From Internal Wards to Intensive Care Units and backwards: the paths of the difficult patient

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ABSTRACT

Sepsis-induced organ dysfunction may be occult; therefore, its presence should be considered in any patient presenting with infection. Conversely, unrecognized infection may be the cause of new-onset organ dysfunction. Any unexplained organ dysfunction should thus raise the possibility of underlying infection. Severe sepsis is a heterogeneous clinical entity with a wide spectrum of manifestations and severity, and over half of patients never receive care in an Intensive Care Unit (ICU). Due to ageing of the population, patients with severe sepsis are frequently admitted to general wards and, given the standard diagnostic approach, treatment must be tailored to the single patient, taking into account the burden of comorbidities. From Internal Medicine Wards the single patient could be transferred to ICU, but again admitted to our Units, due to his/her frailty, to complete the path of cure. First of all, we have to be aware of the illness and more, according to the recent literature, that, generally speaking, limits invasiveness, to be able to take care of this kind of patients.

Introduction

Sepsis, defined as the condition arising when the host response to infection causes organ dysfunction in the host, remains a major killer. Sepsis is a common illness of intensive care unit patients that carries a high morbidity, mortality, and increases hospital cost, but more and more in recent years involves also patients admitted to the general medical wards. Although mortality from sepsis remains high when compared with other critical illnesses, it has declined over the last few decades due to several adjunctive therapies and focused care programs or guidelines. According to the just published Consensus of a task force of 19 critical care, infectious disease, surgical, and pulmonary specialists of the European Society of Intensive Care Medicine and the Society of Critical Care Medicine sepsis should be defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection.[1] For clinical operationalization, organ dysfunction can be represented by an increase in the *sequential [sepsis-related] organ failure assessment* (SOFA) score of 2 points or more, which is associated with an in-hospital mortality greater than 10%. Septic shock should be defined as a subset of sepsis in which particularly profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone. Patients with septic shock can be clinically identified by a vasopressor requirement to maintain a mean arterial pressure of 65 mmHg or greater and serum lactate level greater than 2 mmol/L (>18 mg/dL) in the absence of hypovolemia. This combination is associated with hospital mortality rates greater than 40%. In out-of-hospital, emergency department, or general hospital ward settings, adult patients with suspected infection can be rapidly identified as being more likely to have poor outcomes typical of sepsis if they have at least 2 of the following clinical criteria that together constitute a new bedside clinical score termed quick SOFA (qSOFA): respiratory rate of 22/min or greater, altered mentation, or systolic blood pressure of 100 mmHg or less.[1]

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First of all: awareness

Recently revised international guidelines - the Surviving Sepsis Campaign (SSC) - have been published, they review and recommend many potential primary

and adjunctive therapies for the treatment and management of sepsis.[2] With the publication of 3 trials[3-5] that do not demonstrate superiority of required use of a central venous catheter (CVC) to monitor central venous pressure (CVP) and central venous oxygen saturation ($ScvO_2$) in all patients with septic shock who have received timely antibiotics and fluid resuscitation compared with controls or in all patients with lactate >4 mmol/L, the SSC Executive Committee has revised the improvement bundles (Tables 1 and 2).

Given that physicians working in critical care and respiratory medicine are well aware of sepsis, is there much to be gained by having more comprehensive epidemiological data? Yes, for several reasons, because patients with severe sepsis go from the Emergency Department (ED) directly to the Intensive Care Units (ICU), but more often they go from ED to Internal Medicine Wards, or, from there, to ICU and, if they do not succumb, with a heavy burden of illness, again to the Medical Wards. First of all, it looks like sepsis would remain a Cinderella condition, and in too many cases, its awareness is low or does not exist at all. Second, with an ageing population, both the incidence and case fatality rate of sepsis will increase further, making data critical for healthcare planning. Third, there are no specific treatments for sepsis, and improved awareness among not only physicians, but also healthcare management, may provide the impetus to take sepsis seriously, leading to focused programs to reduce the resultant burden of disease.

