Development of the Guidelines: Focus on Availability, Feasibility, Affordability, and Safety of Interventions in Resource-Limited Settings

Marcus J. Schultz, Martin W. Dünser, and Arjen M. Dondorp

2.1 Introduction

In 2014, the “Global Intensive Care Working Group” of the “European Society of Intensive Care Medicine” (ESICM) and the “Mahidol Oxford Tropical Medicine Research Unit” (MORU) in Bangkok, Thailand, decided to refine and rewrite the guidelines for sepsis treatment in resource-limited settings as published in 2012 [1]. This chapter describes the development of eight sets of recommendations for care of septic patients in resource-limited settings as published in *Intensive Care Medicine* [2–8] and the *Transactions of Royal Society of Tropical Medicine and Hygiene* [9] in 2016 and 2017.

M. J. Schultz (✉)

Department of Intensive Care, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

Laboratory of Experimental Intensive Care and Anesthesiology (L.E.I.C.A), Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

Mahidol–Oxford Research Unit (MORU), Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand

M. W. Dünser

Department of Anesthesiology and Intensive Care Medicine, Kepler University Hospital, Johannes Kepler University Linz, Linz, Austria

A. M. Dondorp

Mahidol–Oxford Research Unit (MORU), Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand

2.2 Heads and Subheads

The chairmen of the newly formed “Sepsis in Resource-Limited Settings” guidelines group, Marcus J. Schultz, Martin W. Dünser, and Arjen M. Dondorp, contacted potential subgroup chairs (Table 2.1) for the development of eight sets of recommendations focusing on (1) intensive care unit (ICU) organization and structure, (2) sepsis recognition, (3) infection management, (4) tropical sepsis, (5) hemodynamic monitoring and support, (6) ventilatory support, (7) general supportive care, and (8) pediatric sepsis. The selection of subgroup chairs was based on interest in specific aspects of sepsis and hands-on experience in ICUs in resource-limited settings. In total, three subgroup chairs per set of recommendations were contacted. Marcus J. Schultz, Martin W. Dünser, and Arjen M. Dondorp set out a protocol for the appraisal of various aspects within each set of recommendations and discussed this with the subgroup chairs.

2.3 Other Subgroup Members

The chairs of each subgroup recruited additional members for each set of recommendations (Table 2.1). Alike selection of subgroup chairs, recruitment of group members was based on interest in specific aspects of sepsis and hands-on experience in ICUs in resource-limited settings. Additional group members were appointed by the group heads to address content needs for the development process. Several group members had experience in “Grading of Recommendations, Assessment, Development and Evaluation” (GRADE) process and the use of the GRADEpro Guideline Development Tool [10].

2.4 Meetings

Initial Internet subgroup chair meetings established the procedures for literature review and drafting of tables for evidence analysis. Subgroup chairs continued work remotely via the Internet. Several meetings occurred at major international meetings, teleconferences, and electronic-based discussions among subgroup chairs and members from other subgroups.

In the first meetings, up to 10 clearly defined questions regarding specific aspects of care for sepsis patients were formulated, using the GRADEpro Guideline Development Tool [10]. These were reviewed for content and clarity by all subgroup members. After the approval by the subgroup members, the subgroup chairs split up, each one to seek for evidence for recommendations regarding three or four of the specific questions posed, seeking help from the subgroup members in identifying relevant publications where necessary. During this process, questions could be combined or adjusted—in some cases extra questions were added. The subgroup chairs summarized the evidence and formulated the recommendations after

