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Systematic screening is essential for early diagnosis of severe sepsis and septic shock

Rastreamento sistemático é a base do diagnóstico precoce da sepse grave e choque séptico

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SEPSIS, EARLY INTERVENTIONS AND MORTALITY

For over a decade, after studies showing the benefit of early goal-directed therapy[1] and the publication of the first Survival Sepsis Campaign (SSC) guidelines in 2004,[2] several other pieces of evidence have demonstrated the importance of early treatment in reducing mortality among patients with severe sepsis or septic shock.[3-7] This evidence led to the analysis of the SSC impact in 2010, which involved 15,022 patients from 165 hospitals. This analysis revealed continuous and sustained improvements in compliance with early interventions, especially with antibiotic therapy (odds ratio - OR 0.70; $p < 0.001$), and blood culture requests (0.78; $p < 0.001$), along with a reduction in the mortality rate associated with severe sepsis or septic shock (from 30.8% to 27%; $p < 0.01$).[8]

Over time, the identification of procedures associated with the reduction in mortality rate has simplified the initial interventions in patients with severe sepsis or septic shock, emphasizing the proper antibiotic therapy (blood culture before antibiotic + broad-spectrum antibiotic within 1 hour) and the control of hemodynamic instability (administration of 30mL/kg crystalloid for mean arterial pressure - < 65mmHg or lactate ≥ 4mmol/L + vasopressors for hypotension refractory to volume).[9]

EARLY INTERVENTIONS AND IDENTIFICATION OF SEPSIS

The precocity of these early interventions depends on the professional's ability to identify patients at risk of developing sepsis. Therefore, suspicion of possible sepsis and early identification are essential for a truly early intervention at the condition's initial stages.[10] Sepsis, severe sepsis or septic shock represent the temporal evolution of the same syndrome, with different spectra of gravity and associated with increasing mortality rates. That is, longer periods of time for diagnosis are associated with higher chances of developing a more severe condition and, therefore, a higher mortality rate. In this context, Freitas et al. identified a strong relationship of the time required for the first record of organ dysfunction and the diagnosis of severe sepsis, with mortality associated with severe sepsis. The risk of death increased by 8.7-fold among patients who were identified 48 hours after organ dysfunction.[11] Three other Brazilian studies have shown that the implementation of an institutional strategy to identify sepsis at earlier stages can significantly reduce the time to identify patients

at risk of developing sepsis and, therefore, to reduce the mortality associated with severe sepsis and septic shock.[12-14] Accordingly, delayed diagnosis is a major obstacle for starting treatment, and reducing the time for diagnosis of severe sepsis seems to be a critical component to reduce mortality associated with sepsis-induced organ dysfunction.[9]

The new SSC guidelines recommend the routine use of severe sepsis screening devices in potentially infected patients for early identification of patients with sepsis, allowing implementation of early sepsis therapy (Grade 1C).[9] Although these screening devices were not formally recommended, they have been available in the SSC since 2004 to be used in all at-risk patients, that is, all patients with a "history suggestive of infection".[2] These patients should receive special attention regarding changes in their vital signs and leukocyte counts in case of the possible coexistence of systemic inflammatory response syndrome (SIRS). However, it is questionable whether the screening and the suspicion of sepsis should occur only among patients with an identified focus of infection or rather be extended to patients with predisposing conditions for developing infections. In this case, who and where would the patients at risk for sepsis be in our hospitals?

Tulli analyzed the critical points of sepsis management at bedside and offered an interesting and instigating reflection on the dynamics and the identification of critically ill patients in hospitals. A critically ill patient is almost intuitively recognized when the following information is known: (1) level of physiological reserve impairment; (2) intensity and number of dysfunctional organs and severity of the underlying disease; and (3) characteristics and level of complexity of the unit in which the patient is hospitalized. The combination of the worst aspects of these three variables - (1) low physiological reserve plus (2) severe or multiple organ dysfunction plus (3) hospitalization in units with high levels of complexity - immediately indicates the patient's complex and risky situation.[15] In contrast, it should be recognized that because of problems involving hospital bed management caused by hospital overcrowding, the distribution of patients into different hospital units does not follow the rule "patients with more complex care needs must be in more complex care units". In the real world, critically ill patients remain on the wards and in emergency rooms in many hospitals. At the same time, many hospitals still address the continuous influx of patients who present

different degrees of severity and seek emergency services and also need to be properly and quickly screened. Therefore, it seems reasonable to assume that "all patients should be considered at risk" until proven otherwise, and institutional strategies needed to be elaborated to identify these at-risk patients; furthermore, these identification strategies must be simple and effective.[15]

The establishment of rapid response teams and at-risk patient teams or the extension of the "extramural" activities of the intensive care unit (ICU) are part of these strategies and are generally based on alert systems defined by the institutions.[16,17] Regardless of the alert systems, it is essential to establish triggers that alert specific situations; additionally, to ensure the specificity of the alerts, understanding the natural course of the clinical condition is crucial.[18]

Based on the TNM, a tumor staging system, the PIRO concept (predisposition, infection, response, and organ failure) is an expansion of the list of signs and symptoms of sepsis, reflecting the clinical experience at bedside[19] and, more recently, proposing to stratify the risk of septic patients in the emergency room.[20] The concept describes septic patients based on four domains and carefully illustrates the relationship between the natural history and diagnosis of sepsis. The natural course of sepsis assumes concurrence of predisposing conditions (*P*), such as genetic factors, comorbidities, medications or immune status, which predispose the body to microbial invasion and infection (*I*). The body then reacts with an inflammatory response (*R*) that can result in organ dysfunction (*O*).[19] However, for the diagnosis, a sequence of symptoms opposite to the natural course of sepsis is observed: in general, the first manifestations are related to the inflammatory response (*R* - fever, tachycardia, tachypnea, leukocytosis) and organ dysfunction (*O* - hypotension, oliguria, need for supplemental oxygen, decreased level of consciousness, coagulation disorders and liver dysfunction). In most cases, the focus of infection (*I*) is sought and the possible predispositions (*P*) are considered only after the manifestations are identified. For example, when individuals with sepsis seek hospital care, they do not usually report to the health care team that they have pneumonia and, therefore, are at risk for sepsis. In contrast, the first signs of sepsis can be identified when patients are admitted and have their vital signs measured by the nursing staff. Thus, the warning signs of severity are not the suspected infection but, instead, mainly involve

the changes in the physiological biomarkers measured by the nurse. Analogous to acute myocardial infarction (AMI) and cerebral vascular accident (CVA), it is known that sepsis patients are not admitted in the emergency department complaining of an AMI or CVA; rather, they complain of chest pain and sudden neurological deficit. Thus, the devices used to screen and warn for the risk of sepsis should be based on the identification of vital signs changes and clinically detectable organ dysfunctions. The detection of these signals strongly suggests the presence of a focus of infection to be identified.[12,13] These physiological changes can objectively provide different patient identification scores: two signs of SIRS, *SIRS* score, Modified Early Warning Score (MEWS), National Early Warning Score (NEWS), and PIRO.[2,19-25]

STRATEGIES OF EARLY IDENTIFICATION IN DIFFERENT HOSPITAL UNITS

In a sub-analysis of a prospective observational study, Varpula et al. concluded that both delayed primary interventions and failure in the early identification resulted in high mortality rates.[26]

A before-and-after study performed in Brazil assessed the impact of the performance of a multidisciplinary team on sepsis management that involved not only implementation of early treatment but also identification of at-risk patients by a nurse dedicated to this activity and showed a significant reduction in mortality associated with severe sepsis or septic shock (before: 56.4% versus after: 34.8%; p = 0.01).[14]

In 2009, we evaluated the effect of a simple form implemented in the workflow of nursing technicians of the wards and the emergency room of a public hospital, where vital signs and organ dysfunction symptoms (i.e., oliguria, supplemental oxygen, hypotension and altered level of consciousness) were recorded. This form allowed the visualization of all patients with two or more changes in vital signs or clinically noticeable organ dysfunctions. After the implementation of this form, we observed reductions in the period of time between screening and diagnosis of severe sepsis or septic shock (from 33.8 hours to 6.8 hours; p < 0.001), hospital mortality (from 67.2% to 41%; p < 0.003) and mortality rate at 28 days (from 54.4% to 30%; p < 0.02).[12] The expansion of the same procedure to a private hospital allowed us to evaluate the impact of this methodology on a larger population. After the implementation of the form listing the vital signs and organ functions,

there was no increase in the rate of compliance with 6- and 24-hour sepsis bundles (32.3% versus 28.7%; p = 0.55). In contrast, there were reductions in the time between the identification of at least two changes of vital signs and/or organ dysfunctions and the diagnosis (34 hours versus 11 hours; p < 0.001) and in mortality rate (from 61.7% to 42%; p < 0.001).[13]

However, it is important to recognize the limitations of the classical manifestation of SIRS to identify patients with sepsis.[20,27] Koukonen et al. recently demonstrated that besides not facilitating the identification of clinically manifested organ dysfunction, the search for two or more SIRS signals did not allow for the identification of a large number of patients who were hospitalized with infection and organ dysfunction in the ICU. These findings directly challenge the concepts of both the high sensitivity of the method and its validity for detecting septic patients among ICU patients.[27]

To rapidly identify ICU patients with sepsis manifestations, Moore et al. evaluated the impact of a score based on the level of SIRS signs in a surgical ICU. Their methodology consisted of the evaluation of SIRS signs twice daily by the nursing staff. The identification of a SIRS score ≥ 4 indicated the alert for an evaluation of possible infectious foci through the completion of a second form. An excellent accuracy for identifying patients with severe sepsis or septic shock was observed (positive predictive value - PPV = 80.2% and negative predictive value - NPV = 99.5%), as was a substantial reduction in mortality after the implementation of the method (35% versus 23%).[22] More recently, the SIRS score was evaluated in a population of 1,637 trauma patients. The sepsis incidence was 7.3%, with a trend towards a reduction in ICU mortality (13% versus 8%; p = 0.08) after the use of the method. The PPV and NPV were 73.5% and 99.4%, respectively.[23]

The MEWS is a validated score used to screen and stratify the severity among patients in the emergency room.[24] This score can assist the health care team, especially nurses, in identifying patients with higher likelihoods of clinical deterioration, allowing greater confidence in the actions of the health care team. The MEWS associates scores with the levels of alteration of vital signs and levels of consciousness. A score ≥ 3 constituted an alert in the wards and allowed for early identification of at-risk patients, implementation of early therapeutics and prevention of clinical deterioration. Lee et al. demonstrated the capacity of the MEWS in

predicting the need for ICU transfers and mortality among patients with severe sepsis or septic shock identified in the wards, suggesting the creation of algorithms that respond to alerts based on a predetermined score to mobilize an assistant team.[28]

The National Health Service (NHS) has proposed changes in the MEWS and has developed an alert system known as the NEWS. The changes consisted of adding the need for supplemental oxygen and changes in the scores for respiratory rate (RR), heart rate (HR) and blood pressure (BP) (MEWS: RR > 16bpm, HR > 100bpm and BP < 100mmHg versus NEWS: RR > 20bpm, HR > 90bpm and BP < 110mmHg). In addition, any neurological disorder began receiving the maximum score. Corfield et al. demonstrated that higher NEWS values were associated with more adverse events, more ICU transfers and higher mortality rates among patients with sepsis. The authors suggest that the method could be used as a screening tool for more complex units and for the mobilization of the healthcare team at earlier stages of sepsis.[25]

