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WHAT'S NEW IN INTENSIVE CARE

Recommendations for infection management in patients with sepsis and septic shock in resource-limited settings

C. Louise Thwaites[1,2*], Ganbold Lundeg[3], Arjen M. Dondorp[4,5] and For the sepsis in resource-limited settings–expert consensus recommendations group of the European Society of Intensive Care Medicine (ESICM) and the Mahidol-Oxford Research Unit (MORU) in Bangkok, Thailand

Introduction

Studies indicate that sepsis and septic shock in resource-limited settings are at least as common as in resource-rich settings. The surviving sepsis campaign (SSC) guidelines have been widely adopted throughout the world, but in resource-limited settings are often unfeasible [1]. The guidelines are based almost exclusively on evidence from resource-rich settings and are not necessarily applicable elsewhere due to differences in etiology and diagnostic or treatment capacity. An international team of physicians with extensive practical experience in resource-limited intensive care units (ICUs) identified key questions concerning the SSC's infection management recommendations, and evidence from resource-limited settings regarding these was evaluated using the grading of recommendations assessment, development and evaluation (GRADE) tools. This article focuses primarily on bacterial causes of sepsis and septic shock. Other infections common in resource-limited settings, such as malaria, are covered in a separate article in this series. Evidence quality was scored as high (grade A), moderate (B), low (C), or very low (D), and recommendations as strong (1) or weak (2). The major difference from the grading of recommendations in the SSC-guidelines was in taking account of contextual factors relevant to resource-limited settings, such as the availability, affordability and feasibility of interventions in resource-limited ICUs. Strong recommendations have been worded as 'we recommend' and weak recommendations as 'we suggest' (details in online supplement).

Results and recommendations for management of infections in resource-limited settings

There are important differences in the causative pathogens of sepsis and septic shock between resource-rich and resource-limited settings, as well as substantial variation between and within resource-limited settings. Hospital, and especially ICU-related, infections are more likely to be caused by multidrug-resistant organisms and previous antibiotic use is a risk factor for antibiotic resistance. Misdirected initial antibiotic therapy is associated with poor outcome [2, 3], but there is a paucity of epidemiological data in most low-resourced settings. We recommend empirical antibiotic therapy should cover all expected pathogens and likely resistance patterns (1C) based on locally-acquired epidemiological data as large regional variations exist (ungraded). We recognize that, in settings with a limited range of available antibiotics, this may be challenging. We suggest that research groups in collaboration with stakeholders provide microbiological data from sentinel sites throughout resource-limited settings to guide local empirical antibiotic choices (ungraded).

There is weak evidence from resource-limited settings suggesting that timely administration of antibiotics is beneficial [2, 4–6]. Observational data suggest that, in many resource-limited settings, the administration of antibiotics to most patients within 1 h of sepsis or septic

*Correspondence: lthwaites@oucru.org
[1] Oxford University Clinical Research Unit, Hospital for Tropical Diseases, 764 Vo Van Kiet, Ho Chi Minh City, Vietnam
Full author information is available at the end of the article

Group members of the sepsis in resource-limited settings–expert consensus recommendations group are listed in the online supplement.

shock recognition is feasible. Therefore, given biological plausibility and evidence from resource-rich settings, we recommend appropriate antibiotics should be given within the first hour following sepsis or septic shock recognition (1C).

In resource-limited settings, microbiological laboratory facilities are often restricted, but there was evidence from these settings that taking blood cultures was associated with improved outcome in sepsis and septic shock and with improved appropriateness of antibiotics [2, 6, 7]. No studies addressed incremental costs of implementing microbiological capacity, or additional benefits of two sets of blood cultures. We recommend that blood cultures should be taken before the administration of antibiotics in locations where this is possible (1B). Ideally, two sets of blood cultures should be obtained. It is realized that in many hospitals routine blood culture is unfeasible, but a recommendation of expanding microbiological laboratory capacity is beyond the scope of these recommendations (Table 1).

Identification of an infection source and source control are additional challenges in resource-limited settings and are affected by the facilities available. There was weak evidence of reasonable sensitivity of both chest radiography and ultrasound in the diagnosis of abdominal hollow viscus perforation (mainly studied in typhoid or tuberculosis) and abscesses in melioidosis [8–11]. We found weak evidence that timely surgery was beneficial in typhoidal gastro-intestinal perforations [5, 12]. We refrained from specific recommendations on use of chest radiography or ultrasound in resource-limited settings. We suggest that source control is carried out within 12 h of admission to hospital (ungraded), except in the specific case of pancreatic necrosis, where there is evidence from resource-rich settings that delay may be beneficial [1].

Combination antimicrobial therapy increases health-care costs and toxicity. Current SSC-guidelines only recommend combination therapy in specific situations. such as when the chances of multidrug-resistance are high. Evidence in multidrug-resistant or extensively drug-resistant bacteria was confined to studies of *Acinetobacter baumannii* infection, where combination therapy was beneficial [3, 13]. Where the chances of multidrug resistance are high, combination antibiotics should be considered (2D). Choice of combination therapy should be guided by local epidemiology and known effective combinations (ungraded). Antimicrobial therapy should be de-escalated whenever possible (ungraded). We recognize that without microbiological information de-escalation is difficult.

In settings of limited microbiological capacity, semi-quantitative C-reactive protein or procalcitonin point-of-care tests are increasingly available and are a potential de-escalation tool. There was evidence that, even in resource-limited settings, procalcitonin-guided antibiotic policies are cost-effective, with test costs off-set by antibiotic savings. Two studies showed benefit of procalcitonin guidance on de-escalation in sepsis and septic shock [14, 15]. Nevertheless, in view of reduced microbiological capacity and higher antimicrobial resistance levels, we believe the use of biomarkers for de-escalation of antimicrobial therapy needs further study in resource-limited settings before a recommendation can be made.

Table 1 Recommendations and suggestions on infection control in patients with sepsis or septic shock in in resource-limited settings

1	Choice of empiric therapy	As poor outcome is associated with inappropriate antibiotic therapy, empirical therapy should aim to cover all expected pathogens and likely resistance patterns (1C). We suggested that research groups in close collaboration with stakeholders provide microbiological data from sentinel sites throughout LMICs to guide empirical antibiotic treatment (ungraded)
2	Timing of antibiotics	We recommend that appropriate antibiotics should be given within the first hour in severe sepsis and septic shock (1C)
3	Taking blood cultures	We recommend that blood cultures should be taken before the administration of antibiotics (1B). It is realized that in many hospitals in resource-limited countries routine blood culture in sepsis is not feasible
4	Source control	We suggest source control is carried out within 12 h of admission to hospital except in the specific case of pancreatic necrosis (ungraded). Radiography and ultrasound are good first line imaging techniques. If an intravascular device is suspected this should be removed (ungraded)
5	Combination antibiotics	Where the possibility of multi-drug resistant micro-organisms is high, we suggest that combination antibiotics should be used (2D). In settings with facilities for blood culture and antibiotic resistance testing, antimicrobial therapy should be de-escalated when culture results are available (ungraded).We suggest that choice of combination therapy should be guided by local epidemiology and known effective combinations (ungraded)
6	Biomarkers	Use of biomarkers like procalcitonin and C-reactive protein for de-escalation of antimicrobial therapy needs further study in resource-limited settings before a recommendation can be made

Conclusion

Large variations in disease etiology and high rates of antimicrobial resistance combined with restricted choice of antibiotics and limited microbiological data pose significant challenges in the management of septic patients in resource-limited settings. Increased use of combination therapy and broad spectrum antibiotics risks increasing antimicrobial resistance. Enhanced surveillance necessitates better collaboration between stakeholders and improved microbiological facilities, which in turn requires significant investment. However, newer technologies which negate the need for specialist staff and equipment may become more available. This would not only improve the management of individual patients but, by providing high-quality epidemiological data, may help combat the global threat of antimicrobial resistance.

Electronic supplementary material

The online version of this article (doi:10.1007/s00134-016-4415-3) contains supplementary material, which is available to authorized users.

Author details

[1] Oxford University Clinical Research Unit, Hospital for Tropical Diseases, 764 Vo Van Kiet, Ho Chi Minh City, Vietnam. [2] Oxford Centre for Tropical Medicine and Global Health, Nuffield Department of Clinical Medicine, Oxford, UK. [3] Department of Critical Care Medicine, Mongolian National University of Medical Sciences, Ulaanbaatar, Mongolia. [4] Mahidol-Oxford Tropical Medicine Research Unit (MORU), Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand. [5] Department of Intensive Care, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands.

Acknowledgments

Infection control subgroup members: Neill KJ Adhikari (Sunnybrook Health Sciences Centre and University of Toronto, Toronto, ON, Canada), Jane Nakibuuka (Mulago National Referral and University Teaching Hospital, Kampala, Uganda), Randeep Jawa (Stony Brook University Medical Center, Stony Brook, NY, USA), Mervyn Mer (Johannesburg Hospital and University of the Witwatersrand, Johannesburg, South Africa), Srinivas Murthy (BC Children's Hospital, University of British Columbia, Vancouver, Canada), Marcus Schultz (Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands and Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand), Binh Nguyen Thien (Trung Vuong Hospital, Ho Chi Minh City, Vietnam), Arthur Kwizera (Mulago National Referral Hospital, Kampala, Uganda).

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