Table 2.1 Group chairs, subgroup chairs, and subgroup members

Group chairs							
Marcus J. Schultz, Martin W. Dünser, and Arjen M. Dondorp							
<i>Group 1</i> ICU organization and structure	<i>Group 2</i> Sepsis recognition	<i>Group 3</i> Infection management	<i>Group 4</i> Tropical sepsis	<i>Group 5</i> Hemodynamic monitoring and support	<i>Group 6</i> Ventilatory support	<i>Group 7</i> General supportive care	<i>Group 8</i> Pediatric sepsis
<i>Subgroup chairs</i>							
Alfred Papali	Arthur Kwizera	Ganbold Lundeg	Mai Nguyen Thi Hoang	David Misango	Ary Serpa Neto	Mervyn Mer	Srinivas Murthy
Marcus J. Schultz	Emir Festic	Louise Thwaites	Arjen M. Dondorp	Timothy Baker	Marcus J. Schultz	Marcus J. Schultz	Ndidamaka Musa
Martin W. Dünser	Martin W. Dünser	Arjen M. Dondorp	Mervyn Mer	Rajyabardhan Pattnaik	Emir Festic	Neill Adhikari	Niranjan Kissoon
<i>Other members</i>							
Neill Adhikari	Rashan Haniffa	Arthur Kwizera	Sanjib Mohanty	Martin W. Dünser	Neill Adhikari	Arthur Kwizera	Rakesh Lodha
Janet Diaz	Neill Adhikari	Mervyn Mer	Marcus J. Schultz	Marcus J. Schultz	Arjen M. Dondorp	David Misango	Suchitra Ranjit
Arjen M. Dondorp	Ganbold Lundeg	Neill Adhikari	Louise Thwaites	Arjen M. Dondorp	Rajyabardhan Pattnaik	Sanjib Mohanty	
Shevin Jacob	Arjen M. Dondorp	Marcus J. Schultz	Martin W. Dünser		Louise Thwaites	Arjen M. Dondorp	
Jason Phua	Derek Angus	Randeep Jawa	Jane Nakibuuka		Pedro Povoa	Ary Serpa Neto	
Marc Romain	Ignacio Martin Loeches	Jane Nakibuuka			Ignacio Martin Loeches	Kobus Preller	
	Niranjan Kissoon	Srinivas Murthy			Luigi Pisani		
		Binh Nguyen Thien					

interactive telephone conferences. These were communicated among subgroup members. After their approval, the subgroup chairs summarized the evidence in a report, which was then sent for approval to all members of all eight subgroups.

2.5 Search Process

The search for literature followed the same methods as described for the development of the Surviving Sepsis Campaign guidelines [11]. In case a question was identical to one in those guidelines, the subgroup chairs searched for additional articles, specifically (new) investigations or meta-analyses related to the questions, in a minimum of one general database (i.e., MEDLINE, EMBASE) and the Cochrane Libraries. Furthermore, subgroup members paid specific attention to identify publication originating in low- and middle-income countries.

2.6 Grading of Recommendations

The subgroup chairs followed the principles of the GRADE process as described for the development of the Surviving Sepsis Campaign guidelines [11]. In short, GRADE classifies the quality of evidence as high (grade A), moderate (grade B), low (grade C), or very low (grade D) and recommendations as strong (grade 1) or weak (grade 2). The factors influencing this classification are presented in Table 2.2.

Different from the grading of recommendations in the Surviving Sepsis Campaign guidelines [11], the subgroup chairs paid extensive attention to several other factors as used before, but now focusing on resource-limited settings, i.e., availability and feasibility in resource-limited ICUs, affordability for low-resource ICUs, and last but not the least its safety in resource-limited ICUs (Table 2.3).

A strong recommendation was worded as “we recommend” and a weak recommendation as “we suggest.” Some recommendations remained as ungraded best practice statements, when in the opinion of the subgroup members, such

Table 2.2 Quality of evidence

A	Randomized controlled trials	High
B	Downgraded randomized controlled trial(s) or upgraded observational studies	Moderate
C	Observational studies	Low
D	Downgraded observational studies or expert opinion	Very low

Factors that may decrease the strength of evidence: poor quality of planning and implementation of available RCTs, suggesting high likelihood of bias; inconsistency of results, including problems with subgroup analyses; indirectness of evidence (differing population, intervention, control, outcomes, comparison); imprecision of results; and high likelihood of reporting bias

Factors that may increase the strength of evidence: large magnitude of effect (direct evidence, relative risk >2 with no plausible confounders); very large magnitude of effect with relative risk >5 and no threats to validity (by two levels); and dose-response gradient

Table 2.3 Strong versus weak recommendations^a

What should be considered	Recommended process
High or moderate evidence	The higher the quality of evidence, the more likely a strong recommendation
Certainty about the balance of benefits vs. harms and burdens	The larger/smaller the difference between the desirable and undesirable consequences and the certainty around that difference, the more likely a strong/weak recommendation
Certainty in or similar values	The more certainty or similarity in values and preferences, the more likely a strong recommendation
Resource implications	The lower/higher the cost of an intervention compared to the alternative, the more likely a strong/weak recommendation
Availability and feasibility in LMICs	The less available, the more likely a weak recommendation
Affordability for LMICs	The less affordable, the more likely a weak recommendation
Safety of the intervention in LMICs	The less safe in an LMIC, the more likely a weak recommendation

^aIn case of a strong recommendation, we use “we recommend ...”; in case of a weak recommendation, we use “we suggest ...”

recommendations were clear, clinically relevant, likely to result in benefit, supported by indirect evidence, and unsuitable for a formal evidence generation and review process (opportunity cost) [12].

