SPECIAL ARTICLE

The Guadalajara Declaration on sepsis: emergency physicians' constructive comments on the Surviving Sepsis Campaign's 2021 updated guidelines

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The Surviving Sepsis Campaign (SSC) published a 2021 update of its 2016 recommendations. The update was awaited with great anticipation the world over, especially by emergency physicians. Under the framework of the CIMU 2022 (33rd World Emergency Medicine Conference) in Guadalajara, Mexico in March, emergency physicians reviewed and analyzed the 2021 SSC guidelines from our specialty's point of view. In this article, the expert reviewers present their consensus on certain key points of most interest in emergency settings at this time. The main aims of the review are to present constructive comments on 10 key points and/or recommendations in the SSC 2021 update and to offer emergency physicians' experience- and evidence-based proposals. Secondarily, the review's recommendations are a starting point for guidelines to detect severe sepsis in emergency department patients and prevent progression, which is ultimate goal of what has become known as the Guadalajara Declaration on sepsis.

Keywords: Sepsis. Septic shock. Emergency medical services. Diagnosis. Prognosis. Mortality. Prevention. Early-warning scores. Biological markers. Lactic acid. Procalcitonin. Recommendations.

Declaración de Guadalajara: una visión constructiva desde el servicio de urgencias a partir de la Surviving Sepsis Campaign 2021

En noviembre del año 2021, la *Surviving Sepsis Campaign* (SSC) publicó una actualización de sus recomendaciones y directrices de 2016. Estas fueron recibidas con una enorme expectativa en todo el mundo, especialmente entre los médicos de urgencias y emergencias (MUE). Recientemente, en el marco del CIMU 2022 (33 Congreso Mundial de Medicina de Urgencias celebrado en marzo de 2022 en Guadalajara – México) se ha revisado y analizado, desde la perspectiva del MUE, la Guía SSC de 2021. Los expertos que realizaron esa tarea y también consensuaron algunos de los puntos clave que más interesan y preocupan a los MUE en la actualidad han elaborado este documento. Su objetivo principal es analizar de forma constructiva diez de los puntos clave y recomendaciones de la SSC 2021 para complementarlas con argumentos y propuestas desde la experiencia, evidencia y perspectiva del urgenciólogo. Además, de forma secundaria, pretende ser el punto de partida de la elaboración de las guías para detectar, prevenir la progresión y atender a los pacientes con infección grave y sepsis en urgencias, que supone la meta final de lo que desde la MUE ya se conoce como "la Declaración de Guadalajara".

Palabras clave: Sepsis. *Shock* séptico. Servicios de urgencias. Diagnóstico. Pronóstico. Mortalidad. Prevención. Escalas de alerta temprana. Biomarcadores. Lactato. Procalcitonina. Recomendaciones.

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Introduction

In November 2021, the Surviving Sepsis Campaign (SSC) published an update of its 2016 recommendations and guidelines.[1,2] The influence that these recommendations have on physicians, centers, institutions and national and international organizations is evident, as is the leap in quality in the care of patients with organ dysfunction and life compromise caused by sepsis when their recommendations are used.[1,2] Today, it is recognized that the SSC has proven to be a backbone of the sepsis care process, which has managed to convey the importance of this clinical entity, the need for its early detection and correct treatment, as well as having improved its prognosis.[1,2]

These guidelines are based in most cases on "solid" recommendations in the opinion of their authors, but based on "weak, very weak and best practice statements".[1,2] Therefore, it is an obligation of all specialists involved, as occurred after the publication of the third international consensus on definitions of sepsis and septic shock,[3] to continue studying and researching to increase the clinical evidence that solidly supports the recommendations that currently exist.[4]

Emergency physicians (EP) were one of the groups of specialists most eagerly awaiting the indications of the world's leading experts, since infection and sepsis are frequent reasons for consultation with whom they must deal daily. Between 15-40% of all patients seen in hospital emergency departments (ED), depending on the different Latin American countries, are diagnosed with infectious processes.[4] Of this large volume of patients, between 5-25%, depending on the different registries, criteria or definitions used, are labeled as sepsis/septic shock. Furthermore, under-diagnosis of these patients is recognized by the ED itself.[4] These data highlight the impact and quantitative and qualitative importance of infectious processes and sepsis in the ED.[4,5]

After carefully analyzing the document and all of its guidelines, along with the references that support them, it is clear that the group of experts who drafted the SSC 2021 guidelines developed these recommendations based on the implicit premise that the diagnosis of sepsis and septic shock is often complicated and, many times, the most important and initial challenge in the ED.[1,2] EPs know that in order to classify and identify the most severe patients, one must first overcome the challenge of making the diagnosis of sepsis in the day-to-day ED, among multiple patients with infection and also with other diagnoses that may simulate a severe infection.[4-6] What is not suspected, is not detected, is not classified and, therefore, is not treated early and appropriately. In this way, the septic syndrome would have a clear path to progress to advanced and sometimes irreversible stages.[4,5]

In this global scenario, the ED and out-of-hospital emergency services (OH-EMS) represent a key link in the care of patients with severe infection, those with sepsis criteria, suspected bacteremia, in special situations such as the immunosuppressed, the elderly, relevant comorbidity, etc., since it is here that clinical suspicion is made, appropriate microbiological samples are taken, and immediate and appropriate treatment should be started for each patient. All this will largely determine the clinical evolution of the patient.[2,7] Thus, it is understood that EMs need guidelines that are more focused on the initial stages of sepsis, which quantitatively represent many more patients in whom early and appropriate action can prevent the appearance of organ dysfunction or reverse it, while at the same time preventing the patient from progressing to septic shock and multiorgan dysfunction.[4,7-11]

Recently, in the framework of the WCEMS 2022 (33rd World Congress of Emergency Medicine held in March 2022 in Guadalajara-Mexico), the SSC Guide 2021 has been reviewed and analyzed from the EP perspective. The experts who carried out this task and reached consensus on some of the key points that are of most interest and concern to EPs today have produced this document. Its main objective is to constructively analyze ten of the key points and recommendations of the SSC 2021 to complement them with arguments and proposals from the experience, evidence, and perspective of emergency medicine. Secondarily, it is also intended to be the starting point for the development of guidelines for detecting, preventing progression, and caring for patients with severe infection and sepsis in the emergency department, which is the goal of what the EP is already known as the Declaration of Guadalajara.[11]

Considerations on some key points of the Surviving Sepsis Campaign 2021

1.- Historical overview: from the first consensus on sepsis definitions (Sepsis-1) to the Surviving Sepsis Campaign 2021 guidelines and the Declaration of Guadalajara (2022)

If we look back, we can see a path that has been carved out since the publication of the recommendations that led to the first consensus document on the definitions of sepsis (Sepsis-1),[12] in 1991. Subsequently, in October 2002, at the annual meeting of the ESICM (European Society of Intensive Care Medicine), the SSC published the Barcelona Declaration[13] in which three scientific societies (the ESICM itself, the International Sepsis Forum, and the SCCM -Society of Critical Care Medicine-) participated. This declaration describes a plan whose main objective would be to achieve a 25% reduction in mortality from severe sepsis by 2009.[13]

In 2003, the agreements of the second conference on the definitions of sepsis (Sepsis-2) were published.[14] And, consecutively, the first SSC guidelines were published in March 2004.[15] Among the 11 societies or organizations that endorse the recommendations, the American College of Emergency Physicians (ACEP) is in-

Table 1. qSOFA criteria

Respiratory rate ≥ 22 breaths per minute
Altered consciousness with Glasglow Coma Scale score ≤ 14 points
Systolic blood pressure ≤ 100 mmHg

qSOFA: quick Sepsis-related Organ Failure Assessment. Table adapted from reference 3.

cluded. Along the same lines, in 2008[16] and 2013,[17] the second and third editions of the SSC guidelines were published, as an update of the previous ones, where we observe the clear leadership of the SCCM and the ESICM, together with the inclusion of more scientific societies (mostly intensive care medicine), as well as the Latin American Sepsis Institute.