Up-to-date guidelines look at Medical Wards

The early administration of fluids and antibiotics is the cornerstone of management for patients with severe sepsis and septic shock. Supplemental oxygen should be supplied to all patients with sepsis and oxygenation should be monitored continuously with pulse oximetry. Once the patient's respiratory status has been stabilized, the adequacy of perfusion should be assessed. Hypotension is the most common sign but critical hypoperfusion can also occur in the absence of hypotension, especially during early sepsis. Warm, flushed skin may be present in the early phases of sepsis. As sepsis progresses to shock, the skin may become cool due to redirection of blood flow to core organs. Additional signs of hypoperfusion include tachycardia >90 per min, obtundation or restlessness, and oliguria or anuria. An elevated serum lactate (*e.g.*, >2 mmol/L) can be a manifestation of organ hypoperfusion in the presence or absence of hypotension and is an important component of the initial evaluation, since elevated lactate is associated with poor prognosis.[6] A serum lactate level ≥4 mmol/L is consistent with, but not diagnostic of, severe sepsis. Additional laboratory studies that help characterize the severity of sepsis include a low platelet count, and elevated international normalized ratio, creatinine, and bilirubin. Venous access should be established as soon as possible in patients with suspected sepsis. While peripheral venous access may be sufficient in some patients, particularly for initial resuscitation, the majority will require central venous access at some point during their course. A CVC can be used to infuse intravenous fluids, medications (particularly vasopressors), and blood products, as well as to draw blood for frequent laboratory studies. In addition, this access can be used for hemodynamic monitoring by measuring the central venous pressure (CVP) and the $ScvO_2$. While in the past, a major purpose of a CVC was the measurement of $ScvO_2$ and CVP, recent clinical trials have shown no clear benefit on the management of patients from the utilization of these parameters.[3,4] Moreover, the use of pulmonary artery catheters (PACs) - reserved to Intensive Care Units - in the routine management of patients with severe sepsis or septic shock is no more recommended. PACs can measure the pulmonary artery occlusion pressure (PAOP) and mixed venous oxyhemoglobin saturation (SvO_2). In theory, this may be helpful to guide circulatory resuscitation. However, the PAOP has proven to be a poor predictor of fluid responsiveness in sepsis and the SvO_2 is similar to the $ScvO_2$, which can be obtained from a CVC. PACs increase complications and have not been shown to improve outcome.[7-9] The rapid restoration of perfusion is predominantly achieved by the administration of intravenous fluids, usually crystalloids and blood transfusions in the presence of anemia. Modalities such as vasopressor therapy and inotropic therapy are added, depending on the response to fluid resuscitation and evidence for myocardial dysfunction: such interventions make the difference between an ICU and a medical

Table 1. qSOFA (quick SOFA) criteria.

Respiratory rate >22/m'
Altered mentation
Systolic blood pressure <100 mmHg

Table 2. To be completed within 3 hours of time of presentation.

1.	Measure lactate level
2.	Obtain blood cultures prior to administration of antibiotics
3.	Administer broad spectrum antibiotics
4.	Administer 30 mL/kg crystalloid for hypotension or lactate ≥4 mmol/L

Time of presentation is defined as the time of triage in the emergency department or, if presenting from another care venue, from the earliest chart annotation consistent with all elements of severe sepsis or septic shock ascertained through chart review.

