR, Carvalho MG: Unfractionated heparin versus low molecular weight heparin for avoiding heparin-induced thrombocytopenia in postoperative patients. *Cochrane Database Syst Rev*. 2012(9):CD007557

520. Cook D, Meade M, Guyatt G, et al: Dalteparin versus unfrac- tionated heparin in critically ill patients. *N Engl J Med.* 2011;364(14):1305–1314

521. Fowler RA, Mittmann N, Geerts W, et al; Canadian Critical Care Trials Group; Australia and New Zealand Intensive Care Society Clinical Trials Group: Cost-effectiveness of dalteparin vs unfraction- ated heparin for the prevention of venous thromboembolism in criti- cally ill patients. *JAMA* 2014; 312:2135–2145

522. Douketis J, Cook D, Meade M, et al; Canadian Critical Care Trials Group: Prophylaxis against deep vein thrombosis in critically ill patients with severe renal insufficiency with the low-molecular-weight heparin dalteparin: an assessment of safety and pharmacodynamics: the DIRECT study. *Arch Intern Med* 2008; 168:1805–1812

523. Arabi YM, Alsolamy S, Al-Dawood A, et al: Thromboprophylaxis using combined intermittent pneumatic compression and pharmaco- logic prophylaxis versus pharmacologic prophylaxis alone in critically ill patients: study protocol for a randomized controlled trial. *Trials* 2016; 17:390

524. Kakkos SK, Caprini JA, Geroulakos G, Nicolaides AN, Stansby GP, Reddy DJ: Combined intermittent pneumatic leg compression and pharmacological prophylaxis for prevention of venous throm- boembolism in high-risk patients. *Cochrane Database Syst Rev*. 2008;(4):CD005258

525. Falck-Ytter Y, Francis CW, Johanson NA, et al: Prevention of VTE in orthopedic surgery patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2012;141(2 Suppl):e278S–e325S

526. Gould MK, Garcia DA, Wren SM, et al: Prevention of VTE in nonor- thopedic surgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(2 Suppl):e227S–e277S

527. Pavon JM, Adam SS, Razouki ZA, et al: Effectiveness of Intermittent Pneumatic Compression Devices for Venous Thromboembolism Prophylaxis in High-Risk Surgical Patients: A Systematic Review. *JArthroplasty* 2016; 31:524–532

528. Sachdeva A, Dalton M, Amaragiri SV, Lees T: Graduated compres- sion stockings for prevention of deep vein thrombosis. *Cochrane Database Syst Rev*. 2014(12):CD001484

529. Arabi YM, Khedr M, Dara SI, et al: Use of intermittent pneu- matic compression and not graduated compression stockings is associated with lower incident VTE in critically ill patients: a multiple propensity scores adjusted analysis. *Chest* 2013; 144:152–159

530. Cook DJ, Griffith LE, Walter SD, et al; Canadian Critical Care Trials Group: The attributable mortality and length of intensive care unit stay of clinically important gastrointestinal bleeding in critically ill patients. *Crit Care* 2001; 5:368–375

531. Bardou M, Quenot JP, Barkun A: Stress-related mucosal disease in the critically ill patient. *Nat Rev Gastroenterol Hepatol* 2015; 12:98–107

532. Cook DJ, Fuller HD, Guyatt GH, et al: Risk factors for gastrointes- tinal bleeding in critically ill patients. Canadian Critical Care Trials Group. *N Engl J Med* 1994; 330:377–381

533. Krag M, Perner A, Wetterslev J, et al; SUP-ICU co-authors: Prevalence and outcome of gastrointestinal bleeding and use of acid suppressants in acutely ill adult intensive care patients. *Intensive Care Med* 2015; 41:833–845

534. Andersson B, Nilsson J, Brandt J, et al: Gastrointestinal complica- tions after cardiac surgery. *Br J Surg* 2005; 92:326–333

535. Bruno JJ, Canada TW, Wakefield CD, et al: Stress-related muco- sal bleeding in critically ill oncology patients. *J Oncol Pharm Pract* 2009; 15:9–16

536. D'Ancona G, Baillot R, Poirier B, et al: Determinants of gastroin- testinal complications in cardiac surgery. *Tex Heart Inst J* 2003; 30:280–285

537. Faisy C, Guerot E, Diehl JL, et al: Clinically significant gastrointes- tinal bleeding in critically ill patients with and without stress-ulcer prophylaxis. *Intensive Care Med* 2003; 29:1306–1313

538. Krag M, Perner A, Wetterslev J, et al: Stress ulcer prophylaxis versus placebo or no prophylaxis in critically ill patients. A systematic review of randomised clinical trials with meta-analysis and trial sequential analysis. *Intensive Care Med* 2014; 40:11–22

539. Sasabuchi Y, Matsui H, Lefor AK, et al: Risks and Benefits of Stress Ulcer Prophylaxis for Patients With Severe Sepsis. *Crit Care Med* 2016; 44:e464–e469

540. Eastwood GM, Litton E, Bellomo R, et al: Opinions and practice of stress ulcer prophylaxis in Australian and New Zealand intensive care units. *Crit Care Resusc* 2014; 16:170–174

541. Krag M, Perner A, Wetterslev J, et al; SUP-ICU Collaborators: Stress ulcer prophylaxis in the intensive care unit: an international survey of 97 units in 11 countries. *Acta Anaesthesiol Scand* 2015; 59:576–585

542. Preslaski CR, Mueller SW, Kiser TH, et al: A survey of prescriber perceptions about the prevention of stress-related mucosal bleeding in the intensive care unit. *J Clin Pharm Ther* 2014; 39:658–662

543. Shears M, Alhazzani W, Marshall JC, et al: Stress ulcer prophy- laxis in critical illness: a Canadian survey. *Can J Anaesth* 2016; 63:718–724

544. Alshamsi F, Belley-Cote E, Cook D, et al: Efficacy and safety of proton pump inhibitors for stress ulcer prophylaxis in critically ill patients: a systematic review and meta-analysis of randomized trials. *Crit Care* 2016; 20:120

545. Alhazzani W, Alenezi F, Jaeschke RZ, et al: Proton pump inhibitors versus histamine 2 receptor antagonists for stress ulcer prophylaxis in critically ill patients: a systematic review and meta-analysis. *Crit Care Med* 2013; 41:693–705

546. Barkun AN, Bardou M, Pham CQ, Martel M: Proton pump inhibi- tors vs. histamine 2 receptor antagonists for stress-related mucosal bleeding prophylaxis in critically ill patients: a meta-analysis. *Am J Gastroenterol*. 2012;107(4):507–520; quiz 21

547. Barkun AN, Adam V, Martel M, et al: Cost-effectiveness analysis: stress ulcer bleeding prophylaxis with proton pump inhibitors, H2 receptor antagonists. *Value Health* 2013; 16:14–22

548. MacLaren R, Campbell J: Cost-effectiveness of histamine receptor-2 antagonist versus proton pump inhibitor for stress ulcer prophylaxis in critically ill patients*. *Crit Care Med* 2014; 42:809–815

549. Villet S, Chiolero RL, Bollmann MD, et al: Negative impact of hypo- caloric feeding and energy balance on clinical outcome in ICU patients. *Clin Nutr* 2005; 24:502–509

550. Adams S, Dellinger EP, Wertz MJ, et al: Enteral versus parenteral nutritional support following laparotomy for trauma: a randomized prospective trial. *J Trauma* 1986; 26:882–891

551. Borzotta AP, Pennings J, Papasadero B, et al: Enteral versus parenteral nutrition after severe closed head injury. *J Trauma* 1994; 37:459–468
552. Dunham CM, Frankenfield D, Belzberg H, et al: Gut failure–predictor of or contributor to mortality in mechanically ventilated blunt trauma patients? *J Trauma* 1994; 37:30–34
553. Harvey SE, Parrott F, Harrison DA, et al; CALORIES Trial Investigators: Trial of the route of early nutritional support in critically ill adults. *N Engl J Med* 2014; 371:1673–1684
554. Justo Meirelles CM, de Aguilar-Nascimento JE: Enteral or parenteral nutrition in traumatic brain injury: a prospective randomised trial. *Nutr Hosp* 2011; 26:1120–1124
555. Kalfarentzos F, Kehagias J, Mead N, et al: Enteral nutrition is superior to parenteral nutrition in severe acute pancreatitis: results of a randomized prospective trial. *Br J Surg* 1997; 84:1665–1669
556. Moore FA, Moore EE, Jones TN, McCroskey BL, Peterson VM: TEN versus TPN following major abdominal trauma—reduced septic morbidity. *J Trauma*. 1989;29(7):916–922; discussion 22–23
557. Peterson VM, Moore EE, Jones TN, et al: Total enteral nutrition versus total parenteral nutrition after major torso injury: attenuation of hepatic protein reprioritization. *Surgery* 1988; 104:199–207
558. Sun JK, Mu XW, Li WQ, et al: Effects of early enteral nutrition on immune function of severe acute pancreatitis patients. *World J Gastroenterol* 2013; 19:917–922
559. Wang G, Wen J, Xu L, et al: Effect of enteral nutrition and ecoimmunonutrition on bacterial translocation and cytokine production in patients with severe acute pancreatitis. *J Surg Res* 2013; 183:592–597
560. Harvey SE, Parrott F, Harrison DA, et al: A multicentre, randomised controlled trial comparing the clinical effectiveness and cost-effectiveness of early nutritional support via the parenteral versus the enteral route in critically ill patients (CALORIES). *Health Technol Assess* 2016; 20:1–144
561. Kudsk KA: Current aspects of mucosal immunology and its influence by nutrition. *Am J Surg* 2002; 183:390–398
562. McClave SA, Heyland DK: The physiologic response and associated clinical benefits from provision of early enteral nutrition. *Nutr Clin Pract* 2009; 24:305–315
563. Casaer MP, Mesotten D, Hermans G, et al: Early versus late paren-teral nutrition in critically ill adults. *N Engl J Med* 2011; 365:506–517
564. Doig GS, Simpson F, Sweetman EA, et al; Early PN Investigators of the ANZICS Clinical Trials Group: Early parenteral nutrition in critically ill patients with short-term relative contraindications to early enteral nutrition: a randomized controlled trial. *JAMA* 2013; 309:2130–2138
565. Rapp RP, Donaldson ES, Bivins BA: Parenteral nutrition in a patient with familial Type IV hypertriglyceridemia: a dilemma. *Drug Intell Clin Pharm* 1983; 17:458–460
566. Young B, Ott L, Haack D, et al: Effect of total parenteral nutrition upon intracranial pressure in severe head injury. *J Neurosurg* 1987; 67:76–80
567. Sadique Z, Grieve R, Harrison D, et al: Cost-Effectiveness Of Early Parenteral Versus Enteral Nutrition In Critically Ill Patients. *Value Health* 2015; 18:A532
568. Chiarelli A, Enzi G, Casadei A, et al: Very early nutrition supplemen- tation in burned patients. *Am J Clin Nutr* 1990; 51:1035–1039
569. Dvorak MF, Noonan VK, Bélanger L, et al: Early versus late enteral feeding in patients with acute cervical spinal cord injury: a pilot study. *Spine (Phila Pa 1976)* 2004; 29:E175–E180
570. Eyer SD, Micon LT, Konstantinides FN, et al: Early enteral feeding does not attenuate metabolic response after blunt trauma. *J Trauma* 1993; 34:639–43; discussion 643
571. Grahm TW, Zadrozny DB, Harrington T: The benefits of early jejunal hyperalimentation in the head-injured patient. *Neurosurgery* 1989; 25:729–735
572. Hasse JM, Blue LS, Liepa GU, et al: Early enteral nutrition support in patients undergoing liver transplantation. *JPEN J Parenter Enteral Nutr* 1995; 19:437–443
573. Minard G, Kudsk KA, Melton S, et al: Early versus delayed feeding with an immune-enhancing diet in patients with severe head injuries. *JPEN J Parenter Enteral Nutr* 2000; 24:145–149
574. Moore EE, Jones TN: Benefits of immediate jejunostomy feeding after major abdominal trauma–a prospective, randomized study. *J Trauma* 1986; 26:874–881
575. Nguyen NQ, Fraser RJ, Bryant LK, et al: The impact of delaying enteral feeding on gastric emptying, plasma cholecystokinin, and peptide YY concentrations in critically ill patients. *Crit Care Med* 2008; 36:1469–1474
576. Peng YZ, Yuan ZQ, Xiao GX: Effects of early enteral feeding on the prevention of enterogenic infection in severely burned patients. *Burns* 2001; 27:145–149
577. Singh G, Ram RP, Khanna SK: Early postoperative enteral feeding in patients with nontraumatic intestinal perforation and peritonitis. *J Am Coll Surg* 1998; 187:142–146
578. Chuntrasakul C, Chinswangwatanakul V, Chockvivatanavanit S, Siltharm S, Pongprasobchai T, Bunnak A: Early nutritional support in severe traumatic patients. *J Med Assoc Thai*. 1996;79(1):21–26
579. Chourdakis M, Kraus MM, Tzellos T, et al: Effect of early compared with delayed enteral nutrition on endocrine function in patients with traumatic brain injury: an open-labeled randomized trial. *JPEN J Parenter Enteral Nutr* 2012; 36:108–116
580. Doig GS, Heighes PT, Simpson F, et al: Early enteral nutrition reduces mortality in trauma patients requiring intensive care: a meta- analysis

of randomised controlled trials. *Injury* 2011; 42:50–56

581. Doig GS, Heighes PT, Simpson F, et al: Early enteral nutrition, provided within 24 h of injury or intensive care unit admission, significantly reduces mortality in critically ill patients: a meta-anal- ysis of randomised controlled trials. *Intensive Care Med* 2009; 35:2018–2027
582. Malhotra A, Mathur AK, Gupta S: Early enteral nutrition after surgi- cal treatment of gut perforations: a prospective randomised study. *J Postgrad Med* 2004; 50:102–106
583. Pupelis G, Austrums E, Jansone A, et al: Randomised trial of safety and efficacy of postoperative enteral feeding in patients with severe pancreatitis: preliminary report. *Eur J Surg* 2000; 166:383–387
584. Arabi YM, Aldawood AS, Haddad SH, et al; PermiT Trial Group: Permissive Underfeeding or Standard Enteral Feeding in Critically Ill Adults. *N Engl J Med* 2015; 372:2398–2408
585. Marik PE, Hooper MH: Normocaloric versus hypocaloric feeding on the outcomes of ICU patients: a systematic review and meta-analy- sis. *Intensive Care Med* 2016; 42:316–323
586. Arabi YM, Tamim HM, Dhar GS, et al: Permissive underfeeding and intensive insulin therapy in critically ill patients: a randomized con- trolled trial. *Am J Clin Nutr* 2011; 93:569–577
587. Charles EJ, Petroze RT, Metzger R, et al: Hypocaloric compared with eucaloric nutritional support and its effect on infection rates in a sur- gical intensive care unit: a randomized controlled trial. *Am J Clin Nutr* 2014; 100:1337–1343
588. Ibrahim EH, Mehringer L, Prentice D, et al: Early versus late enteral feeding of mechanically ventilated patients: results of a clinical trial. *JPEN J Parenter Enteral Nutr* 2002; 26:174–181
589. National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network, Rice TW, Wheeler AP, et al: Initial trophic vs full enteral feeding in patients with acute lung injury: the EDEN randomized trial. *JAMA*. 2012;307(8):795–803
590. Petros S, Horbach M, Seidel F, et al: Hypocaloric vs Normocaloric Nutrition in Critically Ill Patients: A Prospective Randomized Pilot Trial. *JPEN J Parenter Enteral Nutr* 2016; 40:242–249
591. Rice TW, Mogan S, Hays MA, et al: Randomized trial of initial trophic versus full-energy enteral nutrition in mechanically ventilated patients with acute respiratory failure. *Crit Care Med* 2011; 39:967–974
592. Needham DM, Dinglas VD, Bienvenu OJ, et al; NIH NHLBI ARDS Network: One year outcomes in patients with acute lung injury ran- domised to initial trophic or full enteral feeding: prospective follow- up of EDEN randomised trial. *BMJ* 2013; 346:f1532
593. Garcia de Acilu M, Leal S, Caralt B, Roca O, Sabater J, Masclans JR: The role of omega-3 polyunsaturated fatty acids in the treat- ment of patients with acute respiratory distress syndrome: a clinical review. *Biomed Res Int*. 2015;2015:653750
594. Manzanares W, Dhaliwal R, Jurewitsch B, et al: Parenteral fish oil lipid emulsions in the critically ill: a systematic review and meta-anal- ysis. *JPEN J Parenter Enteral Nutr* 2014; 38:20–28
595. Zhu D, Zhang Y, Li S, et al: Enteral omega-3 fatty acid supplementa- tion in adult patients with acute respiratory distress syndrome: a sys- tematic review of randomized controlled trials with meta-analysis and trial sequential analysis. *Intensive Care Med* 2014; 40:504–512
596. Rice TW, Wheeler AP, Thompson BT, et al; NIH NHLBI Acute Respiratory Distress Syndrome Network of Investigators; NHLBI ARDS Clinical Trials Network: Enteral omega-3 fatty acid, gamma- linolenic acid, and antioxidant supplementation in acute lung injury. *JAMA* 2011; 306:1574–1581
597. McClave SA, DeMeo MT, DeLegge MH, et al: North American Summit on Aspiration in the Critically Ill Patient: consensus state- ment. *JPEN J Parenter Enteral Nutr* 2002; 26:S80–S85
598. McClave SA, Lukan JK, Stefater JA, et al: Poor validity of residual volumes as a marker for risk of aspiration in critically ill patients. *Crit Care Med* 2005; 33:324–330
599. Metheny NA, Schallom L, Oliver DA, Clouse RE: Gastric residual volume and aspiration in critically ill patients receiving gastric feed- ings. *Am J Crit Care*. 2008;17(6):512–519; quiz 20
600. Montejo JC, Miñambres E, Bordejé L, et al: Gastric residual volume during enteral nutrition in ICU patients: the REGANE study. *Intensive Care Med* 2010; 36:1386–1393
601. Poulard F, Dimet J, Martin-Lefevre L, et al: Impact of not measuring residual gastric volume in mechanically ventilated patients receiv- ing early enteral feeding: a prospective before-after study. *JPEN J Parenter Enteral Nutr* 2010; 34:125–130
602. Reignier J, Mercier E, Le Gouge A, et al; Clinical Research in Intensive Care and Sepsis (CRICS) Group: Effect of not monitoring residual gastric volume on risk of ventilator-associated pneumonia in adults receiving mechanical ventilation and early enteral feeding: a randomized controlled trial. *JAMA* 2013; 309:249–256
603. Elke G, Felbinger TW, Heyland DK: Gastric residual volume in criti- cally ill patients: a dead marker or still alive? *Nutr Clin Pract* 2015; 30:59–71
604. van Noord C, Dieleman JP, van Herpen G, et al: Domperidone and ven- tricular arrhythmia or sudden cardiac death: a population-based case-control study in the Netherlands. *Drug Saf* 2010; 33:1003–1014
605. Ray WA, Murray KT, Meredith S, et al: Oral erythromycin and the risk of sudden death from cardiac causes. *N Engl J Med* 2004; 351:1089–1096
606. Lewis K, Alqahtani Z, Mcintyre L, et al: The efficacy and safety of prokinetic agents in critically ill patients receiving enteral nutrition: a systematic review and meta-analysis of randomized trials. *Crit Care* 2016; 20:259
607. Freeman BD, Dixon DJ, Coopersmith CM, et al: Pharmacoepidemiology of QT-interval prolonging drug administration in critically ill patients.