In early 2016, the Sepsis Definitions Working Group published updated definitions of sepsis and septic shock (Sepsis-3),[3] with an obvious conceptual and scenario change. That document introduced the concept of qSOFA (quick Sepsis-related Organ Failure Assessment).[3] This synthesized scale (Table 1), which does not require laboratory testing and can be performed quickly at triage, was created for the identification of patients at risk for sepsis mortality outside the intensive care unit (ICU).

Precisely, the 2016 SSC guideline was being developed when the new Sepsis-3 definitions were published that changed the conceptual scenario that existed until then with the Sepsis-2 definitions. However, in the studies used to establish the evidence for the 2016 SSC guidelines,[18] the patient populations were mainly characterized by the Sepsis-1 and Sepsis-2 definitions. Hence, they are considered as a transitional stage until the final version of the SSC in 2021.

After all this progress, the fifth edition of the SSC was published in November 2021.[1,2] On this occasion, 23 organizations endorsed its guidelines, following the path marked since the 2004 SSC. Although ACEP subscribes to them, of the 60 authors, only one shows, in second place, an affiliation related to emergency services.[1,2] This fact is striking since, among others, FLAME (Latin American Federation of Emergency Medicine) and EUSEM (European Society of Emergency Medicine), which bring together most Latin American and European EMs, do not appear in this list and are not represented.[1,2]

Among the main 93 explicit recommendations contained in the SSC 2021, there are some on the identification and initial management of the patient with suspected sepsis. Specifically, the first 9 recommendations refer to the emergency department, which we have adopted in the ED as a nod to EPs. Remarkably, in recent years some scientific evidence has emerged from ED-based studies that we believe could complement the recommendations of the SSC 2021 guidelines.[1,2,4,11]

Nowadays, there is a stream of guidelines and recommendations that are multidisciplinary in nature. However, we believe it is necessary to include the "order of chaos" perspective of an emergency specialist: it is necessary to identify patients with infection among many others and, in addition, to stratify and identify those with the worst prognosis from triage, in order to implement the appropriate package of measures required by each patient.[19]

For this reason, FLAME, SEMES (Spanish Society of Emergency Medicine) and the LATINFURG (Latin American Working Group for the improvement of the care of patients with infection in the ED) believe that it is necessary in the area of emergency medicine, as has been done with great success on other occasions,[20] to develop, with the collaboration of other specialists involved to ensure continuity of care, guidelines aimed at detecting, preventing progression and caring for patients with severe infection and sepsis in the ED.11 In short, to follow the roadmap of the Declaration of Guadalajara.

2.- Epidemiology and relevance of severe infection in the emergency department

The incidence of infectious processes in the ED had already increased significantly before the COVID-19 pandemic to account for around 15-20% of daily attendances in 2019 in Spain and even up to 35% in different Latin American countries.[4,21] But, in addition, in the years 2020-2021, due to the impact of SARS-CoV-2, these figures may have risen during certain months to 50-80%.[22]

In turn, the severity of their clinical presentation (those who meet sepsis criteria, patients with relevant comorbidity, neutropenic and immunocompromised, elderly, suspected bacteremia, among others) and the mortality recorded in the short term (30 days) have also increased in the last decade.[2,4,18,18,23,24] Even during the last year, where EDs have been impacted by the COVID-19 pandemic, both these patients and those treated for bacterial infection have increased their admission rate, the need for intensive care and short-term mortality.[4,21,22]

The incidence and prevalence of sepsis depend on the definitions and registries used in each center, region, or country, which explains why very different data are reported, ranging from 6-10% to 25-30% of sepsis among all patients treated for infectious processes in Spain and Latin America, respectively. Furthermore, it is well known that there is a general medical underdiagnosis of sepsis and in the ED, which has been estimated to affect at least 50% of cases of sepsis and around 25% in episodes of septic shock.[4,20,21,25]

More than half of the cases of sepsis come from the community and are treated in the ED itself. On the other hand, up to 60% of all patients diagnosed with septic shock admitted to the ICU come from the ED.[1,4,8] In general, the most frequent foci or infectious processes treated in the ED are similar in Latin American countries: respiratory infections, urinary tract infections (UTI), abdominal infections (AI) and skin and soft tissue infections (STEMI). Pneumonia, the most frequent source of sepsis, is ranked first, ahead of AI and UTI.[4,21]

In the initial evaluation of all these patients, in the ED itself, samples are taken for the different microbiological studies in up to 45% of cases. Among these, blood cultures (BC) predominate, which are taken in 14.6% of all patients seen with suspected infection in the ED, followed by urine culture (14.3%).[4,20,21,24,26]

Mortality in patients diagnosed with infection/sepsis 30 days after ED care is around 10-12% and, when the criteria for septic shock are met in the ED, it rises to 25-50%.[4,20,21,27] This is related to the severity of the clinical situation (existence of sepsis/septic shock), the type of primary focus (urinary, respiratory, abdominal, nervous system, unknown), the coexistence of bacteremia and the characteristics of the patients (age, comorbidity, particular situations, etc.).[4,21,24]

All this reveals the quantitative and qualitative importance of infection and sepsis in the ED, and the relevance of these devices in their evolution and prognosis, since it is where the clinical suspicion, the collection of timely microbiological samples and the initiation of immediate and appropriate treatment are made, which will largely determine the clinical evolution of the patient.[4,20,26]

3.- Program for early detection of sepsis (triage)

SSC 2021 recommends the use of a program to improve the early detection and treatment of sepsis. Such programs may consist of manual methods or automated use of the electronic medical record. This is a strong recommendation with moderate-quality evidence for screening.[1,2]

Currently, triage systems are essential for the classification and prioritization of patients in the ED and EMS, both in general hospitals that treat all types of patients, as well as those that treat selected populations (mother and child hospitals, oncology, neurological or trauma centers, etc.). In all of them, tools should be implemented that can perform adequate screening and activate alerts to provide diagnostic and therapeutic opportunities for patients, especially in time-dependent diseases such as sepsis, whose prognosis and evolution depend on the correct classification and care in the ED.[4,28]

These tools should be based on the identification of the infectious syndrome and different cardinal alarm data that guide the EPs to detect those patients who require more urgent attention.[19]

When the patient arrives at the ED, only the anamnesis and physical examination with vital signs are available, so clinical identification of a possible infectious process should be a priority. For this purpose, the combination of scales already validated in the ED together with the clinical judgment of the EPs is the strategy that has shown the best results to achieve an adequate diagnosis and to be able to initiate timely treatment packages.[4,24,26,28]

The use of screening programs (manual or automated) has been associated with improved adherence to sepsis care packages along with reduced mortality, with ORs of 0.66 (95% CI 0.61 to 0.72) in patients with sepsis and septic shock.[29]

In turn, automatic electronic systems (AES) achieve a sensitivity of 81% (95% CI: 80-81%) and specificity of 72% (95% CI: 72-72%), and manage to predict sepsis 3-4 hours before its onset, above the SIRS (Systemic Inflammatory Response Syndrome), MEWS (Modified Early Warning Score) and SOFA (Sepsis-related Organ Failure Assessment) criteria.[30]

However, in this last meta-analysis referred to in SSC 2021, only studies performed in ICUs are included, where laboratory analysis, monitoring of vital signs over time and assessment of comorbidities are already available. But they have not been evaluated with ED patients.[30] Furthermore, it should be considered that the AES are dependent on the information incorporated by the users (healthcare personnel) so that errors could occur that are recalibrated according to the quality and volume of the information incorporated into these automatic algorithms that may (or may not) learn from themselves and the feedback provided by the user.[31] So, if the diagnosis or coding by the AES is not correct, false alarms (overdiagnosis) will be triggered. It can also fail if the personnel receiving the information do not report it quickly enough to initiate treatment, or because of the so-called "alarm fatigue", which is explained by a significant increase in the number of alerts or false alarms, leading to less attention to real alarms.[32]

For all these reasons, from the perspective of EP in the ED, it is still difficult to have databases available for the management of acute diseases, which in most cases require immediate intervention. The diagnosis, selection and classification of patients always depends to a large extent on the correct clinical interpretation and the use of scales combined with different biomarkers (BM) that have demonstrated a positive impact on their prognosis.[4,24,26]

In summary, in the case of the ED, the first bundle should begin at triage with a screening strategy to identify the patient with sepsis and stratify its severity in order to favor the treatment and transfer of these patients to the ICU, as well as to establish a control system during the wait in the ED (known as retriage) that allows the patient to be reevaluated if alarm signs or data appear.[4,27-29]

4.- Complexity of the identification of patients with infection in the ED

The diagnosis of patients with sepsis in the ED has multiple barriers. Today it is considered by all, including the SSC 2021, a difficult challenge.[1-4] Although in most of our countries the diagnosis is established mainly by clinical suspicion, there are increasingly more tools available that can help the EP.[1,2,4,23] In addition, there are situations and risk factors for severe infection, such as advanced age, recent post-surgical states, wounds or skin lesions, immunosuppression states, cancer patients, diabetes mellitus, HIV infection, etc., where clinical signs and symptoms are less expressive and more variable, making it more difficult to establish the diagnosis of suspected sepsis.[4,33]

Likewise, the presence of fever (as a pathophysiological response reflecting the activation of the immune system by the pathogen) may or may not be present, especially at extreme ages of life and in immunocompromised individuals.[34]

It is very important to identify the patient with sepsis to address it immediately and prevent it from progressing to a more severe stage. Using the SIRS criteria, qSOFA, both or other early warning scales with the inclusion of other clinical and BM parameters from triage are, nowadays, the basis of suspicion and the preferred strategy in the ED. Table 2 shows different predictors of severe infection, bacteraemia, sepsis and mortality in patients seen in the ED for infection studied in the last 2 years by INFURG-SEMES and GT-LATINFURG.

In the authors' opinion, the existence of specific education and training of emergency physicians (more and better in the EDs of countries where this specialty exists), the adaptation of a triage system,[28] the existence of sepsis EDs,[29-32] and greater human, diagnostic (for example, the availability of BM), material and organizational resources (that can overcome the pressure of care and saturation of the ED) would facilitate the early detection of patients with sepsis and limit under-diagnosis.[4]

5.- Usefulness of the definitions for the early detection of patients with sepsis and establishing their prognosis in the emergency department

The SSC 2021 recommends not using the qSOFA scale as the only tool for detecting sepsis in comparison with other scales or criteria such as SIRS, NEWS (National Early Warning Score) or MEWS. This is a strong recommendation with moderate quality evidence.[1,2]

In February 2016, the Sepsis-33 definitions were published. This consensus defined sepsis as "organ dysfunction caused by an abnormal host response to infection that poses a threat to survival," with an associated mortality of 10%. In turn, the term septic shock came to define those situations of sepsis where circulatory, cellular and metabolic abnormalities were so pronounced as to increase mortality considerably, up to 40%.[3] And it was clinically identified by the need for vasopressors to maintain a mean arterial pressure (MAP) ≥ 65 mmHg and by presenting a serum lactate ≥ 2 mmol/l despite adequate volumic replacement.[3] Another concept introduced is qSOFA as a quick tool to be used in triage, since it does not require laboratory tests (Table 1). In practice, when two of its criteria are present simultaneously, the patient is considered to have positive qSOFA (and suspected sepsis). However, no analysis was performed to support its use as a screening tool or confirmed diagnosis of sepsis.[37] Thus, much controversy arose over the effectiveness of the qSOFA scale in identifying patients with sepsis or severe infection in the ED. This has led multiple meta-analyses to compare the accuracy of the qSOFA and the SIRS criteria in the initial evaluation of patients with suspected infection,[6,36-40] with discrepant results that could be

Table 2. Factors and predictors of severe infection, bacteremia, sepsis and mortality in patients attended in the emergency department for infection studied by INFURG-SEMES and GT-LATINFURG

Criteria or variables	qSOFA	SRIS	NEWS-2	MEWS	5MPB-Toledo	MPB INFURG-SEMES	Other*
Consciousness alteration (ECG ≤ 14 points or with AVPU system)	X		X	X			X
Systolic blood pressure ≤ (90 or 100 mmHg)	X		X	X			X
Respiratory rate ≥ (20 or 22) breaths per minute	X	X	X	X	X	X	X
Heart rate ≥ (90) beats per minute		X	X	X			X
Temperature (≥ 38.3ºC or < 36ºC)		X	X	X	X	X	
Leukocyte count (≥ 12 000/mm³ or 4000/mm³) or young-fallen forms (> 5 or 10%)		X			X	X	X
Platelet count (< 100 000/mm³ or 150 000/mm³)						X	
Charlson index ≥ 3 points					X	X	X
Barthel Index ≤ 60 points							X
Shivering/chills						X	
Oxygen saturation			X				
Procalcitonin ≥ 0.51 ng/ml					X	X	X
Lactate ≥ (2 or 3 or 4) mmol/l							X
suPAR ≥ (3 or 6) ng/ml							X
MR-pro-ADM ≥ (1.5 or 2) nmol/l							X

INFURG-SEMES: Infection Working Group of the Spanish Society of Emergency Medicine. GT-LATINFURG: Latin American Working Group for the improvement of the care of patients with infection in the Emergency Department. ECG: Glasgow Coma Scale; AVPU: Alertness, Voice Response, Pain Response and No Response. qSOFA: quick Sepsis-related Organ Failure Assessment (Reference 3).SIRS: systemic inflammatory response syndrome (Reference 12). NEWS-2: National Early Warning Score-2 (Royal College of physicians. National Early Warning Score (NEWS)2: Standardising the assessment of acute-illness severity in the NHS. Updated report of a working party. London: RCP; 2017.). The score varies according to the recording of each physiological parameter. From 5 points sepsis should be suspected and urgent response and care given and from 7 points an immediate response with continuous monitoring. MEWS: Modified Early Warning Score (Subbe CP, Kruger M, Rutherford P, Gemmel L. Validation of a modified Early Warning Score in medical admissions. QJM. 2001;94:521-6). The score varies according to the recording of each physiologic parameter. Scores ≥ 4 are associated with increased risk of death, admission to intensive care, and need for urgent care.
5MPB-Toledo: Toledo Bacteremia Prediction Model (References 56 and 57). MPB-INFURG-SEMES: INFURG-SEMES bacteremia prediction model (Reference 58). suPAR: soluble urokinase-type plasminogen activator receptor (References 44,45,60,61). MR-pro-ADM: medial region of proadrenomedullin (References 4,42,43,49). Comorbidity: Charlson index (Charlson M, Pompei P, Ales KL, McKenzie CR. A new me- thod of classifying prognostic comorbidity in longitudinal studies: Development and validation. J Chron Dis. 1987;40:373-83). Functional status:Barthel Index (Mahoney FI, Barthel DW.Functional evaluation:The Barthel Index.Md State Med J.1965;14:61-5. *Others: Other INFURG-SEMES studies (References 4,22,24,26,45,46,47,49,50).

related to the heterogeneity of the populations studied. In general, the results show a lower sensitivity of qSOFA (25-43%) with respect to SIRS (75-88%) in relation to the diagnosis of sepsis caused by infection, which could result in a lower capacity for the detection of potentially severe patients in the ED.[36-40]

On the other hand, in relation exclusively to its ability to predict short-term mortality, qSOFA has low sensitivity (60%) and moderate specificity (77%). On the other hand, SRIS has a sensitivity (88%), superior to qSOFA, but with a specificity of only 25%, which would support its use as a screening tool for the detection of patients with possible sepsis and as an indication for initiating treatment.[36-40], neither SRIS nor qSOFA are the ideal tools for ED and both have their limitations.[1-4]