2.7 Reporting

Each report was edited for style and form, with final approval by subgroup heads and then by the entire “Sepsis in Resource-Limited Settings” guidelines group.

Acknowledgments All authors of this chapter are members of the “European Society of Intensive Care Medicine (ESICM) Global Intensive Care” Working Group and the Mahidol–Oxford Research Unit (MORU) in Bangkok, Thailand.

Conflicts of interest Group chairs, subgroup chairs, and subgroup members did not represent industry, and there was no industry input into the development of the recommendations. Group chairs, subgroup chairs, and subgroup members did not receive honoraria for any role in the guideline development process. Group chairs, subgroup chairs, and subgroup members provided a standard conflict of interest form, to be uploaded through the GRADEpro Guideline Development Tool website—none reported conflicts of interest.

References

1. Dunser MW, Festic E, Dondorp A, Kissoon N, Ganbat T, Kwizera A, Haniffa R, Baker T, Schultz MJ, Global Intensive Care Working Group of European Society of Intensive Care M. Recommendations for sepsis management in resource-limited settings. *Intensive Care Med.* 2012;38:557–74.
2. Papali A, Schultz MJ, Dunser MW, European Society of Intensive Care Medicine Global Intensive Care working g, The Mahidol-Oxford Research Unit in Bangkok T. Recommendations

- on infrastructure and organization of adult ICUs in resource-limited settings. *Intensive Care Med.* 2017;44(7):1133–7.
3. Mer M, Schultz MJ, Adhikari NK, European Society of Intensive Care Medicine Global Intensive Care Working G, the Mahidol-Oxford Research Unit BT. Core elements of general supportive care for patients with sepsis and septic shock in resource-limited settings. *Intensive Care Med.* 2017;43:1690–4.
 4. Dondorp AM, Hoang MNT, Mer M, Sepsis in Resource-Limited Settings-Expert Consensus Recommendations Group of the European Society of Intensive Care M, the Mahidol-Oxford Research Unit in Bangkok T. Recommendations for the management of severe malaria and severe dengue in resource-limited settings. *Intensive Care Med.* 2017;43:1683–5.
 5. Thwaites CL, Lundeg G, Dondorp AM, sepsis in resource-limited settings-expert consensus recommendations group of the European Society of Intensive Care M, the Mahidol-Oxford Research Unit in Bangkok T. Recommendations for infection management in patients with sepsis and septic shock in resource-limited settings. *Intensive Care Med.* 2016;42:2040–2.
 6. Serpa Neto A, Schultz MJ, Festic E. Ventilatory support of patients with sepsis or septic shock in resource-limited settings. *Intensive Care Med.* 2016;42:100–3.
 7. Musa N, Murthy S, Kissoon N. Pediatric sepsis and septic shock management in resource-limited settings. *Intensive Care Med.* 2016;42:2037–9.
 8. Kwizera A, Festic E, Dunser MW. What's new in sepsis recognition in resource-limited settings? *Intensive Care Med.* 2016;42:2030–3.
 9. Misango D, Pattnaik R, Baker T, Dunser MW, Dondorp AM, Schultz MJ, Global Intensive Care Working G, of the European Society of Intensive Care M, the Mahidol Oxford Tropical Medicine Research Unit in Bangkok T. Haemodynamic assessment and support in sepsis and septic shock in resource-limited settings. *Trans R Soc Trop Med Hyg.* 2017;111:483–9.
 10. GRADE handbook for grading quality of evidence and strength of recommendations. 2013. <http://gdt.gradepro.org/app/handbook/handbook.html>. Accessed Oct 2013.
 11. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, Sevransky JE, Sprung CL, Douglas IS, Jaeschke R, Osborn TM, Nunnally ME, Townsend SR, Reinhart K, Kleinpell RM, Angus DC, Deutschman CS, Machado FR, Rubenfeld GD, Webb SA, Beale RJ, Vincent JL, Moreno R, Surviving Sepsis Campaign Guidelines Committee including the Pediatric S. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med.* 2013;41:580–637.
 12. Guyatt GH, Alonso-Coello P, Schunemann HJ, Djulbegovic B, Nothacker M, Lange S, Murad MH, Akl EA. Guideline panels should seldom make good practice statements: guidance from the GRADE Working Group. *J Clin Epidemiol.* 2016;80:3–7.

Open Access This chapter is licensed under the terms of the Creative Commons Attribution 4.0 International License (<http://creativecommons.org/licenses/by/4.0/>), which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license and indicate if changes were made.

The images or other third party material in this chapter are included in the chapter's Creative Commons license, unless indicated otherwise in a credit line to the material. If material is not included in the chapter's Creative Commons license and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder.