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Surviving sepsis campaign guidelines 2018 pdf

Despite the gain in terms of hospital survival achieved in the last decades though the application of Surviving Sepsis Campaign (SSC) guidelines, the treatment of sepsis remains challenging for clinicians as more than one in four septic patients is still likely to die in hospital. In this editorial, we would like to remark on the most important novelty introduced by the new SSC guidelines [1] that we believe represent an advanced step in the implementation of precision medicine in this field of respiratory and intensive care medicine. Although is sensible that the SSC evidence-based recommendations remain a "must" in the bundled usual care of the majority of septic patients, it should be borne in mind that the comprehensive panel of the advice provided by these guidelines might not fit all cases in all clinical scenarios [1]. Accordingly, an individualised approach based on best-practice statements is likely to be coherently considered in these specific circumstances. We therefore want to highlight the existing obstacles that limit the capability of these new guidelines of having a strong impact on clinical outcomes of sepsis around the world [2].Sepsis is a life-threatening organ dysfunction caused by an infection-induced dysregulated host response, which may be complicated by septic shock when circulatory and cellular/metabolic dysfunction occur [3, 4]. Sepsis and septic shock are the major causes of morbidity and mortality in the world [4, 5]. Prevalence of sepsis varies from 6% to 30% among intensive care units (ICUs) depending on sepsis definitions used [3–8]. The population-based incidence of sepsis is estimated to be 290–300 cases per 100000 inhabitants per year in large American series, half of which cases require ICU admission and one-fifth mechanical ventilation [5–7]. National Registry data collected in some European countries number hospitalisation rate for sepsis of 86–367 cases per 100000 inhabitants per year, with one-third of cases receiving ICU care and a hospital mortality rate of 12–43% [8–10]. Mortality from sepsis/septic shock differs across continents, countries and regions, with reported in-hospital mortality ranging between 12% and 76% [5–13].Sepsis is a challenging issue not only for intensivists but also for physicians working in pulmonology wards, respiratory high-dependency units (RHDUs) and emergencies departments.Concerning emergency departments, there was an increase from 1.2 to 2.2 million in the annual admissions for sepsis between 2001 and 2009 in the USA [14]. Sepsis/septic shock is a strong prognostic factor in RHDUs, accounting for 36% of the causes of death in severe acute respiratory failure (ARF) [15]. In the clinical setting of a tremendously increasing burden of critically ill respiratory patients, RHDUs provide a specialised quality of care between ICU and wards, with health resources optimisation in Europe [16]. The peculiarity of these units is their predominant choice of providing noninvasive monitoring and assistance by means of noninvasive ventilation (NIV) and high-flow nasal therapy to care for patients at earlier stages of ARF. As a matter of the fact, the chance of acquiring nosocomial infections (e.g. ventilator-acquired pneumonia) and sepsis is lower in patients admitted to RHDCUs compared to those requiring invasive monitoring and mechanical ventilation in ICUs [17]. The potential benefit of RHDCU management of the very early phases of sepsis complicating ARF might be due to the use of fewer invasive devices [16, 17]. In the case that a septic patient does not improve or fulfils the criteria of severe septic shock with multiple organ failure requiring a higher level of care, patients can be transfer to a higher level of ICU care. Unfortunately, RHDCUs do not have an even distribution in Europe and show large differences among countries in terms of number, levels of care provided and structural hospital model; a trend towards an increase in their number and expertise has been reported only in some countries [18].In 2002, this worldwide health phenomenon prompted a the global initiative, the SSC, with the aim of reducing mortality by 25% in 5 years, and improving awareness, diagnosis and treatment of sepsis [19–24].Similar to what has been done for other time-dependent acute illness (i.e. polytrauma, acute myocardial infarction and stroke), the SSC has strongly emphasised the importance of speed and appropriateness of therapy in improving outcomes. Since the application of the first SSC guidelines, a substantial reduction in mortality has been reported [12, 21–23, 25–29]. A recent Spanish multicentre study [29] demonstrated that although the incidence of sepsis/septic shock remained unchanged during a 10-year period, implementation of SSC guidelines decreased the severity of illness and overall mortality. Mortality of sepsis has been shown to be correlated with pre-ICU/RHDCU admission site [13, 15]. Patients with sepsis/septic shock identified in emergency departments, general wards and ICUs in Europe were more severely ill than those in the USA with similar mortality if adjusted for severity of illness and organ dysfunction. Septic patients admitted to European ICUs were more frequently transferred from hospital wards, whereas those in USA were more likely to be admitted directly to ICUs [27]. Similarly, survival is greater in patients admitted to RHDCU as a "step down" from the ICU or emergency department than in those admitted as a "step up" from the wards. This discrepancy could be explained by the fact that the latter patients were more severely ill than the former because they developed a progressive worsening of their conditions while being outside a protected environment [15]. This risk is greater for septic patients whose prognosis is strongly dependent on the prompt application of SSC bundles.Unfortunately, there are still relevant barriers to the large-scale implementation of effective SSC guidelines [26]. Increased awareness of sepsis as a global healthy priority by governments and contextualisation of guidelines to the particular requirements of low-income countries constitute the key points to improve the worldwide fight against sepsis [2, 30].What strategic advantages emerge from the new SCC bundles [1] compared to the previous ones? First of all, the authors have stressed the meaning of recommendations as the translation of a distillation of the current literature into a coherent set of recommendations suitable for the "typical" septic patients included in the randomised controlled trials (RCTs). In other words, the art of medicine remains a precious ingredient in the personalisation of application of recommendations to each real-life scenario. Challenging situations have to be approached with precision medicine, which includes interpretation of data and individualisation of treatment [31]. The new SSC guidelines provide guidance at the bedside to a clinical decision maker who is busy and pressured to see more patients in less time. Concerning resuscitation, the new guidelines emphasise the importance of dynamic targets with frequent haemodynamic reassessment through bedside clinical-physiological examination. While the strongly recommended target (mean arterial pressure (MAP) 65 mmHg) gives benefit for typical patients in early resuscitation, higher targets could be appropriate for the so-called atypical patients that fall outside the RCT-based inclusion criteria, showing, for example, either chronic, poorly controlled hypertension, intra-abdominal compartment syndrome or acute renal hypoperfusion, for whom it is reasonable to achieve higher haemodynamic targets [26].Since not all patients exhibit the same cardiovascular comorbidities, the recommendation given for resuscitation (30 mL·kg^{-1} fluid therapy in 3 h) might result in under-resuscitation in some patients or over-resuscitation in others. A more individualised fluid strategy during early sepsis is necessary to achieve levels of blood pressure and cardiac output compatible with immediate survival [1, 31]. The recommendation of administering 30 mL·kg^{-1} is an arbitrary amount of fluid for initial resuscitation and 3 h is a too long period of time to evaluate the haemodynamic response. A more moderate amount of fluid (e.g. 10 mL·kg^{-1}) is recommended especially in septic patients with acute respiratory distress syndrome or with cardiac or renal failure, evaluating the response in 1 h. The simultaneous use of vasoactive drugs during resuscitation is now recommended to avoid a delay to start vasoactive support to keep the target MAP [32, 33].Moreover, this new guidance takes in consideration sepsis management in different hospital settings, not only in the ICU but also in the emergency department and on the wards. The recommendation of a quick 30 mL·kg^{-1} crystalloid infusion within the first 3 h fits the majority of patients in every environment [26].Second, these guidelines may be variably read according to different depth of concentric layers (statement, rationale and tables), depending on the expertise and level of interest of the clinician, as well as the reasons (e.g. educational or research) for their application [31].Third, the new guidelines have modified the methodology for grading the recommendations. Instead of ungraded recommendations, the 2016 SSC guidelines introduced the best-practice statement [1]. These recommendations are based on the fact that even though they lack evidence-based literature, which will probably never be available, their effects are reasonably judged to be undoubtedly either beneficial or harmful by clinicians according to their daily practice [34]. An example of individualised care is given by the identification of two ARDS subphenotypes that respond differently to fluid resuscitation [35]. Furthermore, the strength of literature-based recommendations has implications for both clinicians and patients. For what strong recommendations concern, patients would accept that intervention and most clinicians should use it in most "typical" situations. However, on an individual basis, even strong recommendation cannot or should not be followed because patient's wishes or clinical features falling outside RCT scenarios make the recommended intervention less/not applicable.Fourth, compared to the previous ones, these new guidelines emphasise much more the importance of early sepsis recognition and appropriate treatment among the five areas of management (haemodynamics, infection, adjunct therapies, metabolic and ventilation) (figure 1). Prognosis of sepsis/septic shock is terribly dependent on the immediateness of treatment, such as administration of empiric broad-spectrum antibiotic therapy within 1 h [36] and infection source control [37].FIGURE 1 Strategic interventions, types of recommendations and setting for sepsis management according to the new Surviving Sepsis Campaign guidelines. NIV: noninvasive ventilation; ICU: intensive care unit.Among the main changes in the new guidelines (table 1), it is worth mentioning those concerning ventilator strategies in sepsis-induced ARDS. Pneumonia is the most frequent cause of sepsis and is related to a worse outcome [3–8, 14, 15, 37]. In addition to slight changes of recommendations for invasive mechanical ventilation (IMV) (i.e. protective ventilation plus high positive end-expiratory pressure levels, and prone ventilation in severe hypoxaemia), which are similar to those applied to nonseptic ARDS patients, dynamic reassessment of fluid administration according to fluid responsiveness, gas-exchange evolution and extravascular lung water to prevent excessive fluid overload has been highlighted to avoid deterioration of the initial sepsis-induced lung injury [1, 38]. Concerning the role of NIV, the new guidelines keep a neutral position (no recommendation), leaving potential room for this technique in specific categories of patients handled in expert settings [1]. The strong rationale in favour of NIV (i.e. early application, prevention of IMV-induced complications and management outside an overcrowded ICU) should be balanced against its risks, which are greater in de novo acute hypoxaemic patients (i.e. interface intolerance and skin breakdown after prolonged ventilation, inability to cope with abundant secretions, and difficulty applying ARDS-protective ventilatory strategies) [38]. Before stronger evidence is available, the use of NIV in hypoxaemic septic patients should be guided by bedside application of precision medicine with dynamic evaluation of pro/con arguments, intensity and level of team expertise, and employment of integrated strategies (i.e. analgosedation, bronchoscopy, interface rotation, etc.) [39].TABLE 1 Main changes in the 2016 Surviving Sepsis Campaign recommendations from the 2012 guidelinesFifth, it should be emphasised that many of the SSC recommendations are not available, affordable or safe in resource-poor settings. This is due to the differences in sepsis management in low- compared to high-income countries, such as setting of treatment (non-ICU environment or poorly equipped ICUs), aetiology (i.e. higher prevalence of tropical diseases with direct damaging effects of pathogens, like malaria), and expertise and training of the staff [30].The guideline authors acknowledged the bias related to the recently published new definitions for sepsis and septic shock [3] while these guidelines have been developed. In the studies included in the guidelines, the patient populations were primarily characterised by the previous definition of sepsis. The new sepsis definition shifts emphasis from the systemic inflammatory response syndrome to organ dysfunction, quantified using the a "quick" version of the Sequential Organ Failure Assessment score [4]. Even if this new proposed score is likely to rapidly identify potentially high-risk infected patients such as those with community-acquired pneumonia [40], its utility in identifying subjects with serious infections before frank sepsis ensues is still under debate [41].In conclusion, these new guidelines turn out to be a "brick in the wall" of the health campaign against the sepsis in the direction of precision medicine. What we should learn is that nothing in the guidance is absolutely true for every patient in every situation. Even if a strong recommendation has to be included in the usual care of the majority of patients, this advice may be not always the best in all individuals. Let us integrate the art of evidenced-based science with that of practically based medicine.Page 2The role(s) that anaerobic bacterial species play in the complex microbial communities inhabiting the airways of people with cystic fibrosis has been the subject of several recent investigations. These studies have demonstrated seemingly conflicting results. much of the 80 years since the initial descriptions of cystic fibrosis (CF), the microbiology of CF airway infection focused on a small set of aerobic bacteria known to be capable of causing human infection. Although anaerobic bacteria could be recovered from CF sputum [1], their presence was most often attributed to contamination by anaerobes in the upper airway. Further, the oxygen-rich environment of the respiratory tract was thought to provide a less than favourable niche to sustain appreciable numbers of strictly anaerobic bacteria. Work by Worlitzsch et al. [2] some 15 years ago showed that steep oxygen gradients occur in mucus in CF airways. Subsequent research by others, including recent work in Dianne Newman's laboratory at Cal Tech, has corroborated these findings, providing compelling evidence that intraluminal conditions in CF airways are capable of supporting the growth of both facultative and obligate anaerobic bacteria [3]. These studies have been complemented during the same 15-year period by research utilising culture-independent (i.e. DNA sequence-based) approaches to characterise CF airway microbial communities. These analyses have consistently shown that anaerobic bacteria are both highly prevalent and present in considerable abundances in CF airways [4–9].The debate about whether anaerobic bacteria are or are not a significant component of CF airway microbial communities is thus giving way to growing interest in better defining the role anaerobic species play in CF airway infection [10]. Several recent studies have addressed this by seeking associations between the presence of anaerobes and clinical outcomes in CF or by exploring mechanistic hypotheses about how anaerobic species may impact lung disease progression. These studies have produced seemingly contradictory results with respect to the question of whether anaerobes contribute to lung pathology or if they may, in contrast, somehow ameliorate disease progression. Experimental evidence suggests, for example, that anaerobic bacteria can elicit strong proinflammatory responses in vivo [11]. Work by Mirković et al. [12] and by Ghorbani et al. [13] has shown that short-chain fatty acids produced by anaerobic bacteria through fermentation mediate the release of proinflammatory cytokines from human bronchial epithelial cells in vitro, an effect that is more pronounced in CF cells than in normal bronchial epithelium. The positive correlation between short-chain fatty acid levels and neutrophils observed in CF sputum suggests a mechanism whereby anaerobes enhance neutrophil recruitment into CF lungs in vivo [13].Other recent work has highlighted interactions between anaerobes and conventional (aerobic) CF pathogens that may contribute to the pathogenicity of the latter. For example, work in Ryan Hunter's laboratory has shown that anaerobic species commonly found in CF microbiota (Prevotella, Veillonella, Fusobacterium and anaerobic streptococci) have the ability to degrade respiratory mucins to produce amino acids and short-chain fatty acids that may serve as nutrient sources for, and enhance the growth of, conventional CF pathogens, including Pseudomonas aeruginosa [14]. Work by several groups has shown that 2,3-butanedione, a fermentation product of several bacterial species, including anaerobic streptococci, increases P. aeruginosa pyocyanin production and biofilm formation in vitro and promotes P. aeruginosa-induced inflammation in a murine airway infection model [15–17]. Still other research has shown that extended-spectrum β-lactamases produced by some anaerobes may protect P. aeruginosa and other CF pathogens from the activity of β-lactam antimicrobials [18].While these studies provide mechanistic and pathophysiologic bases for the role of anaerobes in contributing to CF lung disease, other lines of investigation seem to suggest that the presence of anaerobes may have a positive effect. In cross-sectional analyses, Zemanick et al. [7, 19, 20]found that sputum and bronchoalveolar lavage samples with higher relative abundance of anaerobes were associated with lower inflammation and higher forced expiratory volume in 1 s compared to samples with higher relative abundance of P. aeruginosa or Staphylococcus. In a longitudinal study of children receiving ivacaftor, Bernarde et al. [21] similarly observed a positive correlation between the relative abundance of certain anaerobic species and lung function. Work in George O'Toole's laboratory found that increased relative abundance of facultatively anaerobic streptococci was the strongest predictor of clinically stable lung disease [22]. A limitation of these studies is their reliance on estimates of species relative abundances, wherein a decrease in the relative abundance of some species must be reflected in the increase in the relative abundance of others. This limitation was overcome in a study by O'Neill et al. [23], who used quantitative bacterial culture to show that lower levels of viable anaerobic bacteria were associated with worse lung function and increased inflammation.Thus, while experimental data have identified potential mechanisms whereby anaerobes may promote CF lung disease progression, either alone or in concert with other bacterial species, observational analyses characterising the structure of CF airway microbial communities appear to suggest a beneficial role for anaerobes. What are we to do with these seemingly discordant observations? A practical, clinically relevant question is should we more specifically target anaerobes with antimicrobial therapy, or would strategies to better preserve anaerobes in diverse airway microbial communities yield better clinical outcomes?In this issue of the European Respiratory Journal, Muhlebach et al. [24] provide additional analyses aimed at better understanding the role anaerobic species play in CF airway infection. By applying extended bacterial culture methods to sputum and bronchoalveolar lavage specimens from a large age range of people with CF, these investigators identified age-related prevalence rates of anaerobic species and described relationships between anaerobes and clinical outcomes. For the sake of this study, the authors defined anaerobes as including only obligate, or strict, anaerobic species; facultative anaerobes, including streptococci, or species that can grow anaerobically in oxygen-limited conditions, were categorised with aerobic species. Nevertheless, consistent with prior studies, the presence and abundance of anaerobes were positively associated with markers of milder CF disease, including better lung function, body mass index and pancreatic sufficiency.The use of bacterial culture in this study complements previous studies employing culture-independent analyses to profile airway bacterial communities. While the use of culture is not without caveats (e.g. bacteria are not evenly dispersed in sputum, and culture media and conditions impact results), this approach circumvents limitations inherent in DNA sequence-based analysis, including distinguishing viable from non-viable bacteria, variable target gene copy number, and differential lysis of bacterial cells. And as above, the use of quantitative culture allows an estimation of absolute species density, compared to the measures of species relative abundance provided by DNA sequence-based community profiling. Finally, bacterial culture allows for species-level identification of bacteria, a degree of taxonomic resolution that is often not possible with bacterial 16S rRNA gene sequencing. Although most of the analyses performed by the investigators used genus-level categorisation, the detailing of bacterial species (both aerobic and anaerobic) recovered in this large sample set provides an outstanding resource with which to better assess species-level epidemiology, which, in turn, has potential to inform future mechanistic studies.Based on finding a positive association between anaerobes and milder lung disease, the authors conclude that antibiotic therapy targeting anaerobes may not be warranted in managing CF airway infection. However, the study's design limits broad conclusions in this regard. The study is primarily a cross-sectional analysis of anaerobe prevalence in sputum samples taken from individuals during periods of baseline health. Previous experimental and observational studies of airway microbiota around the time of pulmonary exacerbations paint a different picture of the potential role for anaerobes in CF. Quinn et al. [25] used an in vitro system to simulate CF airways and demonstrated an increase in anaerobe abundance and fermentative metabolism during pulmonary exacerbations. A recent cross-sectional analysis of several hundred CF sputum samples using culture-independent bacterial profiling similarly showed an increase in the relative abundance of anaerobic species at the onset of exacerbation, particularly in subjects with early or intermediate lung disease [9]. These data suggest a role for anaerobes in pulmonary exacerbation and provide rationale for considering the inclusion of antimicrobial agents with activity against anaerobes in the management of exacerbations, perhaps depending on patients' lung disease stage. Clearly, further study is needed before definitive, and more refined, recommendations can be made regarding antimicrobial targeting of anaerobes in CF.The authors were careful not to overreach in drawing conclusions regarding causality in describing the association between anaerobe prevalence and milder lung disease. As they acknowledge, previous studies have consistently shown a positive correlation between CF airway bacterial community diversity and milder lung disease [26]. A corollary observation has been that the reduction in community diversity associated with increasing patient age and lung disease reflects the progressive domination of the community by a conventional CF pathogen (i.e. P. aeruginosa, Burkholderia spp. or Achromobacter spp.), which occurs at the expense of other species, including anaerobes. The authors' data again demonstrate this; the prevalence rates of obligate anaerobes and Streptococcus decreased during the first two decades of life, while the prevalence of Pseudomonas steadily increased. Of interest, following this decline, the prevalence rates of anaerobes and Streptococcus were found to increase in individuals older than 25 years. This inflection point in anaerobe prevalence rates corresponds to the current median age of death in CF, suggesting a "survivor effect"; older individuals with higher rates of anaerobes (i.e. greater microbial community diversity) are likely to have a milder lung disease phenotype.Further investigation of the intriguing relationships between anaerobe microbial diversity, anaerobe abundance and lung function in CF is needed. Does the prevalence and/or abundance of anaerobes merely reflect the lack of domination by a conventional CF pathogen, which seems to portend late stage disease? Is the presence of anaerobes a reflection of other factors (e.g. inflammation, antibiotic use) that more directly impact lung health? Conversely, do anaerobes, or perhaps just certain anaerobic species, play an active role in mitigating CF lung disease (e.g. through antagonism of more pathogenic species or inhibition of inflammation)? Addressing these questions to untangle the causal relationships underlying the observations described by Muhlebach et al. [24] presents a challenge. But advancing our understanding of the role of anaerobes in CF, with studies such as this, promises to pay dividends in improved management of CF airway infection.Page 3