CONSENSUS STATEMENT

Recommendations of the GT-LATINFURG for the identification and initial management of patients with severe infection and sepsis in emergency departments

Agustín Julián-Jiménez[1-3,*], Darío Eduardo García[2,4,*], Juan González del Castillo[1,5], Raffo Escalante-Kanashiro[6], Francisco Javier Candel González[1,7], Graciela Merinos-Sánchez[2,8], Ángel Estella[1,9], Diego Armando Santillán-Santos[2,8], Julio Javier Gamazo del Río[1,10], Matías José Fosco[2,11], Ferrán Llopis-Roca[1,12], Luis Antonio Gorordo-Delsol[2,13], Raúl López Izquierdo[1,14], Marcelo Rodrigo Rodríguez[2,15], Rafael Rubio Díaz[1,3], Helio Penna Guimarães[2,16], Luis García de Guadiana-Romualdo[17], Ricardo Bañuelos Huerta[2,18], Gema Delgado Cárdenas[1,19], Ulises González-Bascuñán[2,20], Rocío Lorenzo Álvarez[1,21], Regina Gualco[2,4], Marcio Borges Sa[22,23], on behalf of the GT-LATINFURG Sepsis Working Group, Improvement of Care for Patients With Infection in the Emergency Department of the Latin American Federation of Emergency Medicine (FLAME) Working Group, and of the Spanish Society of Emergency and Urgent Care Medicine (INFURG-SEMES)

*Both authors should be considered as first authors.

Author Affiliations:
[1]SEMES: Grupo de trabajo de Infecciones de la Sociedad Española de Medicina de Urgencias y Emergencias.
[2]FLAME: Federación Latinoamericana de Medicina de Emergencias.
(Continued at the bottom of the page)

Author Contributions:
All authors have confirmed his authorship in the document of author responsibilities, publication agreement and assignment of rights to EMERGENCIAS.

Corresponding Author:
Agustín Julián-Jiménez
Servicio de Urgencias-Coordinador de Docencia, Formación, Investigación y Biblioteca.
Complejo Hospitalario Universitario de Toledo.
Avda. Río Guadiana s/n.
45071 Toledo, Spain.

Email:
agustinj@sescam.jccm.es

Article Information:
Received: 2-10-2025
Accepted: 24-11-2025
Online: 9-1-2026

Editor in Charge:
Pere Llorens Soriano

Declared of scientific interest by SEMES (Spanish Society of Emergency Medicine)
Declared of scientific interest by FLAME (Latin American Federation of Emergency Medicine).

In November 2021, the Surviving Sepsis Campaign (SSC) published an update to its 2016 guidelines and recommendations. Subsequently, during the CIMU 2022 (33rd World Congress on Emergency Medicine, held in March 2022 in Guadalajara, Mexico), the 2021 SSC Guidelines were reviewed and analyzed from the perspective of emergency physicians (EPs). The experts involved in this task also reached consensus and published several key points of greatest interest and concern to EPs regarding the management of patients with severe infection or sepsis in hospital emergency departments (EDs). These points included several improvement proposals developed by GT-LATINFURG (Latin American Working Group for Improving Infection Care in Emergency Departments) and formally presented in what became known as the "Guadalajara Declaration." That document outlined complementary or alternative considerations to the 2021 SSC Guidelines. The first proposal was to "develop guidelines aimed at detecting, preventing progression, and managing patients with severe infection and sepsis in EDs." Since then—and owing to numerous original research studies and review articles published by the GT-LATINFURG and INFURG-SEMES groups (Infection Study Group of the Spanish Society of Emergency Medicine)—we can now claim that there is scientific evidence generated in EDs themselves, or at least that existing evidence has been reviewed while considering the specific role of EPs. The main aim of this consensus document, as the initial presentation of the first proposal of the Guadalajara Declaration, is to analyze—based on routine clinical practice, experience, available evidence, and the perspective of ED physicians—several key issues and controversies in order to establish recommendations through expert consensus grounded in current scientific evidence.

Keywords: Bacterial infection. Emergency Departments. Diagnosis. Prognosis. Mortality. Prevention. Early warning scores. Biomarkers. Lactate. Procalcitonin. Recommendations.

