Chapter 9

Clinical decision-making in the management of sepsis and septic shock

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Background

The incidence of sepsis remains high despite the increasing array of powerful antibiotics. Septic shock is the most common type of shock encountered by internists, and it is still a growing cause of death in the United States and Europe, affecting 18 million people worldwide every year, with each case costing an average of more than € 22, 000 to treat [1]. In the United States, there is a valued annual incidence of more than 750, 000 cases: the most important cause of death in intensive care units (ICUs) that is not related to cardiac pathologies [2-3]. In an Italian study [4], mortality rates were 36% in patients with sepsis, 52% in those with severe sepsis and 81.8% in those with septic shock. Despite progress in this field of medicine, severe sepsis is still related to a death rate difficult to tolerate, especially if we consider that mortality due to sepsis has an infective start point and is not due to incurable disease (like advanced cancer). The incidence of sepsis is increasing, not just in the ageing of population but also because of the development of antibiotics resistance. Even with successful treatment, the effects of sepsis can be long-lasting, with a significantly lower quality of life for survivors. Considered from the pathophysiologal viewpoint, sepsis can be seen as the pro-inflammatory and pro-coagulative response to an external agent, leading to the destabilisation of both functions. Sepsis can be defined as the sum of clinical conditions originating from the immune response to an infective process or trauma. The inflammation and coagulation systems interact in a chaotic way that leads to systemic derangement of coagulation and fibrinolysis. The result is an important pro-coagulative impulse and disseminated microthrombosis causing severe alteration of the microcirculation and organ failure.

In 1992, a consensus conference by the American College of Chest Physicians and the Society of Critical Care Medicine recognised three steps in the hierarchy of the inflammatory response to infections, with a progressive increase in the risk of organ-insufficiency and death: (1) sepsis, (2) severe sepsis and (3) septic shock. Patients who have infections and two or more SIRS elements meet the "sepsis" standards; those who also have organ dysfunction or hypoperfusion are considered to have a "severe sepsis"; and those with hypotension not responsive to fluid resuscitation belong to the "septic shock" group [5, 6].

An increasing amount of information to aid in clinical decision-making has become available due to the increased sophistication of diagnostic technology; paradoxically, however, this has not always been to the advantage of the clinician. This is also the case when monitoring septic syndrome. While more is known about sepsis, its origin and development, the complexity of the immune response, the importance of genetic factors, etc., if this abundance of information is poorly organised many clinical errors can be made [7].

There is a strong need to improve the quality of health care through increased awareness of proper management techniques for septic patients. One of the most common problems faced by physicians is deciding which therapeutic intervention is the most appropriate for their patients. Clinical decision-making for the management of patients with sepsis and septic shock is very challenging, beginning with the diagnosis, which is often not clear-cut. ICU physicians often miss the diagnosis of sepsis and too much time is lost when sepsis is misdiagnosed. Early and accurate treatment are essential for increasing a person's chances of recovery. Other aspects faced by clinicians are the choice of diagnostic procedure as well as the type of therapy, which frequently requires a multidisciplinary approach.

The situation of a life-threatening illness not being properly treated because clinicians could not identify it or did not identify it until it reached an advanced stage is often the case when it comes to sepsis. In 2002, The Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM) conducted an international survey among physicians to discover their views on sepsis and, in particular, their satisfaction with the current definition. Telephone interviews were conducted with 1,050 physicians from France, Germany, Italy, Spain, United Kingdom and United States. The results showed that 67% of doctors were worried by a lack of a common definition for sepsis; 83% were concerned that the lack of common definition is, at least in part, responsible for misdiagnosis; 81% agreed that a common definition for the global medical community would be a significant step toward better treatment; 87% agreed that the pathogenesis of sepsis is not completely understood; and 82% agreed that the symptoms of sepsis can easily be attributed to other conditions [8]. In this setting, it is clear that a correct medical decision-making procedure would not only increase recognition of the septic condition but also reduce the incidence of errors and decrease the interval between diagnosis and therapy.