Similar findings have also been found when comparing NEWS-2 or MEWS in relation to predictive ability for mortality.[19,41] SCC 2021 notes that although the presence of a positive qSOFA should alert the physician to the possibility of sepsis, given the low sensitivity of qSOFA, the panel issued a strong recommendation against its use as a single screening tool.[1,2] But, it does not do so because of its low ability to predict bacteremia or confirm infection in the patient with qSOFA ≥ 2.[1,2] It does so because only 25% of patients with qSOFA ≥ 2 detected in the ED had an infectious process.[1,4,35]

In this scenario, many EMs have been trying for years to find a definition that achieves optimal sensitivity and specificity both for early detection (diagnosis) and for risk stratification and mortality (prognosis), allowing the clinician to establish rapid action in the ED.[1,4,6,26,36-40,44] The first definitions (Sepsis-1 and Sepsis-2) conditioned diagnosis on the presence of a physiological response to different aggressions (SIRS) and the suspicion or demonstrated presence of an infection.[12] These definitions were confirmed as being quite sensitive but not very specific.[12,14] This fact justified the need for the appearance of the Sepsis-3[3] consensus, which stipulated organ damage as the central axis of the new definition of sepsis and, therefore, the probability that the patient would die.[3] In this sense, today the use of one or other scales as a definition of sepsis, or their combinations, is very variable in the ED and there is no clear consensus.[23] In this search, different proposals are being studied with criteria and variables that are easily obtainable in the ED. For years, combinations have been postulated with the variables of the scales that are usually used (SIRS, qSOFA, NEWS-2, MEWS)[19,40] together with BM with proven results (lactate and procalcitonin-PCT)[44-46] and others that are very promising, although not usually available in the ED (proadrenomedullin, suPAR, pre-sepsin, IL-6, IL-8).[45-49] Table 2 shows the variables included in different INFURG-SEMES and GT-LATINFURG studies with the highest probability of integrating future sepsis defining criteria that meet diagnostic and prognostic objectives. All in all, nowadays the joint and synergic use of scales and BMs is recommended for the initial assessment of patients in EDs with suspected infection. Among these, those known as BM for the diagnosis of bacterial infection, bacteremia and sepsis (PCT at the forefront) and those that achieve the best prognostic performance, especially lactate.[4,24,26,42-50] Thus, based on the results obtained and validated with ED patients, the following strategy can currently be recommended[24,26]:

1) For the diagnosis of severe infection-sepsis, the combined SIRS ≥ 2 model plus PCT0.51 ng/ml.[26]

2) To assess mortality risk, clinical severity and need for more intensive care, the qSOFA ≥ 2 plus lactate ≥ 2 mmol/.[26,50]

6.- Lactate measurement in the emergency department

SSC 2021 suggests measuring blood lactate for adults with suspected sepsis. This is a weak recommendation with low quality evidence.[1,2]

Lactate is considered the best marker of hypoperfusion and tissue hypoxia, it is quick and inexpensive to obtain and is included in all recommendations for the evaluation of patients with sepsis in the ED.[4,42] It is also one of the three criteria for septic shock according to the definition in Sepsis-3[3]. In countries such as Spain or the USA, the availability of lactate measurement in the ED is practically 100%.[4,23] However, different studies have reported its limited availability in hospitals in other countries, where access to this resource is only 5 to 35% of the centers.[51] For all these reasons, its early evaluation is recommended, with rapid results obtained after its extraction (in analytical systems at the patient's bedside -point of care- or in the ED laboratory immediately) in patients with suspected or diagnosed sepsis after arrival at the ED, even without hypotension.[1-4,26,42,44] The unavailability of lactate in different centers should not cast doubt on its indication, but should be the driving force to demand its availability in all EDs.[4,23]

Furthermore, the same SSC 2021 guidelines refer to a low level of evidence quality on the use of lactate to conduct resuscitation from the ED.[1,2] However, EDs are accustomed to using lactate clearance and its serial measurement both to guide resuscitation and to assess the clinical evolution and prognosis of the patient.[4,26,42,44,52,53] Recently, several articles have confirmed the usefulness of lactate assessment (even more so in combination with other BM and scales) in the ED in patients with severe infection and sepsis.[4,26,50,52-54]

In summary, we consider lactate measurement essential both in the first evaluation of the patient in the ED and in decision making, as well as to estimate prognosis and to use it as a guide for resuscitation and evolution of the patient's situation in the ED.

7.- Procalcitonin as an aid to indicate antibiotherapy in the ED

SSC 2021 recommends for adult patients with suspected sepsis or septic shock not to use PCT plus clinical assessment to decide when to start antimicrobials, compared to clinical assessment alone. This is a weak recommendation with very low-quality evidence.[1,2] In

this regard, given the controversies that exist,[1,2,4,42,55] the authors make different considerations regarding the use, interpretation, and usefulness of PCT in the ED:

– The clinical manifestations of infectious processes are often nonspecific, making early recognition difficult. are often nonspecific, which makes early recognition difficult. In addition, the criteria for sepsis (as discussed in point 5) are non-specific and common with other viral infections, non-infectious inflammatory conditions, and other acute illnesses. The WBs have proven to be helpful tools for the clinician to improve diagnosis (and therefore the correct treatment of the infection) and risk stratification and prognosis (and thus facilitate and advance urgent decision making).[4,24,24,26,42]

– It is essential to know the kinetics of PCT after bacterial insult and how it can help, match or surpass clinical assessment in different situations in the ED in its ability to predict a confirmation of bacterial infection, bacteremia and sepsis.[4,24,26,42,56-58]

– Pathophysiologically, elevated PCT values reflect the degree of immune response and activation of the inflammatory cascade, which translates into a systemic inflammatory response, following pathogen recognition.[4,24,26,42]

– The request for PCT in the ED should in no way replace the evaluation of the clinical history, examination, medical judgment and request for the microbiological tests considered appropriate in each case.[42,43] It should always be considered as a tool to assist in the clinical and diagnostic evaluation as referred to in the SSC 2021.[1,2,42] Each patient must be individualized and be aware of the false negative situations and limitations that PCT may have. Therefore, it should be remembered that a negative PCT value does not exclude bacterial infection or sepsis and, in these situations, antimicrobials should be administered according to the recommendations set out in the next section.[1,2,42]

– In the case of suspected bacteremia by the results of the combined SRIS $\geq$ 2 plus PCT $\geq$ 0.51 ng/ml model[26] or by applying a predictive model of bacteremia for EDs (5MPB-Toledo or MPB-INFURG-SEMES Model),[24,56-58] blood cultures should be drawn and antimicrobials administered.

Therefore, in the opinion of the GT-LATINFURG, in the initial clinical assessment of the patient with suspected infection, the determination of PCT is recommended to support the clinical suspicion of bacterial infection, the possibility of bacteremia and to guide the initiation of antibiotherapy. However, the possibility of false negative PCT results should always be considered and the administration of antibiotherapy with low PCT results should be evaluated (especially in immunocompromised, elderly, patients with comorbidity, etc.).[1,2,42] The usefulness of the BM as an aid in the diagnosis, prognosis and adequacy of antibiotic treatment and support is unquestionable, so it is now recommended, along with the initial analysis (sepsis profile),[4] the universal availability and assessment of lactate and PCT in all patients with suspected severe infection-sepsis in the HED.[4,24,26,42]

8.- Administration of the first doses of antibiotics in the emergency department

SSC 2021 recommends:

– In adults with suspected, unconfirmed sepsis.

In adults with unconfirmed suspicion of sepsis, "continually reassess and rule out alternative diagnoses", so that if another disease is confirmed, it is recommended to discontinue empirical antimicrobial therapy. This is a "best practice" recommendation.[1,2]

– In adults with possible, probable, or confirmed septic shock, administer antimicrobial therapy within one hour. This is a strong recommendation with low quality evidence.[1,2]

– In adults with high probability of sepsis, without shock, administer antimicrobial therapy within one hour. This is a strong recommendation with very low-quality evidence.[1,2]

– In those where sepsis is possible, but not confirmed, continue to investigate to try to confirm the diagnosis and within 3 hours decide, if there is concern about the possibility of infection, to administer antibiotics or continue to monitor the patient. These are weak recommendations with very low-quality evidence.[1,2]

After the first care of the patient and having overcome the challenge of the diagnosis of infection-sepsis, together with the indication of the initial measures to stabilize the patient (fluid therapy), it becomes an absolute priority to administer the first doses of appropriate antimicrobials early in the ED, which will determine the evolution of the patient in severe processes.[1-4,55,59] In this sense, early antimicrobials and control of the focus, for example surgical, are decisive for the patient's prognosis.[55,59] Therefore, centers should generate organizational circuits so that antibiotics are immediately available at the request of the emergency physician when indicated, 24 hours a day in all centers, since multiple studies have shown that the administration of the first dose of the appropriate antibiotic in a window of time between the first and third hour after the establishment of the septic syndrome, even without microbiological confirmation of the infection, is relevant and can prevent progression to septic shock or situations of organ dysfunction caused by the effects of the inflammatory response.[55,59-61]

In addition to the door-to-antimicrobial time (early administration) and that these are indicated, because it is really a bacterial infection, the chosen regimen (whether empirical or targeted) should be appropriate or adequate according to the focus and the possible pathogen.[55,62,63] Unfortunately, in this regard, it has been documented that up to 40-50% of the prescriptions in the ED are erroneous or inadequate according to the reference guidelines (use of antibiotics without indication, inappropriate choice of empirical antimicrobial, wrong dosage, delayed time of administration).[4,55,62,63] However, on all other occasions, in addition to being the guarantee of better patient outcome, it is found that the regimen is not changed on the hospital ward or in the ICU.[55,64] It is therefore necessary to

increase adherence to local empirical guidelines, within programs for optimizing the use of antimicrobials (PROA) in the ED, and for the ED physician to actively participate in the multidisciplinary groups (infection committees, PROA, sepsis teams, etc.) that exist in each center.[4,55,63]

To improve the choice and development of the antimicrobial regimen, the GT-LATINFURG adheres to the "4-D" strategy for the selection of the correct antimicrobial for each case:[64] drug, dose, duration and discontinuation (Table 3). On the one hand, it is always necessary to individualize according to the characteristics of each patient and his or her situation (evaluation of possible allergies, renal insufficiency, assessment of the possibility of multidrug-resistant pathogens) and periodically re-evaluate the situation, and on the other hand, although the most important initial premises in the ED are the appropriateness of the indication and the time of administration in the first hour or in the 3-hour window according to the recommendations indicated at the beginning of this section,[1,2,55] the 4 Ds are important both for continuity of care and in those situations where they have to be applied. The latter include patients who remain under observation for 24 hours, 1-3 days in short-stay units dependent on the ED, or for organizational reasons or due to saturation of the centers that cause some patients to be discharged from the ED without having been admitted.[55,62,64]

9.- Considerations on immediate resuscitation in the emergency services

The SSC 2021 recommends in turn:

– Treatment and resuscitation should begin immediately. This is a "best practice" recommendation.[1,2]

– For hypoperfused patients it suggests that at least 30 ml/kg of intravenous crystalloid fluids be administered within the first 3 hours of resuscitation. This is a weak recommendation with low quality evidence.[1,2]

– For adults with sepsis or septic shock, he suggests using dynamic measures to guide fluid resuscitation in addition to physical examination and static parameters. dynamic measures to guide fluid resuscitation in addition to physical examination and static parameters. This is a weak recommendation with very low-quality evidence.[1,2] Dynamic parameters include response to a passive leg elevation or fluid bolus, using systolic volume (SV), systolic volume variation (SVV), pulse pressure variation (PPV) or echocardiography, when available.

– For adults with sepsis or septic shock, it suggests guiding resuscitation to decrease serum lactate in patients with elevated initial concentrations, once the clinical context has been interpreted. This is a weak recommendation with low quality evidence.[1,2]

– For adults with septic shock, it suggests using capillary refill time as an adjunct to other measures of perfusion assessment to guide resuscitation. This is a weak recommendation with low quality evidence.[1,2]

For an adequate hydric resuscitation, different aspects must be considered globally:

– The quantity of fluids to be administered, the response to the infused volume to prevent fluid overload and possible side effects such as capillary leakage and consequent hypoperfusion, pulmonary edema and secondary hypoxia, etc.[64,65]

– The appropriate type of solutions should be selected depending on the different stages of resuscitation in which the patient is found.[65,66]

– Some studies have already pointed out that the goal of 30 ml/kg in the first 3 hours proposed by SSC 2021[1,2] may be inadequate and associated with increased mortality.[51] Therefore, one of the hemodynamic goals is to try to optimize cardiac output with the minimum necessary amount of intravenous fluids provided in total (understood as the sum of loads, "maintenance" solutions, drug infusions, nutrition, etc.) during the initial resuscitation.) during initial resuscitation, with the goal of normalizing mean arterial pressure, heart rate and capillary refill, microhemodynamic parameters that in early stages of sepsis and septic shock correlate closely with what is happening at the microhemodynamic level.[67]

Based on the above, we agree that resuscitation should begin immediately[1,2] and for patients with hypoperfusion that at least 30 ml/kg of intravenous crystalloid fluids should be administered within the first 3 hours of resuscitation, assessing the dynamic parameters and with the essential aid of bedside ultrasound, which is nowadays performed by emergency physi-

Table 3. Four D's for selection of the appropriate antimicrobial

Four D	Action	Consideration
Drug	Inappropriate therapy	Drugs that may aggravate pre-existing organ dysfunctions.
	Appropriate therapy	Appropriate empirical choice, considering local epidemiology and possible risk factors for resistant pathogens.
	Therapeutic combination	Possible synergistic effects, broader spectrum, less induction of resistance or toxicity.
	Appropriate timing	Preferably in the first hour (septic shock and sepsis) with a window up to 3 hours (suspected sepsis).
Dose	Pharmacokinetics	Volume of distrubution, clearance, protein binding and penetration to infected tissue (focus).
	Pharmacodynamics	Drug time-dependent, concentration-dependent, maximum peak.
	Toxicity	Adjustment to renal, hepatic function, renal replacement therapy or others.
Duration	Appropriate duration	Choice of short guidelines if validated.
	Response time	Assessment of resolution of infectious syndrome and microbiological eradication.
Discontinuation	Monitoring	Taking of cultures and biomarkers of therapeutic response.

Adapted from reference 64.

cians.[65-67] Similarly, it should be assessed for adults with sepsis without hypotension but hyperlactacidemia, and in them resuscitation should be oriented to decrease serum lactate in patients with elevated initial concentrations (once each clinical context has been interpreted).[1,2,55]

The absence of volume response in patients with low cardiac output may be an indication to initiate vasopressors or inotropics, with the same macro- and microhemodynamic therapeutic goals: improve oxygen and nutrient delivery to tissues, optimize preload, contractility and afterload while having a positive impact on perfusion.[1,2,65,68] There is little discussion about which drugs should be used. Noradrenaline remains the first choice and most used, followed by vasopressin, adrenaline, dobutamine, and others.[1,2]

In this regard, the debate should focus on the appropriate time for initiation, since there is evidence that early vasopressors, even administered peripherally, have beneficial effects by requiring less intravenous fluid intake, fewer hours of hypotension, and less duration and total dose of vasopressors, among other effects.[68] Thus, vasopressors can, and probably should, be initiated at the same time as volume response assessment and fluid resuscitation.[68-70] This aspect should be specified in future guidelines.

10.- Regarding the indication for admission to the intensive care unit to be effective within 6 hours

The SSC 2021, for adults requiring admission to the ICU with septic syndrome, suggests that admission should be effective before 6 hours. This is a weak recommendation with low quality evidence.[1,2]

Sepsis can progress and evolve to septic shock and, in a significant percentage, finally to the patient's death.[1,2] Of the patients seen in the ED for hemodynamically stable sepsis, 17.8% progress to hemodynamic instability in the following 72 hours, with an increase in mortality to 30.8% in the next 72 hours. hemodynamically stable sepsis, 17.8% progress to hemodynamic instability within 72 hours, with an increase in 30-day mortality from 3.1% to 13.1%, respectively.[71] Therefore, it is essential to identify this subgroup of patients with hemodynamic essential to identify this subgroup of patients to achieve both immediate treatment and faster transfer to the ICU.[4,72] Late admissions of patients from the ED are associated with decreased compliance with established bundles of measures and increased mortality, ICU and hospital length of stay.[72,73]

For all these reasons, we should reflect on and propose solutions to the causes of the delay in the transfer of patients with sepsis/septic shock to the ICU. Given that there may be multiple causes and that there are no exact realities, each center should be analyzed individually. Among the various reasons, there are likely to be a lack of early detection, lack of adequate communication, overcrowding and collapse of the emergency departments and possible lack of ICU beds.[1,2,4,74-76]

Discussion and conclusions

Having reviewed and commented on the ten key points of the SSC 2021 considered by the authors (Table 4) in relation to the care of patients with severe infection or sepsis in the ED, different proposals have been identified for improvement or resolution by the WG-LATINFURG. Table 4 summarizes some strategies or recommendations to be adopted for HEDs that are valid for any setting and reality in Latin America. These should be modulated according to the local characteristics and possibilities existing in each setting, but in all cases with the same objective: to try to overcome the existing deficits, barriers, and controversies in order to improve the care of patients with severe infection and sepsis as much as possible.

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References

1 Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. Crit Care Med. 2021;49:e1063-e1143.
2 Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. Intensive Care Med. 2021;47:1181-247.
3 Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016;315:801-10.
4 Julián-Jiménez A, Supino M, López Tapia JD, Ulloa González C, Vargas Téllez LE, González del Castillo J, et al, en nombre del Grupo de Trabajo Latinoamericano para la mejora de la atención del paciente con Infección en Urgencias (GT-LATINFURG). Puntos clave y

Table 4. Summary of the considerations or proposals from the WG-LATINFURG in relation to the 10 key points or recommendations made by the Surviving Sepsis Campaign of 2021

1.	Elaborate guidelines aimed at detecting, preventing progression and caring for patients with severe infection and sepsis in the ED with the collaboration of the other specialists involved (multidisciplinary) to guarantee continuity of care. In this way, follow the roadmap set out in the Guadalajara Declaration.
2.	To show the quantitative and qualitative importance of the impact of infectious processes, sepsis and bacteremia in the ED, as well as the impact of the ED on the evolution and prognosis of the patient. To highlight the importance of early and adequate care in the ED to avoid the progression of the patient with sepsis to septic shock, from infection without SIRS to sepsis and the prediction of bacteremia.
3.	In the opinion of the authors, the existence of specific education and training of emergency physicians (more and better in the EDs of countries where this specialty exists), the adaptation of a triage system and the existence of sepsis EDs, as well as greater human, diagnostic (for example, the availability of BM), material and organizational resources (which can overcome the pressure of care and saturation of the ED) would facilitate the early detection of patients with sepsis and limit underdiagnosis.
4.	In the case of the ED, the first bundle should begin at triage with a screening strategy to identify the patient with sepsis and stratify its severity in order to favor the treatment and transfer of these patients to the ICU, as well as to establish a control system during the wait in the ED (known as retriage) that allows the patient to be reevaluated if alarm signs or data appear.
5.	Until the validation of a single diagnostic and prognostic prediction model for the patient with severe infection-sepsis, the combined scales strategy is recommended: 1) For the diagnosis of severe infection-sepsis the combined SRIS plus PCT model. 2) To assess the risk of mortality, clinical severity and need for more intensive care, the qSOFA plus lactate model.
6.	Lactate measurement is considered essential both in the first evaluation of the patient in the ED and in decision making, as well as for estimating prognosis and using it as a guide for resuscitation and evolution of the patient's situation in the ED. Therefore, it should be available in all EDs, since its assessment is recommended in all patients with severe infection-sepsis in an early manner with rapid results after extraction (either point of care in triage or with rapid laboratory results).
7.	The determination of PCT is considered and recommended to support the clinical suspicion of bacterial infection, the possibility of bacteremia and to guide the initiation of antibiotherapy, in the initial clinical evaluation of the patient with suspected infection in the ED. However, the possibility of false negatives of PCT should always be considered and the administration of antibiotherapy should be evaluated even with low PCT results. Consider PCT as a helpful tool that should be available in all EDs.
8.	In case of possible severe infection, sepsis (with and without shock) or well-founded suspicion of bacteremia, administer the first dose(s) of antimicrobial(s) in less than one hour. In case of suspicion of infection but not of sepsis, bacteremia or other serious factors, first rule out other acute diseases and try to confirm the possible infectious process with the appropriate tests in order to administer the antimicrobials within 3 hours. In addition, when necessary, perform control of the focus (e.g. surgery) within 6-12 hours.
9.	Consider the amount of fluids to be administered, the appropriate type of solutions depending on the different stages of resuscitation, optimize cardiac output with the minimum necessary amount of intravenous fluids to be given in total during the initial resuscitation, with the aim of normalizing MAP, heart rate and capillary refill. Consider early vasopressors (norepinephrine), even to initiate at the same time as volume response assessment and fluid resuscitation. And use bedside ultrasound and lactate serialization to guide the administration of appropriate fluid therapy in each case.
10.	Each center should reflect on and propose solutions to the causes of the delay in patient transfer to the ICU. There are multiple reasons for this delay: lack of early detection, lack of adequate communication between specialists, saturation and collapse of the ED and possible lack of beds in the ICU, among others.

GT-LATINFURG: Latin American group for the improvement of care of patients with infection in the emergency department; HED: hospital emergency department; ICU: intensive care unit; SIRS: systemic inflammatory response syndrome; qSOFA: quick Sepsis-related Organ Failure Assessment; BM: biomarker; EAS: electronic alert systems; PCT: procalcitonin; MAP: mean arterial pressure.

controversias sobre la sepsis en los servicios de urgencias: propuestas de mejora para Latinoamérica. Emergencias. 2019;31:123-35.
5 Litell JM, Guirgis F, Driver B, Jones AE, Puskarich MA. Most emergency department patients meeting sepsis criteria are not diagnosed with sepsis at discharge. Acad Emerg Med. 2021;28:745-52.
6 Julián-Jiménez A, Supino M, Loro Chero L, en nombre del Grupo de Trabajo Latinoamericano para la mejora de la atención del paciente con Infección en Urgencias (GT-LATINFURG). Hacia la definición de Sepsis-4: poder diagnóstico y pronóstico de los biomarcadores para mejorar el tratamiento de la sepsis en los servicios de urgencias. Med Clin (Barc). 2020;154:147-8.
7 Ang J, Boyle A. Surviving Sepsis Campaign 2021 guideline: fails to appreciate the challenge of evaluating an undifferentiated patient. Eur J Emerg Med. 2022;29:99-100.
8 De Groot B, Jessen MK, Nickel CH. The new 2021 Surviving Sepsis Guidelines: an emergency department perspective may be more effective. Eur J Emerg Med. 2022;29:5-6.
9 De Groot B, Struyk B, Najafi R, Halma N, Pelser L, Vorst D, et al. Inclusion of emergency department patients in early stages of sepsis in a quality improvement programme has the potential to improve survival: a prospective dual-centre study. Emerg Med J. 2017; 34:578-85.
10 Yealy DM, Mohr NM, Shapiro NI, Venkatesh A, Jones AE, Self WH. Early care of adults with suspected sepsis in the emergency department and out- of-hospital environment: a consensus-based task force report. Ann Emerg Med. 2021;78:1-19.
11 Julián-Jiménez A, García DE, González del Castillo J, López Tapia JD. De la guías internacionales "Campaña para sobrevivir a la sepsis 2021" a las guías para "Detectar, prevenir la progresión y atender a los pacientes con infección grave en urgencias" elaboradas por urgenciólogos. Emergencias. 2022;34:471-3.
12 American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Crit Care Med. 1992;20:864-74.
13 Barcelona Declaration. Surviving Sepsis Campaign in the ESICM annual meeting in Barcelona in 2002. (Consultado 13 Abril 2022). Disponible en: https://www.sccm.org/SurvivingSepsisCampaign/About-SSC/History/Barcelona-Declaration
14 Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International sepsis Definitions Conference. Intensive Care Med. 2003;29:530-8.
15 Dellinger RP, Carlet JM, Masur H, Gerlach H, Calandra T, Cohen J, et al. Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. Crit Care Med. 2004;32:858-73.
16 Dellinger RP, Levy MM, Carlet JM, Bion J, Parker MM, Jaeschke R, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. Intensive Care Med. 2008;34:17-60.
17 Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, et al. Surviving Sepsis Campaign Guidelines Committee including the Pediatric Subgroup. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med. 2013;41:580-637.
18 Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. Intensive Care Med. 2017;43:304-77.

19 Arévalo-Buitrago P, Morales-Cané I, Olivares Luque E, Guler I, Rodríguez-Borrego MA, López-Soto PJ. Capacidad predictiva de las escalas de alerta temprana en los servicios de urgencias hospitalarios: revisión sistemática y metanálisis. Emergencias. 2021;33:374-81.
20 León Gil C, García-Castrillo L, Moya Mir M, Artigas Raventos A, Borges Sa M, Candel González FJ, et al. Documento de Consenso (SEMES-SEMICYUC). Recomendaciones del manejo diagnóstico-terapéutico inicial y multidisciplinario de la sepsis grave en el Servicios de Urgencias Hospitalarios. Emergencias. 2007;19:260-72.
21 Martínez Ortiz de Zárate M, González del Castillo J, Julián-Jiménez A, Piñera Salmerón P, Llopis Roca F, Guardiola Tey JM, et al. Estudio INFURG-SEMES: Epidemiología de las Infecciones en los Servicios de Urgencias Hospitalarios y evolución en la última década. Emergencias. 2013;25:368-78.
22 Julián-Jiménez A, García DE, González del Castillo J, Guimarães HP, García-Lamberechts EJ, Menéndez E, et al, en nombre del Grupo de Trabajo Latinoamericano para la mejora de la atención del paciente con Infección en Urgencias (GT-LATINFURG). Puntos clave sobre la COVID-19 en los servicios de urgencias: propuestas de mejora para su atención en Latinoamérica. Emergencias. 2021;33:42-58.
23 Llopis-Roca F, López Izquierdo R, Miro O, García-Lamberechts EJ, Julián-Jiménez A, González del Castillo J. Mapa de la situación actual de la atención a la sepsis en los servicios de urgencias españoles. Rev Esp Quimioter. 2022;35:192-203.
24 Julián-Jiménez A, Rubio-Díaz R, González del Castillo J, Candel González FJ. Nuevos modelos predictivos de bacteriemia en el servicio de urgencias: un paso adelante. Rev Esp Quimioter. 2022;35:344-56.
25 Julián-Jiménez A, Palomo MJ, Laín N, Estebaran J. Nuevas alternativas terapéuticas para la sepsis grave, pero sin olvidar los viejos retos: detección y manejo precoz de los pacientes. Med Intensiva. 2011;35:588-90.
26 Rubio-Díaz R, Julián-Jiménez A, González del Castillo J, García-Lamberechts EJ, Huarte Sanz I, Navarro Bustos C, et al. Capacidad del lactato, procalcitonina y criterios definitorios de sepsis para predecir mortalidad a 30 días, bacteriemia o infección confirmada microbiológicamente en los pacientes atendidos por sospecha de infección en urgencias. Emergencias. 2022;34:182-90.
27 Gorordo Delsol LA, Mérida García JA, López Gómez A. Sepsis: Más allá de la enfermedad. Arch Med Urg Mex. 2014;6;12-6.
28 García-Regalado JF, Arellano-Hernández N, Loría-Castellanos J. Triaje hospitalario. Revisión de la literatura y experiencia en México. Pren Med Argent. 2016;102:233-41.
29 Damiani E, Donati A, Serafini G, Rinaldi L, Adrario E, Pelaia P, et al. Effect of performance improvement programs on compliance with sepsis bundles and mortality: A systematic review and meta-analysis of observational studies. PLoS One. 2015;10:e0125827.
30 Islam MM, Nasrin T, Walther BA, WU CC, Yang HC, Li YC. Prediction of sepsis patients using machine learning approach: A meta-analysis. Comput Methods Programs Biomed. 2019;170:1-9.
31 Kausch SL, Moorman JR, Lake DE, Kiem-Malpass J. Physiological machine learning models for prediction of sepsis in hospitalized adults: an integrative review. Int Crit Care Nurs. 2021;65:103035.
32 Warttig S, Alderson P, Evans DJW, Lewis SR, Kourbeti IS, Smith AF. Automated monitoring compared to standard care for the early detection of sepsis in critically ill patients. Cochrane Database of Systematic Reviews. 2018;6:CD012404.
33 Hunt A. Sepsis: an overview of the sings, symtoms, diagnosis, treatment and pathophysiology. Emerg Nurse. 2019;27:32-41.
34 Holub M, Závada J. Clinical aspects of sepsis. Contrib Microbiol. 2011;17:12-30.
35 Seymour CW, Liu VX, Iwashyna TJ, Brunkhorst FM, Rea TD, Scherag A, et al. Assessment of clinical criteria for sepsis: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016:315:762-74.
36 Hamilton F, Arnold D, Baird A, Albur M, Whiting P. Early Warning Scores do not accurately predict mortality in sepsis: A meta-analysis and systematic review of the literature. J Infect. 2018;76:241-8.
37 Fernando SM, Tran A, Taljaard M, Cheng W, Rochwerg B, Seely AJE, et al. Prognostic accuracy of the quick sequential organ failure assessment for mortality in patients with suspected Infection: a systematic review and meta-analysis. Ann Intern Med. 2018;168:266-75.
38 Herwanto V, Shetty A, Nalos M, Chakraborty M, McLean A, Eslick GD, et al. Accuracy of quick sequential organ failure assessment score to predict sepsis mortality in 121 studies including 1,716,017 individuals: A systematic review and meta-analysis. Crit Care Explor. 2019;1:e0043.
39 Serafim R, Gomes JA, Salluh J, Serafim R, Póvoa P. A comparison of the quick-SOFA and systemic inflammatory response syndrome criteria for the diagnosis of sepsis and prediction of mortality: A systematic review and meta-analysis. Chest. 2018;153:646-55.
40 Liu VX, Lu Y, Carey KA, Gilbert ER, Afshar M, Akel M, et al. Comparison of early warning scoring systems for hospitalized patients with and without infection at risk for in-hospital mortality and transfer to the intensive care unit. JAMA Netw Open. 2020;3:e205191.
41 González J, Clemente C, Candel FJ, Martín-Sánchez FJ. New sepsis criteria: Do they replace or complement what is known in the approach to the infectious patient? Rev Esp Quimioter. 2017;30 (Supl. 1):48-51.
42 Julián-Jiménez A, Candel-González FJ, González del Castillo J. Utilidad de los biomarcadores de inflamación e infección en los servicios de urgencias. Enferm Infecc Microbiol Clin. 2014;32:177-90.
43 Vincent JL, Bogossian E, Menozzi M. The Future of Biomarkers. Crit Care Clin. 2020;36:177-87.
44 Londoño J, León AL, Rodríguez F, Barrera L, de la Roca G, Dennis R, et. al. Láctico sérico en urgencias como factor pronóstico en pacientes con sepsis sin hipotensión. Med Clin (Barc). 2013;141:246-51.
45 Julián-Jiménez A, Yañez MC, González del Castillo J, Salido-Mota M, Mora-Ordóñez B, Arranz-Nieto MJ, et al. Poder pronóstico de mortalidad a corto plazo de los biomarcadores en los ancianos atendidos en Urgencias por infección. Enferm Infecc Microbiol Clin. 2019; 37:11-8.
46 González Del Castillo J, Clemente-Callejo C, Llopis F, Irimia A, Oltra-Hostalet F, Rechner C, et al; INFURG-SEMES investigators. Midregional proadrenomedullin safely reduces hospitalization in a low severity cohort with infections in the ED: a randomized controlled multi-centre interventional pilot study. Eur J Intern Med. 2021;88:104-13.
47 González del Castillo J, Wilson DC, Clemente-Callejo C, Román F, Bardés-Robles I, Jiménez I, et al. Biomarkers and clinical scores to identify patient populations at risk of delayed antibiotic administration or intensive care admission. Crit Care. 2019;23:335.
48 Kumar P, Kakar A, Gogia A, Waziri N. Evaluation of soluble urokinase-type plasminogen activator receptor (suPAR) quick test for triage in the emergency department. J Family Med Prim Care. 2019;8:3871-5.
49 Rubio Díaz R, De Rafael González E, Martín Torres E, Valera Núñez E, López Martos AM, Melguizo Melguizo D, et al. Poder pronóstico de mortalidad a corto plazo del receptor soluble activador del plasminógeno tipo uroquinasa (suPAR) en los pacientes atendidos en urgencias por infección. Rev Esp Quimioter. 2022;35:50-62.
50 Yañez MC, Salido Mota M, Fuentes Ferrer M, Julián-Jiménez A, Piñera P, Llopis F, et al. Comparación de distintas estrategias para la predicción de muerte a corto plazo en el paciente anciano infectado Rev Esp Quimioter. 2019;32:156-64.
51 Gorordo-Delsol LA, Merinos-Sánchez G, Estrada-Escobar RA, Medveczky-Ordóñez NI, Amezcua-Gutiérrez MA, Morales-Segura MA, et al. Sepsis y choque séptico en los servicios de urgencias de México: estudio multicéntrico de prevalencia puntual. Gac Med Mex. 2020:156:495-501.
52 Morris E, McCartney D, Lasserson D, Van den Burel A, Fisher R, Hayward G. Point-of-care lactate testing for sepsis at presentation to health care: a systematic review of patient outcomes. Br J Gen Pract. 2017;67:e859-70.
53 Dettmer M, Holthaus CV, Fuller BM. The impact of serial lactate monitoring on emergency department resuscitation interventions and clinical outcomes in severe sepsis and septic shock: an observational cohort study. Shock. 2015;43:55-61.
54 Julián-Jiménez A, Márquez Alonso JA, Fernández Elías E, Flores-Chacartegui M. Capacidad del lactato y la procalcitonina para predecir bacteriemia y mortalidad en Urgencias. Med Clin (Barc). 2014;143:330-1.
55 González-Castillo J, Candel FJ, Julián-Jiménez A. Antibiotics and timing in infectious disease in the emergency department. Enferm Infecc Microbiol Clin. 2013;31:173-80.
56 Julián-Jiménez A, Zafar Iqbal-Mirza S, De Rafael González E, Estévez-González R, Serrano-Romero de Ávila V, Heredero-Gálvez E, et al. Modelo 5MPB-Toledo para predecir bacteriemia en los pacientes atendidos por infección en el servicio de urgencias. Emergencias. 2020;32:81-9.
57 Julián-Jiménez A, García-Lamberechts EJ, González del Castillo J, Navarro Bustos C, LLopis-Roca F, Martínez-Ortiz de Zárate M, et al. Validación del modelo predictivo de bacteriemia (5MPB-Toledo) en los pacientes atendidos en el servicio de urgencias por infección. Enferm Infecc Microbiol Clin. 2022;40:102-12.
58 Julián-Jiménez A, González Del Castillo J, García-Lamberechts EJ, Huarte Sanz I, Navarro Bustos C, Rubio Díaz R, et al. A bacteraemia risk prediction model: development and validation in an emergency medicine population. Infection. 2022;50:203-21.
59 Sterling SA, Ryan Miller W, Pryor J, Puskarich MA, Jones AE. The Impact of timing of antibiotics on outcomes in severe sepsis and septic shock: a systematic review and meta-analysis. Crit Care Med. 2015;43:1907-15.
60 Seymour CW, Gesten F, Prescott HC, Friedrich ME, Iwashyna TJ,

Phillips GS, Lemeshow S, Osborn T, Terry KM, Levy MM. Time to Time to treatment and mortality during mandated emergency care for sepsis. N Engl J Med. 2017;376:2235-44.
61 Peltan ID, Brown SM, Bledsoe JR, Sorensen J, Stat M, Samore MH, et al. ED Door-to-Antibiotic Time and Long-term Mortality in Sepsis. Chest. 2019;155:938-46.
62 Denny KJ, Gartside JG, Alcorn K, Cross JW, Maloney S, Keijzers G. Appropriateness of antibiotic prescribing in the Emergency Department. J Antimicrob Chemother. 2019;74:515-20.
63 Yunquera-Romero L, Márquez-Gómez I, Henares-López A, Morales-Lara MJ, Gallego Fernández C, Asensi-Díez R. Adecuación de las prescripciones antimicrobianas realizadas en el área de urgencias de un hospital de tercer nivel. Rev Esp Quimioter. 2018;31:209-16.
64 Malbrain MLNG, Van Regenmortel N, Saugel B, De Tavernier B, Van Gaal PJ, Joannes-Boyau O, et al. Principles of fluid management and stewardship in septic shock: it is time to consider the four D's and the four phases of fluid therapy. Ann Intensive Care. 2018;8:66.
65 Gorordo-Delsol LA, Montoya-Rojo JO, Merinos-Sánchez G, Amezcua-Gutiérrez MA, Hernández-López GD. Reanimación hídrica: fisiología de la respuesta a volumen. Rev Educ Investig Emer. 2019;1:145-51.
66 Merinos-Sánchez G, Gorordo-Delsol LA, Guamán-Crespo JO, Hernández-López GD. Reanimación hídrica: tipos de líquidos y efectos adversos. Rev Educ Investig Emer. 2019;1:23-31.
67 Asfar P, Meziani F, Hamel JF, Frelon F. High versus low blood -pressure target in patients with septic shock. N Eng J Med. 2014;370:1583-93.
68 Tian DH, Smuth C, Keijzers G, Macdonald SP, Peake A, Udy A, et al. Safety of peripheral administration of vasopressor medications: a systematic review. Emerg Med Australas. 2020;32:220-7.
69 Ospina-Tascón GA, Hernández G, Álvarez I, Calderón-Tapia LE, Manzano-Nunez R, Sánchez-Ortiz AI, et al. Effects of very early start of norepinephrine in patients with septic shock: a propensity score-based analysis. Crit Care. 2020;24:52.
70 Bai X, Yu W, Ji W, Lin Z, Tan S, Duang K. Early versus delayed administration of norepinephrine in patients with septic shock. Crit Care. 2014;18:532.
71 Glickman SW, Cairns CB, Otero RM, Woods CW, Tsalik EL, Langley RJ, et al. Disease progression in hemodynamically stable patients presenting to the emergency department with sepsis. Acad Emerg Med. 2010;17:383-90.
72 Kiekkas P, Tzenalis A, Gklava V, Stefanopoulos N, Voyagis G, Aretha D. Delayed admission to the intensive care unit and mortality of critically ill adults: systematic review and meta-analysis. Biomed Res Int. 2022:4083494.
73 Cardoso LT, Grion CM, Matsuo T, Anami EH, Kauss IA, Seko L, et al. Impact of delayed admission to intensive care units on mortality of critically ill patients: a cohort study. Crit Care. 2011;15:R28.
74 Singer AJ, Thode HCJ, Viccellio P, Pines JM. The association between length of emergency department boarding and mortality. Acad Emerg Med. 2011;18:1324-9.
75 Colmenero M. El ritual de la falta de camas. Med Intensiva. 2011;35:139-42.
76 Tudela P, Mòdol JM. La saturación en los servicios de urgencias hospitalarios. Emergencias. 2015;27:113-20.