Recomendaciones del GT-LATINFURG para la identificación y atención inicial del paciente con infección grave y sepsis en los servicios de urgencias

En noviembre del año 2021 la *Surviving Sepsis Campaign* (SSC) o "Campaña Sobrevivir a la Sepsis" publicó una actualización de sus recomendaciones y directrices de 2016. Posteriormente, hace varios años, en el marco del CIMU 2022 (33 Congreso Mundial de Medicina de Urgencias) se revisó y analizó desde la perspectiva del médico de urgencias y emergencias (MUYE) la Guía SSC de 2021. Los expertos que realizaron esa tarea también consensuaron y publicaron

[3]Servicio de Urgencias, Complejo Hospitalario Universitario de Toledo, IDISCAM (Instituto de Investigación Sanitaria de Castilla La Mancha), Toledo, Spain. [4]Hospital de Alta Complejidad El Cruce, Florencio Varela, Buenos Aires, Argentina. [5]Servicio de Urgencias, Hospital Universitario Clínico San Carlos, IDISSC & IML, Madrid, Spain. [6]Unidad de Cuidados Intensivos, Oficina de Gestión de la Calidad, Instituto Nacional de Salud del Niño, Lima, Peru. Universidad Peruana de Ciencias Aplicadas, Escuela de Medicina, Lima, Peru. [7]Servicio de Microbiología Clínica, Hospital Universitario Clínico San Carlos, IDISSC & IML, Madrid, Spain. [8]Servicio de Urgencias Médico Quirúrgicas, Hospital General de México "Dr. Eduardo Liceaga", Ciudad de México, Mexico. [9]Servicio de Urgencias, Hospital Universitario de Jerez, Cádiz, Departamento de Medicina Universidad de Cádiz, INIBiCA, Spain. [10]Servicio de Urgencias, Hospital Universitario de Galdakao-Usansolo, Biocruces Bizkaia Health Research Institute, Vizcaya, Spain. [11]Servicio de Urgencias, Hospital Universitario Fundación Favaloro, Buenos Aires, Argentina. [12]Servicio de Urgencias, Hospital Universitari de Bellvitge, l'Hospitalet de Llobregat, Barcelona, Spain. [13]Unidad de Cuidados Intensivos Adultos, Hospital Juárez de México, Ciudad de México, Mexico. [14]Servicio de Urgencias, Hospital Universitario Río Hortega de Valladolid, Spain. [15]Departamento de Emergencias, Hospital Universitario Austral, Buenos Aires, Argentina. [16]Hospital Israelita Albert Einstein, São Paulo, Brasil. [17]Servicio de Análisis Clínicos, Hospital General Universitario Santa Lucía, Cartagena, Murcia,Spain. [18]Servicio de Urgencias, Hospital General Tlaxcala "Lic. Anselmo Cervantes Hernández", Tlaxcala, Mexico. [19]Servicio de Urgencias, Hospital Universitario de Fuenlabrada, Madrid, Spain. [20] Hospital de Urgencia Asistencia Pública, Santiago de Chile, Chile. [21]Servicio de Urgencias, Hospital de La Axarquía, Vélez-Málaga, Málaga, Spain. [22]Unidad Multidisciplinar de Sepsis, Servicio Medicina Intensiva, Hospital Universitario Son Llàtzer, Palma de Mallorca, Spain. [23]Grupo Multidisciplinar de Sepsis, Instituto de Investigación sanitaria de las Islas Baleares, (Idisba), Spain.

algunos de los puntos clave que más interesaban y preocupaban a los MUYE en relación a la atención del paciente con infección grave o sepsis en los servicios de urgencias hospitalarios (SUH), e identificaron distintas propuestas para su mejora o resolución por parte del GT-LATINFURG (grupo de trabajo latinoamericano para la mejora de la atención del paciente con infección en urgencias) en lo que dio a conocer como "La Declaración de Guadalajara". En dicho documento se desarrollaron las consideraciones y propuestas complementarias o alternativas a la Guía SSC de 2021. La primera de ellas era "elaborar unas guías orientadas a detectar, prevenir la progresión y atender a los pacientes con infección grave y sepsis en los SUH". Desde entonces y gracias a múltiples artículos originales de investigación y de revisión publicados por GT-LATINFURG e INFURG-SEMES (grupo de estudio de infecciones de la Sociedad Española de Medicina de Urgencias y Emergencias), hoy en día existe cierta evidencia científica generada en los propios SUH o, al menos, se ha revisado la existente teniendo en consideración el papel de estos MUYE. El objetivo principal de este documento de consenso como presentación inicial de la primera propuesta de la Declaración de Guadalajara es analizar, desde la base de la práctica clínica habitual, experiencia, evidencia y perspectiva de los médicos de los SUH, algunos de los puntos clave y distintas controversias para establecer una serie de recomendaciones en la infección grave y la sepsis mediante un consenso de expertos basadas en la evidencia científica actual.

Palabras clave: Sepsis. Infección bacteriana. Servicios de Urgencias. Diagnóstico. Pronóstico. Mortalidad. Prevención. Escalas de alerta temprana. Biomarcadores. Lactato. Procalcitonina. Recomendaciones.

Introduction

Background and historical overview

In November 2021, the Surviving Sepsis Campaign (SSC) published an update of its 2016 recommendations and guidelines.[1] The influence of these guidelines on physicians, healthcare centers, institutions, and national and international organizations is evident, as is the improvement in the quality of care provided to patients with organ dysfunction and life-threatening conditions caused by sepsis when these recommendations are implemented.[1] Currently, the SSC is widely recognized as a cornerstone of the sepsis care process, having successfully conveyed the importance of this clinical entity, the need for early detection and appropriate treatment, and having contributed to improved patient prognosis.[1-3]

However, although these guidelines are often presented as being based on "strong" recommendations according to the authors' assessment, they are frequently supported by "weak" or "very weak" evidence or framed as best practice statements.[1] For this reason, as occurred following the publication of the Third International Consensus Definitions for Sepsis and septic shock (SS) (Sepsis-3),[4] emergency and urgent care medicine (EUCM) specialists, along with other involved disciplines, have emphasized the priority of continuing research efforts to generate robust clinical evidence that can firmly support existing recommendations or contribute new ones derived from emerging findings.[2,3]

The management of patients with suspected or confirmed infection in emergency departments (EDs) has increased significantly over recent decades. Currently, such cases account for approximately 15%–20% of all ED visits in Spain and between 15% and 40% in EDs across Latin American countries.[3] Of this large patient population, between 5% and 25% are classified as having sepsis or SS (depending on the registry, criteria, or definitions used in each country).[4] In addition, underdiagnosis of patients with severe infection and sepsis in the ED is well recognized.[2,3] These data highlight both the quantitative and qualitative importance of infectious processes and sepsis in EDs.[3]

Moreover, in recent years, both the incidence rate of severe infection and its in-hospital and short-term (30-day) mortality have increased gradually.[2-5] Nevertheless, the spectrum of disease severity is wide, ranging from mild acute illness to systemic processes leading to sepsis, SS, or infection-associated bacteremia. In the latter scenarios, mortality may reach 10%–40%.[2,5]

EUCM specialists are aware that, to classify and identify patients with poorer prognosis, it is first necessary to diagnose severe infection or sepsis in the ED among numerous patients presenting with possible infectious conditions, as well as among those with alternative diagnoses that may mimic severe infection.[3,6-8] What is not suspected cannot be detected, stratified, or treated early and appropriately; consequently, septic syndromes are allowed to progress to advanced—and sometimes irreversible—stages.[2,3]

In this global context, EDs and prehospital emergency medical services (EMS) represent a key link in the care of patients with severe infection—a concept that includes patients meeting sepsis criteria, those with suspected bacteremia, and special populations such as immunocompromised patients, older adults, and individuals with significant comorbidities.[2,3] These settings are where clinical suspicion is raised, microbiological samples are obtained, and individualized, immediate, and appropriate treatment is initiated, largely determining the patient's clinical course.[1-3,9,10] Thus, the "sepsis survival chain" in the ED has evolved into the "chain of detection, prevention of progression, and care of patients with sepsis in emergency settings," which begins at triage at "time zero" with the implementation of individualized care bundles as early as possible (Figure 1, Supplementary data: https://revistaemergencias.org/extra/5189.pdf).

For all these reasons, EUCM specialists have long called for guidelines more focused on the early stages of sepsis, which quantitatively represent a much larger patient population in whom early and appropriate in-

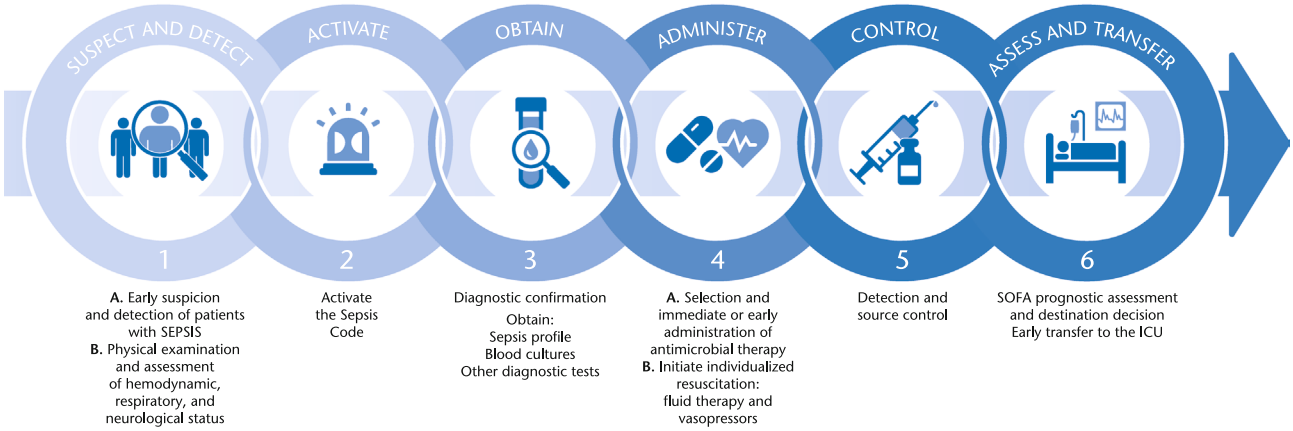

Figure 1. Chain of detection, prevention of progression, and care of the patient with sepsis in emergency departments. SOFA: Sequential Organ Failure Assessment; ICU: intensive care unit.

tervention can prevent the development of organ dysfunction or reverse it, thereby avoiding progression to SS or multiple organ dysfunction.[1-3,9,10]

Within the framework of CIMU 2022 (the 33rd World Congress of Emergency Medicine, held in March 2022 in Guadalajara, Mexico), the 2021 SSC guidelines were reviewed and analyzed from the perspective of EUCM specialists. The experts involved also reached consensus and highlighted key aspects of particular relevance to EUCM in the care of patients with suspected or confirmed severe infection or sepsis in the ED. They developed several proposals for improvement or resolution through the GT-LATINFURG (Latin American Working Group for the Improvement of Care for Patients with Infection in Emergency Departments), which were presented in the "Guadalajara Declaration."[3,10] That publication detailed additional considerations and alternative proposals to the 2021 SSC guidelines. The first of these proposals was the development of guidelines specifically oriented toward detecting, preventing progression, and managing patients with severe infection and sepsis in EDs.[3] Since then, and thanks to multiple original research and review articles published by the GT-LATINFURG and INFURG-SEMES (Infection Study Group of the Spanish Society of Emergency and Urgent Care Medicine), a growing body of scientific evidence has been generated within EDs themselves, or at least existing evidence has been critically reviewed while considering the specific role of these settings.

Evolution of operational definitions (criteria) of sepsis

Sepsis-1: In 1992, the first consensus statement from the American College of Chest Physicians/Society of Critical Care Medicine established the concept of systemic inflammatory response syndrome (SIRS), defined as a response to a variety of severe clinical insults and manifested by the presence of 2 or more of the following 4 criteria: 1) temperature > 38 °C or < 36 °C; 2) heart rate > 90 beats per minute; 3) respiratory rate > 20 breaths per minute or $PaCO_2$ < 32 mmHg; and 4) white blood cell count > 12,000/mm^3, < 4,000/mm^3, or > 10% immature forms (bands).

The same consensus defined sepsis as the presence of SIRS caused by infection, severe sepsis as sepsis associated with hypotension, hypoperfusion, or organ dysfunction attributable to sepsis, and SS as persistent arterial hypotension despite adequate fluid resuscitation.[11]

Sepsis-2: In 2001, experts from multiple scientific societies recommended maintaining the 1992 definitions of sepsis, severe sepsis, and SS, but considered the defining criteria for sepsis to be insufficient due to limited specificity. Consequently, this consensus expanded the list of diagnostic criteria to include several biomarkers as tools to support early sepsis diagnosis, such as lactate, C-reactive protein (CRP), and procalcitonin (PCT).[12]

Sepsis-3: In February 2016, the Sepsis Definitions Task Force published updated definitions of sepsis and SS (Sepsis-3),[6] followed by two articles providing evidence to validate these new definitions.[13,14] This consensus defines sepsis as "life-threatening organ dysfunction caused by a dysregulated host response to infection," implying a nonhomeostatic host response and explicitly incorporating the concept of organ dysfunction.

All of this implies severity, the need for early diagnosis and management, and consequently renders the term "severe sepsis" superfluous, leading to its abandonment. In turn, the term SS is redefined as a subcategory of sepsis in which the underlying circulatory, cellular, and metabolic abnormalities are profound enough to substantially increase mortality. Clinically, SS is identified by the need for vasopressors to maintain a mean arterial pressure (MAP) ≥ 65 mmHg and by a blood lactate level ≥ 2 mmol/L (18 mg/dL) despite adequate fluid resuscitation.[6]

This consensus proposes the use of the SOFA (Sequential Organ Failure Assessment) score[6,15] (Table 1) to define sepsis. SOFA incorporates a series of clinical, laboratory, and management-related criteria. A baseline SOFA score of zero is assumed in patients without preexisting organ dysfunction, and, for the identification of

Table 1. SOFA Scale (Sepsis-related Organ Failure Assessment)

System/Marker	Points				
	0	1	2	3	4
Respiratory: PaO_2/FiO_2	≥ 400	< 400	< 300	< 200*	< 100*
SpO_2/FiO_2**		221-301	142-220	67-141	< 67
Coagulation: Platelets ($\times 10^3/mm^3$)	> 150	< 150	< 100	< 50	< 20
Liver: Bilirrubin (mg/dl)	< 1.2	1.2-1.9	2-5.9	6-11.9	≥ 12
Cardiovascular: Blood pressure (mmHg)	MAP ≥ 70	MAP < 70	DA < 5 o DBT	DA > 5.1-15 or NE/Epi ≤ 0.1	DA > 15 or NE/Epi > 0.1
Central nervous system: CGS	15	13-14	10-12	6-9	< 6
Renal: Creatinine (mg/dL)	< 1.2	1.2-1.9	2-3.4	3.5-4.9	≥ 5
Urine output (ml/day)				< 500	< 200

To define the clinical criteria identifying patients with infection and sepsis, an initial SOFA score ≥ 2 is required to represent the presence of organ dysfunction.
*Respiratory: Scores of 3 and 4 apply only if the patient is receiving ventilatory support.
**If arterial blood gas analysis is not available but pulse oximetry is, an SpO_2/FiO_2 ratio of 235 corresponds to a PaO_2/FiO_2 ratio of 200, and an SpO_2/FiO_2 ratio of 315 corresponds to a PaO_2/FiO_2 ratio of 300.
***Vasoactive drugs administered for at least 1 hour to maintain MAP > 65 mmHg. Doses of vasoactive agents are expressed in µg/kg/min.
MAP: mean arterial pressure; DA: dopamine; NE/Epi: norepinephrine/epinephrine; DBT: dobutamine; GCS: Glasgow Coma Scale.
Adapted from: Singer M, *et al.* JAMA. 2016;315:801–810 and Vincent JL, *et al.* Intensive Care Med. 1996;22:707–710.

patients with infection and sepsis, an increase in the SOFA score of 2 points or more from baseline is recommended as indicative of organ dysfunction.

Another operational concept introduced is the qSOFA[6] which does not require laboratory tests and can be rapidly applied at triage. It was developed to identify patients with suspected sepsis who are at increased risk of mortality. Thus, in EDs, qSOFA can be used immediately to assess organ dysfunction, initiate or escalate therapy when appropriate, and consider the need for transfer to the intensive care unit (ICU). In this regard, Seymour *et al.*[13] concluded that, in patients outside the ICU, a qSOFA score ≥ 2 had significantly greater predictive validity for in-hospital mortality than SIRS criteria or the full SOFA score. qSOFA is considered positive when 2 or more of the following criteria are present: (1) respiratory rate ≥ 22 breaths per minute; (2) altered mental status, defined as a Glasgow Coma Scale score ≤ 14; and (3) systolic blood pressure ≤ 100 mmHg.

Importance of early detection of patients with severe infection and sepsis from triage: "time zero" (recognition bundle)

The diagnosis of sepsis in emergency settings faces multiple barriers and is considered challenging by all stakeholders, including the SSC 2021.[1-3] In addition to early phases of infection, there are situations and risk factors for severe infection—such as advanced age, recent postoperative status, wounds or skin lesions, immunosuppression, cancer, diabetes mellitus, HIV infection, among others—in which symptoms and clinical signs are less pronounced and more variable, making suspicion of sepsis more difficult.[3,16] Similarly, fever (as a pathophysiological immune response to pathogens) may be absent, particularly at extremes of age and in immunocompromised patients.[17]

Early identification of patients with sepsis is essential to allow immediate intervention and prevent progression to more severe stages. From "time zero," the use of SIRS criteria, qSOFA, or other early warning scores such as the National Early Warning Score 2 (NEWS-2),[17,18] (Table 2), along with the inclusion of additional clinical parameters at triage and biomarkers—such as classical markers (lactate, CPR, PCT) and others with less accumulated evidence but high potential (midregional proadrenomedullin [MR-proADM] or soluble urokinase-type plasminogen activator receptor [suPAR])—has become a fundamental strategy for the suspicion and confirmation of sepsis in EDs.[1-3]

The first recommendation of the SSC 2021 advocates the use of a program to improve early detection and treatment of sepsis. Such programs may consist of manual methods or automated use of electronic health records with alert systems.[20] This recommendation is classified as strong with moderate-quality evidence for detection and strong with very low-quality evidence for standard procedures.[1]

Currently, triage systems are indispensable for patient classification and prioritization in EDs and EMS. The use of detection programs (manual or automated) has been associated with improved adherence to sepsis care bundles and reduced mortality, with an odds ratio (OR) of 0.66 (95% CI, 0.61–0.72) in patients with sepsis and SS.[21]

Automated electronic systems (AES) achieve a sensitivity of 81% (95% CI, 80–81) and a specificity of 72% (95% CI, 72–72), and can predict sepsis 3–4 hours before clinical onset, outperforming SIRS and SOFA criteria.[22] However, the meta-analysis cited in the SSC 2021 included only studies conducted in ICUs, where laboratory data, continuous vital sign monitoring, and comorbidity assessment are readily available; these systems have not been evaluated in ED populations.[22]

In EDs, the first recognition bundle or time zero should begin at triage with activation of the sepsis code, initiating a screening strategy that allows identification of patients with sepsis and stratification of severity to facilitate treatment, ICU transfer, and monitoring during ED stay (retriage) to allow reassessment if warning signs or clinical deterioration occur.[2,3] Thus, the sepsis code should be activated as soon as patients with signs of or-

Table 2. NEWS-2 Scale (National Early Warning Score 2)

Parameter	Points						
	3	2	1	0	1	2	3
Respiratory rate (breaths/min)	≤ 8		9-11	12-20		21-24	≥ 25
Oxygen saturation (%)	≤ 91	92-93	94-95	≥ 96			
Oxygen saturation % (hypercapnic respiratory failure)	≤ 83 on O_2	84-85 on O_2	86-87 on O_2	88-92 on O_2 or ≥ 93 on room air	93-94 on O_2	95-96 on O_2	≥ 97 on O_2
Supplemental oxygen		Yes*		No			
Systolic blood pressure (mmHg)	≤ 90	91-100	101-110	111-219			≥ 220
Heart rate (beats/min)	≤ 40		41-50	51-90	91-110	111-130	≥ 131
Level of consciousness				A			C, V, P, U
Temperature (°C)	≤ 35		35.1-36	36.1-38	38.1-39	≥ 39.1	

*Record the type of oxygen delivery device used (nasal cannula, face mask, non-rebreather mask, etc.).
Risk interpretation: 1–4 points: Low risk → routine care, observation; Any single parameter scoring 3: Clear risk → urgent clinical review; 5–6 points: Medium risk → urgent response; ≥ 7 points: High risk → immediate response, consider intensive care
In patients with suspected sepsis: activate the sepsis code if 3 points in any single parameter or NEWS-2 ≥ 5.
O_2: oxygen therapy; rpm: respirations per minute; bpm: beats per minute; °C: degrees Celsius; A: alert; C: confusion (new onset); V: response to voice; P: response to pain; U: unresponsive. Adapted from: Reference 18 (NEWS-2).

gan dysfunction and clinical suspicion of infection are identified.[1-3,6] In clinical practice, organ dysfunction should prompt investigation for infection as an underlying cause, and any patient with suspected or confirmed infection should be assessed for organ dysfunction. Activation of the sepsis code initiates immediate diagnostic and therapeutic measures, pending diagnostic confirmation, both in prehospital and in-hospital settings.[1-3,6]

Objective of the consensus document

The main objective of this Consensus Document (CD), presented as the initial proposal of the Guadalajara Declaration (to develop guidelines aimed at detecting, preventing progression, and managing patients with severe infection and sepsis in EDs),[3] is to analyze—based on routine clinical practice, experience, evidence, and the perspective of ED physicians—key issues and controversies in order to establish a series of expert consensus recommendations grounded in the current scientific evidence.

Methodology

The project was led by a scientific committee composed of 9 EUCM experts with extensive clinical experience in the management of patients with severe infection and sepsis, as well as a strong research background. These experts were drawn from representative hospitals across Spain and Latin America (DEG, JGC, REK, FJCG, AEG, JJGR, MJF, FLR, and AJJ).

Through FLAME (Latin American Federation of Emergency Medicine) and SEMES (Spanish Society of Emergency and Urgent Care Medicine), a group of 70 emergency medicine experts from different hospitals was convened at the end of 2022, representing more than 50 hospitals from 19 Spanish- and Portuguese-speaking countries (author and reviewer information available in Supplementary Table 1 at: https://revistaemergencias.org/extra/5189.pdf).

Phases (Figure 2)

In the first phase, the scientific committee was formed during the 3 months following publication of the Guadalajara Declaration at the beginning of 2023.[3] The general project design was established, and an exhaustive literature review was conducted focusing on clinical practice guidelines, particularly the SSC 2021,[1] and the Sepsis-1,[11] Sepsis-2,[12] and Sepsis-3[6] consensus conferences. This review gathered crucial information on the presence or absence of scientific evidence in the clinical management of severe infection and sepsis specifically in ED settings. This phase concluded with the development of a document containing 50 research questions formulated according to the PICO format (Population/Patient, Intervention, Comparator, and Outcomes), aimed at evaluating current management and identifying areas for improvement in EDs. Definitions, criteria, and potentially controversial concepts were unanimously agreed upon to standardize terminology and facilitate bibliographic searches. A glossary of terms is available in Supplementary Table 2 at: https://revistaemergencias.org/extra/5189.pdf.

In the second phase, the 9 members of the scientific committee selected and reached consensus—through an individual scoring system applied to each question—on 20 of the original 50 questions, considering them the most relevant and impactful for the initial management of patients in EDs. Of these, the first 15 questions, shown in Table 3, were developed as described in the third phase below. For the remaining 5 questions (questions 16–20), either a systematic or a narrative review was performed, depending on whether studies meeting the inclusion criteria described in Table 4 were available, or because—when addressing patients with SS and in the presence of robust existing evidence with which the scientific committee agreed—it was decided to include them as part of a narrative discussion. These reviews were incorporated either into the discussion of related PICO questions or directly into the final recommendations section. In all cases, unanimous consensus

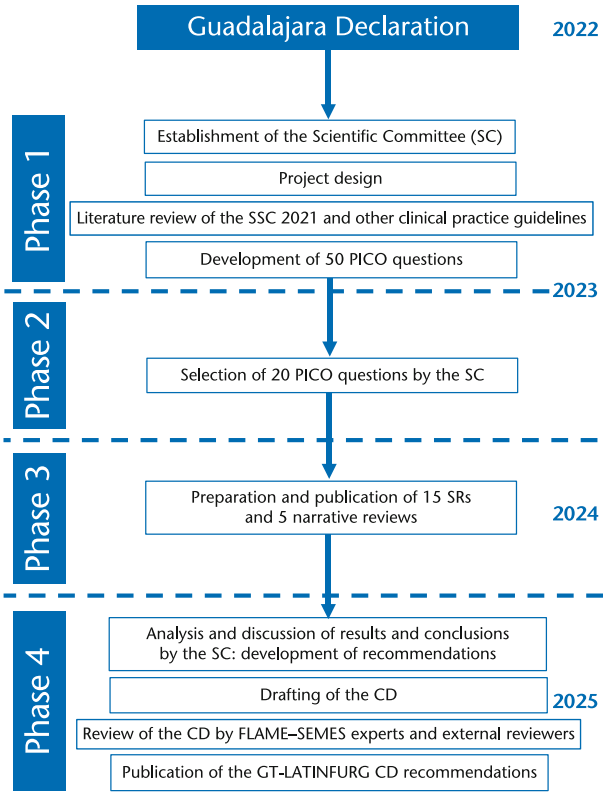

Figure 2. Description of the project phases.
SSC-21: 2021 Surviving Sepsis Campaign; CPG: clinical practice guidelines; PICO: Population/Patient, Intervention, Comparator, Outcomes; SC: Scientific Committee; FLAME: Latin American Federation of Emergency Medicine; SEMES: Spanish Society of Emergency Medicine.

was achieved among members of the scientific committee and internal and external reviewers (Supplementary Table 1; https://revistaemergencias.org/extra/5189.pdf).

The third phase was conducted over a 12-month period. During this phase, several working groups were organized, each led by a member of the scientific committee, and each group performed a comprehensive review of its assigned question. Whenever articles meeting the predefined inclusion criteria were identified, a systematic review (SR) was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[13] To this end, bibliographic searches were performed in at least the following databases: PubMed, Web of Science, EMBASE, LILACS, Cochrane, Epistemonikos, Tripdatabase, and ClinicalTrials.gov. Searches were designed to identify articles relevant to each PICO question in adult patients with sepsis managed in EDs. The search strategy combined appropriate terms and descriptors together with (Infection OR Bacterial Infection OR Sepsis) AND (Emergencies OR Emergency OR Emergency Department), covering the period from January 1st, 2010 through at least December 31st, 2023. Ultimately, priority was given to SRs, SRs with meta-analyses, randomized clinical trials (RCTs), and cohort studies. Some of these SRs were registered in PROSPERO (the international prospective register of SRs). Registration numbers for reviews not yet published are included in this CD, while published reviews can be consulted in the cited articles. When no scientific evidence meeting the common inclusion criteria for all reviews (Table 4) was identified, a narrative review was conducted.

Study selection followed the PRISMA methodology,[23] including 4 phases: (1) identification, (2) screening, (3) eligibility, and (4) final inclusion of studies in the review. To assess methodological quality and risk of bias of the included studies, different tools were applied according to study design, with independent assessment by 2 reviewers and subsequent consensus:

– For SR and meta-analyses included at the eligibility stage, AMSTAR 2 (A MeaSurement Tool to Assess SRs)[25] was used to evaluate risk of bias and methodological quality.