The tools that can be used in the decision–making procedure are, synthetically, the following.

Evidence-based medicine

There is no doubt that the "best available evidence" is an important component of medical decision-making, and evidence-based medicine should be seen as a powerful method to identify this evidence [9]. Evidence-based medicine (EBM) is an approach to caring for patients that involves use of the clinical research literature combined with an understanding of pathophysiology and a recognition of clinical

experience. Enthusiasm for EBM has grown at a time of increasingly overt economic constraints in healthcare.

The EBM approach may improve clinical decision-making by:

1. Incorporating the best available scientific literature.
2. Reducing the bias that occurs when medical decisions are based on most recent patients.
3. Explicity balancing the risks and benefits of a clinical decision.

EBM is an important strategy for assessing the vast amounts of published data and applying the conclusions drawn from them to patients. However, in intensive care medicine, there is often a shortage of "gold standard" randomised controlled trial evidence to support specific therapeutic or diagnostic decisions [10].

EBM is widely used in internal medicine, but there is a great need to apply it to critical care medicine as well. Clinical decision-making may be improved by encouraging physicians to explain their medical decision-making, including citation of the literature on which their decisions were based.

A large number of important clinical trials focusing on critically ill patients have been concluded in the last few years [11]. Positive strides have been made in clinical trials, where it was shown that an increased number of interventions results in better outcomes. Most of these studies have focused on patients with severe sepsis, because this population has been the source of frequent mortality and augmented hospital costs. These trials have been among the first critical-care clinical trials to demonstrate reduced mortality in the critically ill. As in any adaptation of EBM, it is essential to strongly examine the trials and to verify whether the benefits can be translated to the individual patient. Some of the interventions, such as small tidal volume mechanical ventilation in patients with acute lung injury or the administration of low-dose corticosteroids to patients with septic shock, are cost-effective and relatively simple to put into practice. Others, such as use of activated protein C in patients with severe sepsis or "tight" glycaemic control in patients with hyperglycaemia, require either significant pharmaceutical expenditure or, possibly, additional health care staff. Nevertheless, the trials represent substantial advances in the field of critical care medicine and should at least be considered for implementation in all ICUs.

EBM-oriented intensive-care physicians face four tasks:

1. To use evidence summaries in clinical practice.
2. To update selected systematic reviews or evidence-based guidelines in their field.
3. To enrol patients in studies of treatment, diagnosis and prognosis on which medical practice is based.
4. Not to consider EBM as a tool to avoid health-care changes that may benefit the patient but which are uncomfortable or challenge the established order.

Guidelines

Clinical guidelines describe how a medical practitioner should respond under certain circumstances for certain patients. Application of such guidelines requires a specialist to collect and interpret the clinical data, apply standard therapeutic or diagnostic programmes and revise them if necessary.

For the management of sepsis and septic shock, a priceless instrument is available: the "Surviving Sepsis Campaign" (SCC) guidelines, which are a product of the collaboration of three major intensive-care organisations: the European Society of Intensive Care Medicine (ESICM), the Society of Critical Care Medicine (SCCM), and the International Sepsis Forum (ISF) [12]. The initial funding for the campaign was provided by the Eli Lilly Company, with subsequent contributions from both Baxter and Edwards Lifesciences. The evidence-based guidelines are aimed at treating sepsis and are of practical utility at the bedside. They are listed by category and not by importance or hierarchy and originate from a systematic examination of scientific literature of the last 10 years. Using a modified Delphi method (expert agreement), the consensus conference made five recommendations, from A to E, with A being derived from studies of more scientific relevance (Table 1).

Table 1. Grading system for SCC guidelines

Grading of recommendation		
	I.	Supported by at least two level I investigation
	II.	Supported by one level I investigation
	III.	Supported by level II investigation only
	IV.	Supported by at least one level III investigation
	V.	Supported by level IV or V evidence
Grading of evidence		
	I.	Large, randomised trials with clear-cut results
	II.	Small, randomised trial with uncertain results
	III.	Nonrandomised, contemporaneous controls
	IV.	Nonrandomised, historical controls and expert opinion
	V.	Case series, uncontrolled studies and expert opinion

Thanks to the SCC, a very useful tool to aid in the therapy of sepsis has been provided. These recommendations regard each aspect of the acute management of severe sepsis and septic shock [13]: initial resuscitation with the correct use of fluids, vasopressors and inotropes; an aetiologic diagnosis; a definitive therapy, such as source control and antimicrobials; adjunctive therapy, including steroids and the use of recombinant human activated protein C; nutritional strategies; the correct use of haemoderivatives; metabolic control; respiratory strategies; sedation-analgaesia protocols; and deep-vein thrombosis and stress-ulcer prophylaxis (Table 2).

Table 2. Arguments of SCC guidelines

A.	Initial resuscitation
B.	Diagnosis
C.	Antibiotic therapy
D.	Source control
E.	Fluid therapy
F.	Vasopressors
G.	Inotropic therapy
H.	Steroids
I.	Recombinant human activated protein C
J.	Blood-products administration
K.	Mechanical ventilation of sepsis-induced ALI/ARDS
L.	Sedation, analgesia and neuromuscular blockade in sepsis
M.	Glucose control
N.	Renal replacement
O.	Bicarbonate therapy
P.	Deep-vein thrombosis prophylaxis
Q.	Stress-ulcer prophylaxis
R.	Consideration for limitation of support

The SCC action plan is based on six points:

1. Increase the awareness of health-care professionals, governments, health and funding agencies and the public of the high frequency and mortality associated with sepsis.
2. Improve early and accurate diagnosis by providing a clear definition of sepsis.
3. Increase the use of appropriate treatment, urging its timely use.
4. Encourage the education of all health-care professional who manage septic patients.
5. Provide a framework for improving and accelerating access to post-ICU care and counselling for sepsis patients.
6. Recognise the need for clear referral guidelines that are accepted and adopted at a local level in all countries by initiating the development of global guidelines.

The hope is to increase awareness and improve outcome for the critically ill patient. The SCC guidelines are not a formally static document: their impact will be tested and the recommendations will be updated almost annually as important new knowledge becomes available.

Although the SCC campaign aims to provide guidance for the clinical care of a patient with severe sepsis or septic shock, the recommendations are not applicable to all patients and should not be implemented indiscriminately. They cannot replace the clinician's common sense and decision-making capability when he or she is confronted with a patient's unique set of clinical variables.

Local protocols

The role of medical protocols is becoming increasingly important in intensive care medicine as a mean to support both diagnosis and treatment. Their importance is due to the potential to promote high-quality medical practice and reduce variations in care while improving cost-effectiveness. For this aim, protocols need to be optimised, that is, without ambiguity and incompleteness. It is necessary to keep in mind that the need for a rapid clinical decision may complicate application of EBM in the ICU setting. In fact, in the ICU, decisions must be much more rapid than in the normal care setting of hospitalised patients. In such cases, pre-scripted information may be extremely effective.

It is becoming generally accepted that implementation of the latest evidence-based research in clinical practice, in the form of protocols, can improve the quality, consistency and cost-effectiveness of health care. It should be noted that medical protocols presume its users to have a certain background knowledge, and that it is unnecessary to explain in complete detail.

New telematic technologies offer great potential in streamlining guideline development and updating activities by supporting remote collaborations in reviews of the literature and the setting of guidelines and by enabling hypermedia versions of literature reviews [14].