IDENTIFICATION OF RISK OF SEPSIS WITH ELECTRONIC DEVICES

Accuracy of electronic devices

With the large amounts of electronic medical records, the screening of patients at risk for sepsis with electronic devices is a real prospect. A prospective observational study evaluated an electronic warning system that triggered and sent alerts to caregivers when two or more SIRS criteria were detected in patients over 70 years old. A sensitivity of 14% and a specificity of 98% to detect the infectious events were observed.[29] Nelson et al. used an automated text message system that warned the caregivers whenever a patient in the emergency room manifested two or more SIRS criteria and two or more systolic blood pressures < 90 mmHg. The sensitivity and specificity of this method were 64% and 99%, respectively.[30] Alsolamy et al. evaluated an electronic alert system consisting of the integration of vital signs on electronic medical records and the identification of two or more SIRS signals. Among 49,838 patients who received care in the emergency department, 222 (0.4%) cases of severe sepsis or septic shock were identified, with a sensitivity of 93.2% and a specificity of 98.4%. The average period of time between the electronic alert and ICU admission was 4.02 hours.[31]

Electronic devices, early interventions and mortality

In 2011, Sawyer et al. published a comparative study in which one group of patients was electronically identified (based on laboratory information and vital signs) and another group was identified with a warning system manually provided by nurses. Although there was no impact on mortality rate, early diagnostic and therapeutic interventions were observed among patients at risk for sepsis, providing greater safety to the care process.[32]

An electronic alert system was implemented in the wards in 2010, after 3 years of using a stable manual alert system triggered by nurses. Based on the implementation of electronic medical records containing information on vital data, level of consciousness and need for supplemental oxygen, an algorithm identifies the presence of two changes in SIRS and/or organ dysfunction and MEWS scores ≥ 3. In the first phase, the alert was sent by e-mail to a telephone service, which was responsible for informing the nurses responsible for each ward. One year later, this information began to be sent to mobile devices available to each hospital nurse responsible for the ward where the patients were hospitalized. The alert sent by e-mail decreased the interval between screening and diagnosis from 11 hours (previous period) to 3 hours and 30 minutes in 2010 (p < 0.01). With the use of the mobile device, there were further reductions in the interval between screening and diagnosis (2010: 3 hours and 30 minutes; 2011: 1 hour and 50 minutes; 2012: and 1 hour and 26 minutes; p < 0.02) and in the interval between screening and initiation of antibiotic therapy (2010: 5 hours and 36 minutes; 2011: 3 hours; 2012: 2 hours and 30 minutes; p < 0.01). In addition, a trend towards reduced mortality rates was also observed (2010: 38.1%; 2011: 29.5%; 2012: 27.4%; p = 0.08).[33] In the subsequent two years, a further decrease was observed in mortality rates: 19.6% in 2013 (p = 0.002) and 24.1% in 2014 (p = 0.03) (unpublished data). In 2015, Kurczewski et al. compared 30 adult patients with sepsis or septic shock who were identified via an electronic alert system with other 30 patients with the same diagnosis but who were identified before the use of this electronic alert system. The primary endpoint was time to any sepsis-related intervention. Patients in the post-alert group demonstrated a shorter time to any sepsis-related intervention, with a mean difference of 3.5 hours (p = 0.02).[34] As demonstrated by Sawyer et al.,[32] the electronic alerting system does not significantly affect the mortality rate. In contrast, the agility the electronic system

displays in performing a diagnosis appears to offer greater safety to the care process, as evidenced by the reduction in the interval between screening and antibiotic therapy.

FINAL CONSIDERATIONS

Sepsis, severe sepsis and septic shock represent the chronological evolution of the same syndrome, and early therapeutic interventions promote the interruption of this time-dependent condition. Therefore, early recognition of the risk of sepsis is central for reducing the mortality associated with severe sepsis or septic shock.

Recognizing that all hospitalized patients are part of the population at risk for sepsis and developing early alert systems based on the initial clinical signs of the condition are essential for the diagnosis of sepsis before the development of more severe conditions.

Due to the low accuracy of the classical method (two or more signs of SIRS) for identifying patients at risk for sepsis, it is reasonable to consider alternative methods, such as the use of scores as sepsis alert triggers and the expansion of the list of clinical and laboratory biomarkers to increase the degree of suspicion.

Electronic devices based on alert triggers add value to the process of detection and management of patients with severe sepsis or septic shock by providing faster and safer care.

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