ward. While an early study of early goal-directed therapy (EGDT) reported mean infusion volume in the first six hours of 3 to 5 L,[7] later trials were reporting mean infusion volumes of 2 to 3 L.[3,4] Thus, rapid, large volume infusions of intravenous fluids are indicated as initial therapy for severe sepsis or septic shock, unless there is coexisting clinical or radiographic evidence of heart failure. The term EGDT refers to the administration of intravenous fluids within the first six hours of presentation using physiologic targets to guide fluid management. EGDT has gained widespread acceptance in clinical practice but the optimal targets are unknown. Parameters such as urine output ≥0.5 mL/kg/h, CVP 8 to 12 mmHg when central access is available (static measurement) and superior vena cava $ScvO_2$ ≥70 percent (when central access is available) can be measured in an internal medicine ward, meanwhile mean arterial pressure (MAP) ≥65 mmHg (MAP = [(2 x diastolic) + systolic]/3), dynamic predictor of fluid responsiveness such as respiratory changes in the radial artery pulse pressure or SvO_2 ≥65 percent (if a pulmonary artery catheter is being used) are devoted to the ICU. The optimal physiologic target(s) of EGDT is unknown. There is also conflicting evidence on the value of measuring such targets, particularly CVP and $ScvO_2$, which require central catheter placement.[3-5,7] In addition, the generalizability of a standard targeted approach to both resource-poor (Medical wards) and resource-rich (ICUs) facilities is unknown. In Internal Medicine wards urine output, together with blood pressure (non-invasive), heart rate are universal targets that can be readily measured in all patients with sepsis, with the addition of CVP and/or $ScvO_2$ in those in whom central access is otherwise required. Nowadays in many medical wards a team of registered nurses attend or have attended courses to insert central venous catheters through eco-guided, peripheral access, the so called peripherally inserted central catheters, known for several years to reproduce good results in measuring central venous pressure, if they are correctly inserted in vena cava or right atrium and without valves, and data correlate with those provided by centrally inserted central catheters.[10]

This approach differs slightly from that of the SSC guidelines that recommend central venous access for CVP/$ScvO_2$ measurement together with MAP and urine output in all patients with severe sepsis.[11] However, these guidelines were created before the results of three major randomized trials (ProCESS, ARISE, ProMISe), that showed no mortality benefit to an EGDT-based approach, were published.[3-5]

Table 3. Internal Medicine at the center of the stage.

Despite the general ward's importance in the spectrum of sepsis care, few studies of severe sepsis have examined functional outcomes of patients initially cared for in the general medical ward, and it is possible that the adverse outcomes reported after severe sepsis are driven by the subset of Intensive Care Unit patients

Complexity and multimorbidity are standards in Internal Medicine Wards

We have all the experience that our patients have clinical findings modified by preexisting disease or medications. As examples, older patients, diabetic patients, and patients who take beta-blockers may not exhibit an appropriate tachycardia as blood pressure falls. In contrast, younger patients frequently develop a severe and prolonged tachycardia and fail to become hypotensive until acute decompensation later occurs, often suddenly. Patients with chronic hypertension may develop critical hypoperfusion at a higher blood pressure than healthy patients (*i.e.,* relative hypotension).

Research on the functional outcomes of patients with severe sepsis to date has generally not differentiated between patients with severe cardiopulmonary failure cared for in ICU and those cared for on the general medical ward. Severe sepsis however is a heterogeneous clinical entity with a wide spectrum of manifestations and severity, and over half of patients never receive care in an ICU[12,13] (Table 3).

Severe sepsis in hospitalized medical patients is sometimes under-recognized by treating physicians but is associated with a high burden of functional disability and persistent organ dysfunction.

Due to the increasing burden on hospital systems and to the limited ICU resources, most elderly patients with non-surgical sepsis, including patients with severe sepsis, are currently admitted to general internal medicine wards.[13] The aging of Western populations is an important contributing factor to the increasing incidence of sepsis in recent years, because older people are more prone to infections. All in all, elderly patients with sepsis occupy an increasing proportion of hospital beds in general internal medicine wards. Disease-severity scoring systems are used for stratification of patients for utilization management, performance assessment, and clinical research. Some widely used scoring systems for septic patients are inappropriate when rating non-surgical patients in a non-ICU environment mainly because their calculations require types of data that are frequently unavailable developed for use with patients *at risk for infection*.

Patients are frequently discharged to a higher level of care than was required prior to admission regardless of whether they ever received care in an ICU. Novel interventions to improve recognition and management of severe sepsis outside the ICU are urgently needed. Such interventions should be targeted to hospitalists.[14] Many disease severity-scoring systems related to sepsis have been developed over the years.[11,15-18] Most methods were devised for assessment of patients with sepsis who

underwent surgery and were admitted to the ICU,[19] or for specific infectious conditions (*e.g.*, bacteremia, pneumonia).[16,18] These classifications may not be appropriate for patients with sepsis who are being admitted to general internal medicine departments.