The referral guidelines must be accepted and adopted at a local level, and transformed into local protocols, which are instruments of more practical application than generalised guidelines. Local protocols provide a patient approach that is well-known to the entire intensive-care staff, which thereby forms a single instrument to care for the patient. They also act as a reusable skeletal plan that can be refined when applied to a particular patient. Local protocols must be obtained by adapting and eventually adjusting the generalised guidelines to the local reality, (which can be very different from country to country or from region to region), with its organisational problems, its personal practices and limits. The resulting protocols, usually written in text combined with some additional formats, e.g. tables, flow-charts and graphs, can greatly improve patient outcome based on improvements in the quality of care and in methodology [15].

The most advantageous characteristics of a local protocol are: it is defined by the physician and under appropriate medical direction; it is easily modifiable (not being a static document, it has to be reviewed periodically); it is clearly stated, easily intelligible and easily accessed by all components of the health-care staff .

Mortality risk prediction in sepsis

Clinical judgment remains a major part of medical decision-making. The prognosis of the septic patient can actually influence the strategies that can be applied, the correct evaluation of risk/benefits assessment of treating patients with particular devices or drugs, and lastly (but not applicable to all countries) withholding or withdrawing life support from critically ill patients.

Mortality risk prediction in sepsis has evolved from identification of risk factors and a simple count of organ failure to sophisticated techniques that mathematically transform a raw score into a predicted risk of death that is made depending on the expression of specific biomarkers that reflect the septic course of action and its severity [16].

Illness scoring systems

Although early scoring systems were designed only for comparing observed and expected outcomes, some second and third generation scoring systems have been promoted as methods to guide clinical care and treatment, for example, when to withdraw treatment or when to discharge a patient. While the subject of considerable debate, these scoring systems have been shown to be as good as clinical experience in predicting survival. However, current scoring systems only provide probabilities and do not accurately predict whether an individual will survive. Therefore, they should not be used alone to influence clinical decisions about the septic patient and do not replace common sense, which must remain a key aspect of decision-making.

The use of severity-of-illness scoring systems in treating patients with sepsis or septic shock has mainly been aimed at stratifying the numbers in clinical trials or evaluating the performance of the ICU. Few studies have determined whether a scoring system can be used at the onset of sepsis to predict the mortality of a patient who fulfils the sepsis criteria [17].

The first generic physiological scoring system developed to quantify severity of illness according to patient characteristics was the Acute Physiology and Chronic Health Evaluation (APACHE) method. Since the original system was too complex and time-consuming to be used routinely, two derivations were developed: the Simplified Acute Physiology Score (SAPS) and the APACHE II system. These were both subsequently updated to APACHE III and SAPS II [18-19]. At almost the same time, several intensive care scores were developed for the evaluation and quantification of organ failure: Multiple Organ Dysfunction Score (MODS) and the Sequential Organ Failure Assessment (SOFA) [20]. These scoring systems are aimed more at patient description than at outcome prediction. Based on a review of the literature comparing various severity-of-illness scoring systems (APACHE II & III, MPM II0 & MPM II24, SAPS II, SOFA), it can be assumed that APACHE II is the most widely used and perhaps the most appropriate [21]. It is probably therefore also important to calculate SAPS II and SOFA in order to be assured of the validity of the results and their reliability in assisting in clinical decision-making.

Biomarkers

A biomarker is a specific biochemical in the human body with molecular feature useful for measuring the progress of disease or the effects of treatment. Since sepsis

involves complex molecular changes, the identification of specific and sensitive molecular markers is of utmost importance. Modern sepsis research focuses on the inflammatory/immunologic host response to the infection, although the best biomarker of sepsis remains to be determined.

Calcitonin precursors, especially procalcitonin (PCT), is a reliable markers for diagnosing sepsis in critically ill patients. In fact, it may be even more accurate than established markers such as C-reactive protein, lactate, and leukocyte count [22-23]. Elevated PCT concentration appears to be a promising indicator of prognosis, although its low specificity prevents it from being 100% reliable. This is because there are many causes of increased procalcitonin, and only one of these is sepsis; however, a low procalcitonin level makes the diagnosis of sepsis much less likely [24].