Pharmacoepidemiol Drug Saf 2008; 17:971–981

608. Fruhwald S, Kainz J: Effect of ICU interventions on gastrointestinal motility. *Curr Opin Crit Care* 2010; 16:159–164
609. Mentec H, Dupont H, Bocchetti M, et al: Upper digestive intolerance during enteral nutrition in critically ill patients: frequency, risk factors, and complications. *Crit Care Med* 2001; 29:1955–1961
610. Dive A, Foret F, Jamart J, et al: Effect of dopamine on gastroin- testinal motility during critical illness. *Intensive Care Med* 2000; 26:901–907
611. Dive A, Miesse C, Jamart J, et al: Duodenal motor response to con- tinuous enteral feeding is impaired in mechanically ventilated criti- cally ill patients. *Clin Nutr* 1994; 13:302–306
612. Zaloga GP, Marik P: Promotility agents in the intensive care unit. *Crit Care Med* 2000; 28:2657–2659
613. Tiancha H, Jiyong J, Min Y: How to Promote Bedside Placement of the Postpyloric Feeding Tube: A Network Meta-Analysis of Randomized Controlled Trials. *JPEN J Parenter Enteral Nutr* 2015; 39:521–530
614. Alhazzani W, Almasoud A, Jaeschke R, et al: Small bowel feeding and risk of pneumonia in adult critically ill patients: a systematic review and meta-analysis of randomized trials. *Crit Care* 2013; 17:R127
615. Deane AM, Dhaliwal R, Day AG, Ridley EJ, Davies AR, Heyland DK: Comparisons between intragastric and small intestinal delivery of enteral nutrition in the critically ill: a systematic review and meta- analysis. *Crit Care*. 2013;17(3):R125
616. Alhazzani W, Jacobi J, Sindi A, et al: The effect of selenium therapy on mortality in patients with sepsis syndrome: a systematic review and meta-analysis of randomized controlled trials. *Crit Care Med* 2013; 41:1555–1564
617. Valenta J, Brodska H, Drabek T, et al: High-dose selenium substitu- tion in sepsis: a prospective randomized clinical trial. *Intensive Care Med* 2011; 37:808–815
618. Bloos F, Trips E, Nierhaus A, et al; for SepNet Critical Care Trials Group: Effect of Sodium Selenite Administration and Procalcitonin-Guided Therapy on Mortality in Patients With Severe Sepsis or Septic Shock: A Randomized Clinical Trial. *JAMA Intern Med* 2016; 176:1266–1276
619. Bertolini G, Iapichino G, Radrizzani D, et al: Early enteral immuno- nutrition in patients with severe sepsis: results of an interim analysis of a randomized multicentre clinical trial. *Intensive Care Med* 2003; 29:834–840
620. Suchner U, Kuhn KS, Fürst P: The scientific basis of immunonutri- tion. *Proc Nutr Soc* 2000; 59:553–563
621. Bower RH, Cerra FB, Bershadsky B, et al: Early enteral administra- tion of a formula (Impact) supplemented with arginine, nucleotides, and fish oil in intensive care unit patients: results of a multicenter, prospective, randomized, clinical trial. *Crit Care Med* 1995; 23:436–449
622. Caparrós T, Lopez J, Grau T: Early enteral nutrition in critically ill patients with a high-protein diet enriched with arginine, fiber, and antioxidants compared with a standard high-protein diet. The effect on nosocomial infections and outcome. *JPEN J Parenter Enteral Nutr* 2001; 25:299–308; discussion 308
623. Galbán C, Montejo JC, Mesejo A, et al: An immune-enhancing enteral diet reduces mortality rate and episodes of bacteremia in septic intensive care unit patients. *Crit Care Med* 2000; 28:643–648
624. Santora R, Kozar RA: Molecular mechanisms of pharmaconutrients.
625. *J Surg Res* 2010; 161:288–294
626. Kieft H, Roos AN, van Drunen JD, et al: Clinical outcome of immu- nonutrition in a heterogeneous intensive care population. *Intensive Care Med* 2005; 31:524–532
627. Marik PE, Zaloga GP: Early enteral nutrition in acutely ill patients: a systematic review. *Crit Care Med* 2001; 29:2264–2270
628. Avenell A: Glutamine in critical care: current evidence from system- atic reviews. *Proc Nutr Soc* 2006; 65:236–241
629. Avenell A: Hot topics in parenteral nutrition. Current evidence and ongoing trials on the use of glutamine in critically-ill patients and patients undergoing surgery. *Proc Nutr Soc* 2009; 68:261–268
630. Jiang H, Chen W, Hu W, et al: [The impact of glutamine-enhanced enteral nutrition on clinical outcome of patients with critical illness: a systematic review of randomized controlled trials]. *Zhonghua Shao Shang Za Zhi* 2009; 25:325–330
631. Novak F, Heyland DK, Avenell A, et al: Glutamine supplementation in serious illness: a systematic review of the evidence. *Crit Care Med* 2002; 30:2022–2029
632. Grau T, Bonet A, Miñambres E, et al; Metabolism, Nutrition Working Group, SEMICYUC, Spain: The effect of L-alanyl-L-glutamine dipep- tide supplemented total parenteral nutrition on infectious morbidity and insulin sensitivity in critically ill patients. *Crit Care Med* 2011; 39:1263–1268
633. Wang Z, Forceville X, Van Antwerpen P, et al: A large-bolus injection, but not continuous infusion of sodium selenite improves outcome in peritonitis. *Shock* 2009; 32:140–146
634. Wernerman J, Kirketeig T, Andersson B, et al; Scandinavian Critical Care Trials Group: Scandinavian glutamine trial: a pragmatic multi- centre randomised clinical trial of intensive care unit patients. *Acta Anaesthesiol Scand* 2011; 55:812–818
635. Heyland D, Muscedere J, Wischmeyer PE, et al; Canadian Critical Care Trials Group: A randomized trial of glutamine and antioxidants in critically ill patients. *N Engl J Med* 2013; 368:1489–1497
636. Beale RJ, Sherry T, Lei K, et al: Early enteral supplementation with key pharmaconutrients improves Sequential Organ Failure Assessment score in critically ill patients with sepsis: outcome of a randomized, controlled, double-blind trial. *Crit Care Med* 2008; 36:131–144
637. Fuentes-Orozco C, Anaya-Prado R, González-Ojeda A, et al: L-alanyl- L-glutamine-supplemented parenteral nutrition improves infectious morbidity in secondary peritonitis. *Clin Nutr* 2004; 23:13–21

638. PuskarichMA,KlineJA,KrabillV,etal:Preliminarysafetyandefficacy of L-carnitine infusion for the treatment of vasopressor-dependent septic shock: a randomized control trial. *JPEN J Parenter Enteral Nutr* 2014; 38:736–743

639. White DB, Engelberg RA, Wenrich MD, et al: The language of prognostication in intensive care units. *Med Decis Making* 2010; 30:76–83

640. Chiarchiaro J, Buddadhumaruk P, Arnold RM, et al: Quality of com- munication in the ICU and surrogate's understanding of prognosis. *Crit Care Med* 2015; 43:542–548

641. Downar J, You JJ, Bagshaw SM, et al; Canadian Critical Care Trials Group: Nonbeneficial treatment Canada: definitions, causes, and potential solutions from the perspective of healthcare practitioners*.*Crit Care Med* 2015; 43:270–281

642. Kon AA, Shepard EK, Sederstrom NO, et al: Defining Futile and Potentially Inappropriate Interventions: A Policy Statement From the Society of Critical Care Medicine Ethics Committee. *Crit Care Med* 2016; 44:1769–1774

643. Nelson JE, Curtis JR, Mulkerin C, et al; Improving Palliative Care in the ICU (IPAL-ICU) Project Advisory Board: Choosing and using screening criteria for palliative care consultation in the ICU: a report from the Improving Palliative Care in the ICU (IPAL-ICU) Advisory Board. *Crit Care Med* 2013; 41:2318–2327

644. Detering KM, Hancock AD, Reade MC, et al: The impact of advance care planning on end of life care in elderly patients: randomised con- trolled trial. *BMJ* 2010; 340:c1345

645. Scheunemann LP, McDevitt M, Carson SS, et al: Randomized, con- trolled trials of interventions to improve communication in intensive care: a systematic review. *Chest* 2011; 139:543–554

646. Bosslet GT, Pope TM, Rubenfeld GD, et al; American Thoracic Society ad hoc Committee on Futile and Potentially Inappropriate Treatment; American Thoracic Society; American Association for Critical Care Nurses; American College of Chest Physicians; European Society for Intensive Care Medicine; Society of Critical Care: An Official ATS/AACN/ACCP/ESICM/SCCM Policy Statement: Responding to Requests for Potentially Inappropriate Treatments in Intensive Care Units. *Am J Respir Crit Care Med* 2015; 191:1318–1330

647. Kon AA, Davidson JE, Morrison W, et al; American College of Critical Care Medicine; American Thoracic Society: Shared Decision Making in ICUs: An American College of Critical Care Medicine and American Thoracic Society Policy Statement. *Crit Care Med* 2016; 44:188–201

648. Aslakson R, Cheng J, Vollenweider D, et al: Evidence-based pallia- tive care in the intensive care unit: a systematic review of interven- tions. *J Palliat Med* 2014; 17:219–235

649. Schulz V, Novick RJ: The distinct role of palliative care in the sur- gical intensive care unit. *Semin Cardiothorac Vasc Anesth* 2013; 17:240–248

650. Khandelwal N, Kross EK, Engelberg RA, et al: Estimating the effect of palliative care interventions and advance care planning on ICU utilization: a systematic review. *Crit Care Med* 2015; 43:1102–111

651. DeCato TW, Engelberg RA, Downey L, et al: Hospital variation and temporal trends in palliative and end-of-life care in the ICU. *Crit Care Med* 2013; 41:1405–1411

652. Sprung CL, Truog RD, Curtis JR, et al: Seeking worldwide profes- sional consensus on the principles of end-of-life care for the critically ill. The Consensus for Worldwide End-of-Life Practice for Patients in Intensive Care Units (WELPICUS) study. *Am J Respir Crit Care Med* 2014; 190:855–866

653. Davidson JE: Family presence on rounds in neonatal, pediat- ric, and adult intensive care units. *Ann Am Thorac Soc* 2013; 10:152–156

654. Flanders SA, Strasen JH: Review of evidence about family pres- ence during resuscitation. *Crit Care Nurs Clin North Am* 2014; 26:533–550

655. Oczkowski SJ, Mazzetti I, Cupido C, et al: The offering of family presence during resuscitation: a systematic review and meta-analy- sis. *J Intensive Care* 2015; 3:41

Implementation References
(Not included in SSCG) Please *Note for final draft these will be in Harvard style in the text.*

1. Rhodes A et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. Intensive Care Med. 2017 Mar;43(3):304-377.

2. National Clinical Guideline No 6: Sepsis Management, 2014

3. National Clinical Guideline No. 1: NEWS
4. Centers for Disease Control and Prevention. (2016). CDC Vital Signs. Making Healthcare Safer. Think Sepsis. Time Matters. Available at: https://www.cdc.gov/vitalsigns/pdf/2016-08-vitalsigns.pdf

5. National Sepsis Outcome Report 2017

6. Christopher W. Seymour, M.D., Foster Gesten, M.D., Hallie C. Prescott, M.D., Marcus E. Friedrich, M.D., Theodore J. Iwashyna, M.D., Ph.D., Gary S. Phillips, M.A.S., Stanley Lemeshow, Ph.D., Tiffany Osborn, M.D., M.P.H., Kathleen M. Terry, Ph.D., and Mitchell M. Levy, M.D. Time to Treatment and Mortality during Mandated Emergency Care for Sepsis. N Engl J Med 376;23, June 8, 2017.

7. Martin GS, Mannino DM, Eaton S, Moss M. The epidemiology of sepsis in the United States from 1979 through 2000. NEngl J Med 2003 Apr 17;348(16):1546-54.

8. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. Crit Care Med. 2001 Jul;29(7):1303-10

9. Singer M., Deutschman C.S., Seymour C.W. et al (2016). The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 315(8):801-810.
10. Brun-Buisson C. Doyon F. Carlet J. et al. (1995). Incidence, risk factors, and outcome of severe sepsis and septic shock in adults. A multicentre prospective study in intensive care units. French ICU Group for Severe Sepsis. JAMA. 274:968-74.
11. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. Chest. 1992 Jun. 101 (6):1644-55

12. Churpek MM, Zadravecz FJ, Winslow C, Howell MD, Edelson DP. Incidence and prognostic value of the systemic inflammatory response syndrome and organ dysfunctions in ward patients. Am J Respir Crit Care Med. 2015;192(8):958-964.

13. Comstedt P, Storgaard M, Lassen AT. The Systemic Inflammatory Response Syndrome (SIRS) in acutely hospitalised medical patients: a cohort study. *Scand J Trauma Resusc Emerg Med*. 2009 Dec 27. 17(1):67.

14. Kaukonen K-M, Bailey M, Pilcher D, Cooper DJ, Bellomo R. Systemic inflammatory response syndrome criteria in defining severe sepsis. N Engl J Med. 2015;372(17):1629-1638.

15. Thoeni RF. The revised atlanta classification of acute pancreatitis: its importance for the radiologist and its effect on treatment. *Radiology*. 2012 Mar. 262(3):751-64.

16. Deaths involving sepsis in Canada. T Navaneelan, S Alam, PA Peters, O Philips/ January 21, 2016. www.statcan.gc.ca.

17. Chang D.W., Tseng C., Shapiro M.F. (2015). Rehospitalizations Following Sepsis: Common and Costly. Critical Care Medicine. 43(10):2085–2093.

18. Department of Health. (2017). Ireland's National Action Plan on Antimicrobial Resistance 2017-2020. (iNAP). Available at: https://health.gov.ie/wp-content/uploads/2017/10/iNAP_web-1.pdf

19. HSE Health Protection Surveillance Centre. (2009). Guidelines for Antimicrobial Stewardship in Hospitals in Ireland. SARI Hospital Antimicrobial Stewardship Working Group. HSE Health Protection Surveillance Centre. Dublin. Available at: http://www.hpsc.ie/az/microbiologyantimicrobialresistance/infectioncontrolandhai/guidelines/File,4116,en.pdf

20. www.antibioticprescribing.ie - get full link

21. link to patient info leaflets & booklets

22. Aylin P, Bottle A, Majeed A: Use of administrative data or clinical data- bases as predictors of risk of death in hospital: Comparison of models. BMJ 2007; 334:10.

23. Healthcare Pricing Office, 2018.

24. Pfuntner et al. Costs for Hospital Stays in the United States. HCUP Statistical Brief #168.

25. Silva E., Araujo D.V. (2009) Economic and Social Burden of Severe Sepsis. In: Vincent JL. (eds) Yearbook of Intensive Care and Emergency Medicine. Yearbook of Intensive Care and Emergency Medicine, vol 2009. Springer, Berlin, Heidelberg. https://doi.org/10.1007/978-3-540-92276-6_13

26. Rachel J Mitchell Measuring Health-related Productivity Loss. Popul Health Manag. 2011 Apr; 14(2): 93–98. doi: 10.1089/pop.2010.0014

27. Chalfin DB, Cohen IL, Lambrinos J. The economics and cost effectiveness of critical care medicine. Intensive Care Med 1995; 21: 925-61.

28. Brun-Buisson C, Roudot-Thoraval F, Girou E, Grenier-Sennelier C, Durand-Zaleski I. The costs of septic syndromes in the intensive care unit and influence of hospital-acquired sepsis. Intensive Care Med. 2003 Sep; 29(9):1464-71. 28.

29. Burchardi H,& Schneider H. Economic aspects of severe sepsis: a review of intensive care unit costs, cost of illness and cost effectiveness of therapy. Pharmacoeconomics 2004; 22 (12):793-813.

30. Sogayar AM, Machado FR, Rea-Neto A, et al (2008) A multicentre, prospective study to eval-

uate costs of septic patients in Brazilian intensive care units. Pharmacoeconomics 26: 425 – 434

31. Anne Marie McLaughlin, Judy Hardt, James B. Canavan, Maria B. Donnelly. Determining the economic cost of ICU treatment: a prospective ''micro-costing'' study. Intensive Care Med (2009) 35:2135–2140 DOI 10.1007/s00134-009-1622-1.

32. Cheng B, Xie G, Yao S, et al (2007) Epidemiology of severe sepsis in critically ill surgical patients in ten university hospitals in China. Crit Care Med 35: 2538–2546.

33. Schmid A, Burchardi H, Clouth J, Schneider H (2002) Burden of illness imposed by severe sepsis in Germany. Eur J Health Econ 3: 77–82.

34. Shorr AF, Micek ST, Jackson WL Jr, Kollef MH (2007) Economic implications of an evidence-based sepsis protocol: can we improve outcomes and lower costs? Crit Care Med 35: 1257 – 1262

35. HSE Health Protection Surveillance Centre. (2011). Guidelines for the Prevention of Catheter-associated Urinary Tract Infection. HSE Health Protection Surveillance Centre. Dublin. Available at: https://www.hpsc.ie/a-z/microbiologyantimicrobialresistance/infectioncontrolandhai/guidelines/File,12913,en.pdf

36. Phua Jason, Ngerng WJ, See KC, Tay CK, Kiong T, Lim HF, Chew MY, Yip HS, Tan A, Khalizah HJ, Capistrano R, Lee KH, Mukhopadhyay A. Characteristics and outcomes of culture-negative versus culture-positive severe sepsis. Crit Care 2013, 17:R202.

37. Raith EP, Udy AA, Bailey M, et al. Prognostic Accuracy of the SOFA Score, SIRS Criteria, and qSOFA Score for In-Hospital Mortality Among Adults With Suspected Infection Admitted to the Intensive Care Unit. *JAMA*.2017;317(3):290–300. doi:10.1001/jama.2016.20328

38. Yvonne Young, (ULHG ADON), Ronan O'Cathasaigh, (Saolta HG), Christina Doyle, (Programme Manager), Mary Bedding (RCSI HG ADON), Celine Conroy, (IEHG ADON), Karn Cliffe, (DMHG ADON), Sinead Horgan, (S/SWHG), Dr Vida Hamilton, (National Clinical Lead Sepsis). Development of a sepsis 3 compliant pathway and Clinical Decision support tool for the Emergency Department. Abstract NPSO 2016.

39. Goulden R, Hoyle MC, Monis J, Railton D, Riley V, Martin P, Martina R, Nsutebu E. qSOFA, SIRS and NEWS for predicting inhospital mortality and ICU admission in emergency admissions treated as sepsis. Emerg Med J. 2018 Jun;35(6):345-349.

40. Churpek MM, Snyder A, Han X, Sokol S, Pettit N, Howell MD, Edelson DP. Quick Sepsis-related Organ Failure Assessment, Systemic Inflammatory Response Syndrome, and Early Warning Scores for Detecting Clinical Deterioration in Infected Patients outside the Intensive Care Unit. Am J Respir Crit Care Med. 2017 Apr 1;195(7):906-911.

41. National Clinical Guideline Handover

42. Snyder SR, Favoretto SM, Baetz RA, Derzon JH, Madison BM, Mass D, Shaw CS, Layfield CD et al. Effectiveness of Practices to reduce Blood Culture Contamination: A Laboratory Medicine Best Practices systematic review and meta-analysis. Clin Biochem. 2012;45:999–1011.

43. Bentley J., Thakore S., Muir L et al. (2016). A change of culture: reducing blood culture contamination rates in an Emergency Department. BMJ Qual Improv Rep. 5(1): u206760.w2754

44. Royal College of Physicians of Ireland Antimicrobial Stewardship Working Group (2012). Start Smart Then Focus. Available at: https://www.hse.ie/eng/services/publications/clinical-strategy-and-programmes/start-smart-stay-focused.pdf Accessed: 24 August 2018

45. Campagna JD, Bond MC, Schabelman E, Hayes BD. The use of cephalosporins in penicillin-allergic patients: a literature review. J Emerg Med, 2012 May;42(5):612-20. doi: 10.1016/j.jemermed.2011.05.035. Epub 2011 Jul 13.

46. Rogić D, Juroš GF, Petrik J, Vrančić AL. Advances and Pitfalls in Using Laboratory Biomarkers for the Diagnosis and Management of Sepsis. *EJIFCC*. 2017;28(2):114-121.

47. Sager R, Kutz A, Mueller B, Schuetz P. Procalcitonin-guided diagnosis and antibiotic stewardship revisited. *BMC Medicine*. 2017;15:15. doi:10.1186/s12916-017-0795-7.

48. David T. Huang, M.D., M.P.H., Donald M. Yealy, M.D., Michael R. Filbin, M.D., Aaron M. Brown, M.D., Chung-Chou H. Chang, Ph.D., Yohei Doi, M.D., Ph.D., Michael W. Donnino, M.D., Jonathan Fine, M.D., Michael J. Fine, M.D., Michelle A. Fischer, M.D., M.P.H., John M. Holst, D.O., Peter C. Hou, M.D., et al., for the ProACT Investigators. Procalcitonin-Guided Use of Antibiotics for Lower Respiratory Tract Infection. N Engl J Med 2018; 379:236-249 DOI: 10.1056/NEJMoa1802670

49. Levy M.M., Evans L.E., Rhodes A. (2018). The Surviving Sepsis Campaign Bundle: 2018 Update. Critical Care Medicine. 46(6):997-1000.

50. Lars W Anderson, Julie Mackenhauer, Johathon C Roberts, Katherine M Berg, Michael N Cocchi, Michael W Donnino. Etiology and therapeutic approach to elevated lactate. Mayo Clin Proc. 2013 October; 88(10):1127-1140.

51. Yealy D.M., Kellum J.A., Huang D.T. et al. (2014). A Randomized Trial of Protocol-Based Care for Early Septic Shock. The New England Journal of Medicine. 370(8):1683-1693

52. Mouncey P.R., Osborn T.M., Power S. (2015). Trial of Early, Goal-Directed Resuscitation for Septic Shock. The New England Journal of Medicine. 372(14):1301-1311

53. Peake S.L., Delaney A., Bailey M. et al. (2014). Goal-Directed Resuscitation for Patients with Early Septic Shock. The New England Journal of Medicine. 371(16):1496-1506.

54. Wiedemann H.P., Wheeler A.P., Bernard G.R. et al. (2006). Comparison of two fluid-management strategies in acute lung injury. The New England Journal of Medicine. 354(24):2564-2575.

55. Hjortrup P.B., Haase N., Bundgaard H. et al.(2016). Restricting volumes of resuscitation fluid in adults with septic shock after initial management: the CLASSIC randomised, parallel-group, multicentre feasibility trial. Intensive Care Med. 42(11):1695-705

56. Annane D. (2011). Corticosteroids for severe sepsis: an evidence-based guide for physicians. Ann Intensive Care. 1(1):7.

57. Keh D., Trips E., Marx G. et al. (2016). Effect of hydrocortisone on development of shock among patients with severe sepsis. The HYPRESS Randomised Clinical Trial. JAMA. 316(17):1775-85.

58. Barr J et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. Crit Care Med. 2013 Jan;41(1):263-306. doi: 10.1097/CCM.0b013e3182783b72.

59. Parisa Mansouri, Shohreh Javadpour, Farid Zand, Fariba Ghodsbin, Golnar Sabetian, Mansoor Masjedi, Hamid Reza Tabatabaee. Implementation of a protocol for integrated management of pain, agitation, and delirium can improve clinical outcomes in the intensive care unit: A randomized clinical trial. J Crit Care. 2013 Dec;28(6):918-22. doi: 10.1016/j.jcrc.2013.06.019.

60. Trogrlić Z, van der Jagt M, Bakker J, Balas MC, Ely EW, van der Voort PH, Ista E. A systematic review of implementation strategies for assessment, prevention, and management of ICU delirium and their effect on clinical outcomes. Crit Care. 2015 Apr 9;19:157. doi: 10.1186/s13054-015-0886-9.

61. Fleischmann C, Scherag A, Adhikari NKJ, et al; International Forum of Acute Care Trialists. Assessment of global incidence and mortality of hospital-treated sepsis: current estimates and limitations. Am J Respir Crit Care Med. 2016;193(3):259-272.

62. Iwashyna TJ, Ely EW, Smith DM, Langa KM. Long-term cognitive impairment and functional disability among survivors of severe sepsis. JAMA. 2010;304(16):1787-1794.

63. Shah FA, Pike F, Alvarez K, et al. Bidirectional relationship between cognitive function and pneumonia. Am J Respir Crit Care Med. 2013;188(5): 586-592.

64. Yende S, Linde-Zwirble W, Mayr F,Weissfeld LA, Reis S, Angus DC. Risk of cardiovascular events in survivors of severe sepsis. Am J Respir Crit Care Med. 2014;189(9):1065-1074.

65. Zielske J, Bohne S, Brunkhorst FM, Axer H, Guntinas-Lichius O. Acute and long-term dysphagia in critically ill patients with severe sepsis: results of a prospective controlled observational study. Eur Arch Otorhinolaryngol. 2014;271(11):3085-3093.

66. Prescott HC, Langa KM, Iwashyna TJ. Readmission diagnoses after hospitalization for severe sepsis and other acute medical conditions. JAMA. 2015;313(10):1055-1057.

67. Ou S-M, Chu H, Chao P-W, et al. Long-term mortality and major adverse cardiovascular events in sepsis survivors: a nationwide population-based study. Am J Respir Crit Care Med. 2016;194(2):209- 217.

68. Annane D, Sharshar T. Cognitive decline after sepsis. Lancet Respir Med. 2015;3(1):61-69.

69. Davydow DS, Hough CL, Langa KM, Iwashyna TJ. Symptoms of depression in survivors of severe sepsis: a prospective cohort study of older Americans. Am J Geriatr Psychiatry. 2013 Sep;21(9):887-97.

70. Rabiee A, Nikayin S, Hashem MD, et al. Depressive symptoms after critical illness: a systematic review and meta-analysis. Crit Care Med. 2016;44(9):1744-1753.

71. Nikayin S, Rabiee A, Hashem MD, et al. Anxiety symptoms in survivors of critical illness: a systematic review and meta-analysis. Gen Hosp Psychiatry. 2016;43:23-29.

72. Wintermann G-B, Brunkhorst FM, Petrowski K, et al. Stress disorders following prolonged critical illness in survivors of severe sepsis. Crit Care Med. 2015;43(6):1213-1222.

73. Parker AM, Sricharoenchai T, Raparla S, Schneck KW, Bienvenu OJ, Needham DM. Posttraumatic stress disorder in critical illness survivors: ameta-analysis. Crit Care Med. 2015;43 (5):1121-1129.

74. Shen H-N, Lu C-L, Yang H-H. Risk of recurrence after surviving severe sepsis: a matched cohort study. Crit Care Med. 2016;44(10):1833-1841.

75. Winters BD, Eberlein M, Leung J, Needham DM, Pronovost PJ, Sevransky JE. Long-term mortality and quality of life in sepsis: a systematic review. Crit Care Med. 2010;38(5):1276-1283.

76. Yende S, Austin S, Rhodes A, et al. Long-term quality of life among survivors of severe sepsis: analyses of two international trials. Crit Care Med.2016;44(8):1461-1467.

77. Poulsen JB, Møller K, Kehlet H, Perner A. Long-term physical outcome in patients with septic shock. Acta Anaesthesiol Scand. 2009;53(6):724-730.

78. Prescott HC, Angus DC Enhancing Recovery From Sepsis: A Review. JAMA. 2018 Jan 2;319(1):62-75. doi: 10.1001/jama.2017.17687.