Even more, in many situations, death is due to the physician's decision, shared with the patient's family, to change from aggressive support measures to comfort measures because of his or her many, severe preexisting comorbidities and small probability of meaningful recovery.

Only a few scoring systems exist that are not restricted to a specific medical condition or ICU setting. The study of Ghanem-Zoubi *et al*.[20] aimed to assess the fitness of four scoring systems for septic patients hospitalized in general internal medicine departments: modified early warning score (MEWS), simple clinical score (SCS), mortality in emergency department sepsis (MEDS) score, and rapid emergency medicine score (REMS). The study included consecutive patients admitted to a 110-bed general internal medicine department from 1 February 2008 to 30 April 2009 in a 450-bed community-based university hospital in Haifa, Israel.

The MEWS is a simple physiological scoring system suitable for bedside application that was validated in a prospective cohort study on 709 medical emergency admissions. It is not a disease specific score. It was found that a MEWS of more than four predicts increased risk of mortality with an odds ratio of 5.4. The area under the curve (AUC) for predicting 60-day mortality was 0.67.[21] The SCS was developed and validated on 9964 patients admitted as acute medical emergencies. It is also not disease-specific. The SCS receiver operating characteristics curve for 30-day mortality had an AUC of between 0.85 and 0.9.[22] The MEDS score was developed for use with patients *at risk for infection*. The study included 3179 surgical and medical patients. It was found to predict 28-day in-hospital mortality with an AUC of 0.82 and 0.78 for derivation and validation groups, respectively.[23] The REMS was developed in non-surgical adults admitted to emergency departments over a period of one year. The AUC for predicting in-hospital mortality was found to be 0.85.[24]

Matching these data has shown that two of the examined scoring systems, REMS and SCS, can predict mortality in septic patients admitted to general internal medicine departments with good accuracy, and can thus be utilized in this enlarging clinical setup.[20]

Inflammation at the top or (immune)-depression as the rule?

The increasing prevalence of infections caused by antimicrobial-resistant bacteria makes empirical treatment of these infections more difficult.[25,26] In other articles on this issue this topic is treated and examined in depth, but obviously is critical in the management of patients with sepsis, due to the time taken to have the results of blood culture, so that between Ward and Microbiology Unit there must be a hot line of telephone calls to follow their development: Gram stain at first, then the more sophisticated, automated results, with breakpoints for antibiotics, and so on.

Whereas some patients rapidly succumb to massive proinflammatory cytokine-driven inflammation as occurs, for example, in toxic shock syndrome and meningococcemia, improved treatment algorithms have resulted in most patients surviving the early hyperinflammatory phase of sepsis and entering a more protracted phase. More than 70% of deaths in sepsis occur after the first 3 days of the disorder, with many deaths occurring weeks later. In fact, the real cause of death and organ failure in most patients dying of sepsis is unknown. Postmortem study results have shown a relative paucity of cell death in most major organs in patients who died of sepsis. One theory is that much of the organ dysfunction in sepsis might be a result of a so-called cellular hibernation response. However, the crucial message remains that many patients in intensive care units do not recover because there is ongoing infection. Despite broad-spectrum antibiotics and aggressive source control measures, many patients do not eradicate their infections and develop secondary hospital-acquired infections. Therefore, therapy that boosts immune competence could affect outcomes by leading to more rapid resolution of the primary infection and prevention of lethal secondary infections. Although both proinflammatory and anti-inflammatory processes begin promptly after sepsis initiation, in general there is predominance of an initial hyperinflammatory phase, the scale of which is determined by many factors including pathogen virulence, bacterial load, host genetic factors, age, and host comorbidities. An elderly patient with diabetes undergoing hemodialysis who develops pneumonia might not show any obvious signs of sepsis. The only clues to diagnosing sepsis in such a patient might be reduced mental status, inability to tolerate dialysis because of hypotension, hypothermia, and glucose intolerance-there could be no obvious response to infection or predominant anti-inflammatory reaction. As a matter of fact, sepsis is increasingly a disease of elderly people: 60% of patients who develop sepsis and 75% of the deaths in sepsis, in countries with advanced healthcare delivery and modern intensive care units, are in patients older than 65 years. The immune system of elderly people is less effective than earlier in life, the so-called immunosenescence. Increased comorbidities and immunosenescence contribute to the greater incidence of and mortality from sepsis in elderly people. New therapies and treatment protocols have resulted

in more prolonged disease with a shift toward the immunosuppressive phase. Sepsis has many of the same immunosuppressive mechanisms that operate in cancer, including increased production of the immunosuppressive cytokine interleukin 10, T regulatory cells, myeloid derived suppressor cells, and PD-1 and PD-L1 with T-cell exhaustion. For each patient with sepsis, the scale, persistence over time, various mechanisms sustaining this immunosuppression or occurrence of some particular clinical event (*e.g.*, viral reactivation) will help to define the appropriate drug and time of administration. After onset of sepsis, every patient has activation of transient immunosuppressive mechanisms that normally reflect compensatory measures, which counterbalance the initial inflammatory response. Generally, after 2-3 days, most patients recover substantial immune function; however, some will have persistent immunosuppression associated with increased nosocomial infections and mortality. This would be a sort of *Copernican revolution*, an approach that takes into account stratification of patients, comorbid conditions influencing the common soil where grows the proinflammatory *versus* the anti-inflammatory balance after sepsis.[27]

Step by step: fluid therapy first

Resuscitation with crystalloids compared with colloids for critically ill patients has been evaluated in large randomized, controlled trials and meta-analyses. One meta-analysis[24] including 74 trials reported no difference in mortality between critically ill patients resuscitated with crystalloids and albumin [relative risk (RR): 1.01, 95% confidence interval (CI): 0.93 to 1.10], hydroxyethyl starch (RR: 1.10, CI: 0.91 to 1.32), gelatin (RR: 0.91, CI: 0.49 to 1.72), or dextran (RR: 1.24, CI: 0.94 to 1.65). Another meta-analysis[28] reported that resuscitation with an albumin-containing solution in patients with sepsis might decrease mortality compared with solutions containing no albumin (RR: 0.82, CI: 0.67 to 1.00). ALBIOS (*albumin Italian outcome sepsis*) trial confirmed these data.[29] Recent evidence suggests that starches, compared with other fluids and regardless of molecular weight, may be associated with acute kidney injury in the general population of critically ill patients and in those with sepsis.[30-34] A recent large pragmatic trial comparing colloids (mostly starches) with crystalloids (mostly 0.9% sodium chloride) suggested a 90-day mortality benefit with colloids (RR: 0.92, CI: 0.86 to 0.99).[35] The presence of buffering substances and chloride content is often overlooked when choosing resuscitative fluids in the clinical setting and is rarely transparently reported in clinical trials. Balanced solutions may be preferable to unbalanced solutions if crystalloids are used and albumin may be a reasonable alternative to other resuscitation fluids. However, relative to balanced crystalloids, albumin confers a small risk associated with transfusion of blood products and costs markedly more. Anyway, clinicians should be aware of the possible effect of the mineral content and the presence or absence of buffering anions in resuscitation fluids.

Conclusions

In general hospital ward settings, adult patients with suspected infection can be rapidly identified as being more likely to have poor outcomes typical of sepsis if they have at least 2 of the following clinical criteria that together constitute a new bedside clinical score termed qSOFA: respiratory rate of 22/min or greater, altered mentation, or systolic blood pressure of 100 mmHg or less. Age, comorbidities and the burden of illness of the single patient will let us decide to consult the intensivist for an aggressive approach, but we have to wait that, in case of survival, our patient with severe sepsis and shock will come back to us with more clinical problems on top of the index illness.

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