Interleukin (IL)-6 levels correlate well with prognosis: patients who die earlier have higher IL-6 levels at baseline than those who die later or who eventually survive. Nonetheless, the pattern is not uniform, since biosynthesis is triggered in both infectious and non-infectious processes [25].

Septic shock and multiple organ failure are associated with coagulation activation, disseminated fibrin formation, and consumption of coagulation inhibitors, such as antithrombin III and protein C. Antithrombin III activity decreases from normal baseline levels and is significantly lower in the group of patients who progress to septic shock than in those who develop severe sepsis. In this sense, it can be a sensitive (but not specific) marker of an unfavourable outcome [26].

Protein C (PrC) is the zymogene of activated protein C (APC), an enzyme that plays an important role in the regulation of haemostasis. This property derives from its ability to inactivate factors Va and VIIIa, with consequent inhibition of thrombin formation. The activation of PC to APC occurs locally and through the thrombin/thrombomodulin complex at the level of receptors (EPCR) located on the endothelial surface [27]. The activated form (APC) becomes linked to protein S on the surface of activated cells, where it can induce anticoagulant and fibrinolytic functions (by directly blocking the inhibitor of fibrinolysis, PAI-1) as well as anti-inflammatory functions (through reduced production of thrombin and direct inhibition of NF-kB, an important nuclear transcriptor of inflammatory cytokines) leading to the inhibition of cytokine responses to endotoxin. The reduction in PC concentration may play a central role in the development of disseminated microthrombosis and organ failure in sepsis. The plasma PC level has been shown to be a valid index of severity in sepsis [28]. Furthermore, PC levels at the start of sepsis seem to be highly predictive of outcome within that phase, with an inversely proportional correlation between plasma levels and mortality. Severe PC deficiency (<40% of the level of PC in pooled normal human plasma) and continued PC deficiency are associated with mortality resulting predominantly from refractory shock and multiple organ dysfunction [29].

Age, underlying co-morbidities, and level of disability are predictive of overall outcome but do not differentiate between early and late death, the latter being primarily the result of non-sepsis-related events. The findings suggest that hospital survival may be dependent on the interplay between the extent of the host response to infection and the patient's physiologic reserve. The latter is the basis on which

abnormalities in biomarkers of inflammation and coagulation are related to disease severity and mortality outcome in patients with severe sepsis.

Personal clinical experience

Human factors are essential in the process of decision-making. There is little use in knowing that an intervention is supported by high-grade evidence if the clinical expertise to treat the individual patient is lacking. In this sense, the importance of good teamwork (doctors, nurses, and physiotherapists) emerges. It must be remembered that not every patient is the same, that randomised controlled studies do not give the answer for individual patients and that the clinical profile of each patient is important [30].

Clinical decision-making capability based on personal experiences embraces a three-phase hierarchy (Fig. 1]):

1. Hypothetical/deductive synthetic thought (originate a solution, diagnosis or treatment for patients for whom no obvious pattern or rules fit the case).
2. Use of rules (rules, algorithms, clinical pathways, heuristics).
3. Pattern recognition (recognise patterns of symptoms, signs and diagnostic tests to reach a diagnosis or treatment strategy).

It is important to remark that medical decision-making cannot be based on most recent or most significant patients; this can lead to a hazardous bias and erroneous conclusions. In addition, during the management of a septic patient