79. Prescott HC, Costa DK. Improving Long-Term Outcomes After Sepsis. Crit Care Clin. 2018 Jan;34(1):175-188.

80. Doiron KA, Hoffmann TC, Beller EM. Early intervention (mobilization or active exercise) for critically ill adults in the intensive care unit. Cochrane Database Syst Rev. 2018 Mar 27;3:CD010754

81. Sepsis: recognition, assessment and early management. https://www.nice.org.uk/guidance/ng51/evidence/full-guideline-pdf-2551523297.

82. Rehabilitation after critical illness in adults. https://www.nice.org.uk/guidance/cg83/chapter/About-this-guideline.

83. Chao PW, Shih C-J, Lee Y-J, et al. Association of postdischarge rehabilitation with mortality in intensive care unit survivors of sepsis. Am J Respir Crit Care Med. 2014;190(9):1003-1011.

84. Schmidt K,Worrack S, Von Korff M, et al; SMOOTH Study Group. Effect of a primary care management intervention on mental health-related quality of life among survivors of sepsis: a randomized clinical trial. JAMA. 2016;315(24):2703-2711.

85. Mehlhorn J, Freytag A, Schmidt K, et al. Rehabilitation interventions for postintensive care syndrome: a systematic review. Crit Care Med. 2014;42(5):1263-1271.

86. Connolly B, Salisbury L, O'Neill B, Geneen L, Douiri A, Grocott MP, Hart N, Walsh TS, Blackwood B; ERACIP Group. Exercise rehabilitation following intensive care unit discharge for recovery from critical illness. Cochrane Database Syst Rev. 2015 Jun 22;(6):CD008632.

87. Mikkelsen ME, Jackson JC, Hopkins RO, et al. Peer support as a novel strategy to mitigate post-intensive care syndrome. AACN Adv Crit Care. 2016;27(2):221-229.

88. Jones C, Bäckman C, CapuzzoM, et al; RACHEL group. Intensive care diaries reduce new onset post traumatic stress disorder following critical illness: a randomised, controlled trial. Crit Care. 2010;14(5):R168.

89. Jones C, Bäckman C, Griffiths RD. Intensive care diaries and relatives' symptoms of posttraumatic stress disorder after critical illness: a pilot study. Am J Crit Care. 2012;21(3):172-176.

90. World Health Organization. Statement on maternal sepsis. Geneva: WHO; 2017. [http://apps.who.int/iris/bitstream/10665/254608/1/WHO-RHR-17.02- eng.pdf]. Accessed: 20 Feb 2017.

91. Carlin, A., & Alfirevic, Z. (2008) Best Practice & Research Clinical Obstetrics and Gynaecology Vol. 22, No. 5, pp. 801–823. DOI:10.1016/j.bpobgyn.2008.06.005

92. Hayes, Meghan; Larson, Lucia (2012). "Chapter 220. Overview of Physiologic Changes of Pregnancy". *Principles and Practice of Hospital Medicine*. The McGraw-Hill Companies. ISBN 978-0071603898.

93. Soma-Pillay, P., Catherine, N.-P., Tolppanen, H., Mebazaa, A., Tolppanen, H., Mebazaa, A., (2016). Physiological changes in pregnancy. Cardiovasc. J. Afr. 27, 89–94. https://doi.org/10.5830/CVJA-2016-021

94. Bauer ME, Bauer ST, Rajala B, MacEachern MP, Polley LS, Childers D, Aronoff DM. Maternal physiologic parameters in relationship to systemic inflammatory response syndrome criteria: a systematic review and meta- analysis. Obstet Gynecol. 2014; 124(3):535–41.

95. Buddeberg BS, Aveling W. Puerperal sepsis in the 21st century: progress, new challenges and the situation worldwide. Postgrad Med J. 2015; 91(1080):572–8.

96. Lappen JR, Keene M, Lore M, Grobman WA, Gossett DR. Existing models fail to predict sepsis in an obstetric population with intrauterine infection. Am J Obstet Gynecol. 2010 Dec;203(6):573.e1-5. doi: 10.1016/j.ajog.2010.07.040. Epub 2010 Sep 15.

97. Basha S, Surendran N, Pichichero M. Immune Responses in Neonates. *Expert review of clinical immunology*. 2014;10(9):1171-1184. doi:10.1586/1744666X.2014.942288.

98. Delves PJ, Roitt IM. The Immune System, First of two parts. New Engl J Med July 2000; 343(1): 37-49.

99. Delves PJ, Roitt IM. The Immune System, First of two parts. New Engl J Med July 200; 343(2): 108-117.

100. Hanson & Korotkova (2002)The role of breastfeeding in prevention of neonatal infection. Seminars in Neonatology Aug; 7(4): 275.

101. Toxoplasmosis (2017) Available at: https://www.hse.ie/eng/health/az/t/toxoplasmosis/causes-of-toxoplasmosis.html . Accessed: 24 August 2018.

102. Mor G, Cardenas I. The Immune System In Pregnancy: a unique Complexity. Am J Reprod Immunol. 2010 Jun; 63(6): 425-433.

103. Alexander et al (2014) Enhaced natural killer-cell and T-responses to influenza A virus during pregnancy. PNAS vol. 111 no. 40 14506-14511

104. HSE (2017) Flu vaccine during pregnancy. Available at: https://www.hse.ie/eng/health/immunisation/pubinfo/flu-vaccination/flu-vaccine-pregnancy/ Accessed: 14 August 2018.

105. Centre for Maternal and Child Enquiries (CMACE) (2011). Saving Mother's Lives: reviewing maternal deaths to make motherhood safer: 2006-2008. BJOG; 118(suppl.1):1-203.

106. Knight M, Tuffnell D, Kenyon S, Shakespeare J, Gray R, Kurinczuk JJ (Eds.) on behalf of MBRRACE-UK (2014). Saving Lives, Improving Mothers' Care - Surveillance of maternal deaths in the UK 2011-13 and lessons learned to inform maternity care from the UK and Ireland Confidential Enquiries into Maternal Deaths and Morbidity 2009-13. Oxford: National Perinatal Epidemiology Unit, University of Oxford

107. Knight M, Nair M, Tuffnell D, Shakespeare J, Kenyon S, Kurinczuk JJ (Eds.) on behalf of MBRRACE-UK (2017). Saving Lives, Improving Mothers' Care - Lessons learned to inform maternity care from the UK and Ireland Confidential Enquiries into Maternal Deaths and Morbidity 2013–15. Oxford: National Perinatal Epidemiology Unit, University of Oxford.

108. Chau A, Tsen LC. Fetal optimization during maternal sepsis: relevance and response of the obstetric anesthesiologist. Curr Opin Anaesthesiol 2014; 27: 259–266.

109. NCEC (2014) Communication (Clinical Handover) in Maternity Services National Clinical Guideline No. 5. DoH available at: www.health.gov.ie/patient-safety/ncec.

110. Bowyer et al (2017) SOMANZ guidelines for the investigation and management sepsis in pregnancy. Aust N Z J Obstet Gynaecol 2017; 1–12