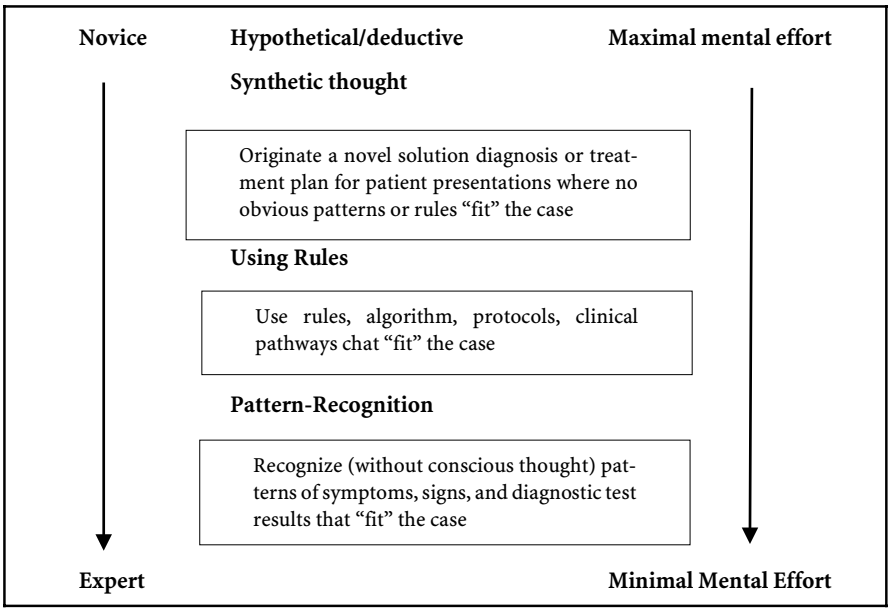

Fig. 1. Clinical decision-making hierarchy

relevant decisions often have to be made without the aid of pre-written protocols and guidelines and without clear indications from the literature. These decisions are made on the base of competence and common sense, by understanding the nature and the consequences of different options, with the aim of making an accurate choice among options using a best risk/benefit assessment. Examples of such situations include the decision to transfer the patient from the emergency room or normal care rooms to the ICU, and vice-versa; which broad-spectrum antibiotic therapy is indicated, based on our hypothesis regarding the source of the infection; or when a surgical intervention is indicated for the source control of infection. Other points to consider are the indication for a continuous or intermittent renal replacement, the need for haemodynamic invasive monitoring, and when to perform a tracheostomy to protect airways from prolonged intubation.

Some studies have indicated that the presence of a properly skilled critical-care physician can have a significant impact on outcome [31]. Rounds at the bedside may also result in better outcomes. To increase the value of bedside rounds, a sequence of questions should be raised systematically in front of each patient, for example, whether the patient is mechanically ventilated, can he/she be weaned from mechanical ventilation? Is nutrition adequate? Is the head of the bed elevated?

Conclusions

Many residents prefer to work in the ICU. The units are almost continuously active, require rapid decision-making and have the aura of life and death. Nevertheless working in ICU is extremely stressful, and there is not always time enough for each patient. In addition, potential tension with the patient's family may lead to their lack of trust in health-care providers, anger, hostility, and litigation. In this landscape, clinical decision-making requires particular attention as well as strategies for reducing errors to a minimum or even zero. It is not possible (and perhaps it is not the "gold standard") to remain a coolly dispassionate, hyper-rational physician systematically considering well defined options on the basis of careful weighing of the evidence [32].

The optimal decision-making strategy in the management of a critically ill patient with severe sepsis or septic shock can be summarised as follows:

1. Sit at the patient's bedside to collect a thorough history and perform an uninterrupted physical exam.
2. Collect data to exclude or confirm the diagnosis of sepsis, keeping in mind widely accepted definitions.
3. Assess, if possible, the gravity of sepsis and its prognosis.
4. Use guidelines and protocols.
5. Allow 2-3 min of uninterrupted time to mentally process each patient.
6. Avoid decision-making when overly stressed or angry.
7. Call for help if the decision is exceptionally difficult.

The use of guidelines and protocols for specific diagnostic or therapeutic decision conserves mental energies while on duty. The clinician should use EBM

techniques to substantiate decisions with facts – while understanding the limits of the evidence – and to consider specific issues, such as the utility of diagnostic tests, the risk/benefit of a therapy, the proper management plan and disease prognosis.

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