– For cohort studies included in SRs, the Newcastle–Ottawa Scale (NOS)[26] was applied.

– RoB 2 (Risk of Bias in Randomized Trials 2)[26] was used to assess randomized clinical trials.

– ROBINS-I (Risk of Bias in Non-randomized Studies of Interventions)[27] was used to evaluate nonrandomized clinical trials.

– AGREE II (Appraisal of Guidelines for Research and Evaluation)[28] was used for the assessment of clinical practice guidelines.

– GRADE (Grading of Recommendations Assessment, Development and Evaluation)[29] was used to evaluate the certainty of the evidence.

Finally, in the fourth phase, the scientific committee met on multiple occasions to jointly review and analyze the results of all reviews and their conclusions. Initial recommendations were formulated by the different working groups for each PICO question and were subsequently discussed and agreed upon by the entire scientific committee.

Because the duration of the review process and the volume of evidence identified varied considerably across PICO questions, SRs or special narrative review articles were published throughout 2024 and up to July 31, 2025. In addition, for all 20 questions, a complementary literature search was conducted from the closing date of each review through July 31, 2025, using the same original search strategy. When new relevant evidence was identified, it was incorporated into the discussion and drafting of the corresponding PICO question, at the discretion of the scientific committee.

The final result was the drafting of this manuscript, which was reviewed and approved by all members of the scientific committee and by the remaining authors (members of the working groups for each question). The CD was subsequently reviewed and discussed by a group of internal reviewers representing SEMES and all member societies of FLAME, as well as by external experts from other emergency medicine societies in different countries and by independent experts of recognized standing from related medical specialties (Supplementary Table 1; https://revistaemergencias.org/extra/5189.pdf).

Table 3. List of the 20 PICO questions selected by the authors for adult patients with suspected severe infection or sepsis attended in the emergency department

1. In adult patients < 65 years, is the qSOFA score vs SIRS criteria, NEWS-2, and other scores/models (qSOFA–lactate, qSOFA–procalcitonin, qSOFA–suPAR, qSOFA–proADM, SIRS–procalcitonin, SIRS–lactate), a better predictor of sepsis for initial assessment?
2. In adult patients ≥ 65 years, is the qSOFA score vs SIRS criteria, NEWS-2, and other scores/models (qSOFA–lactate, qSOFA–procalcitonin, qSOFA–suPAR, qSOFA–proADM, SIRS–procalcitonin, SIRS–lactate), a better predictor of sepsis for initial assessment?
3. Does the use of serum lactate vs non-use, improve prognostic prediction and the identification of poor clinical outcomes in the ED?
4. Does the use of procalcitonin vs non-use, improve the diagnostic accuracy for bacterial infection in the ED?
5. In patients with a clinical diagnosis of infection and suspected bacteremia, does the use of procalcitonin vs non-use, improve diagnostic prediction of bacteremia in blood cultures obtained in the ED?
6. In patients with a clinical diagnosis of infection and suspected bacteremia, do alternative predictive models vs the Shapiro score, improve the prediction of bacteremia in blood cultures obtained in the ED?
7. Which patients should undergo blood culture sampling in the ED, based on the prognostic, clinical, and mortality impact of microbiological isolation?
8. Is the use of molecular microbiological diagnostic techniques in addition to blood cultures more effective and safer?
9. Is early empirical antibiotic therapy (< 3 hours from ED triage) vs no administration or delayed administration (≥ 3–6 hours), safer and more effective in improving clinical outcomes, reducing progression to SS, short- and long-term mortality, complications, hospital length of stay, or ICU admission?
10. In suspected or confirmed sepsis, is normal saline vs balanced crystalloids/Ringer lactate/colloids/albumin/gelatins, more effective and safer?
11. In suspected or confirmed SS, is normal saline vs balanced crystalloids/Ringer lactate/colloids/albumin/gelatins, more effective and safer?
12. In suspected or confirmed SS requiring vasopressors, is NE vs dopamine/epinephrine/vasopressin/other agents, more effective and safer?
13. In patients with suspected or confirmed SS requiring vasopressors, is peripheral venous administration vs central venous administration, effective and safe?
14. In suspected or confirmed SS requiring vasopressors, is early vasopressor initiation vs delayed initiation, more effective and safer?
15. Is early source identification and control (< 6 hours) vs no source control or delayed control (> 6–12 hours), safer and more effective in improving clinical outcomes, mortality, complications, hospital length of stay, or ICU admission?
16. In suspected sepsis, is the use of a multidisciplinary sepsis team or "sepsis code" vs non-use, more effective and safer?
17. In suspected or confirmed SS, is early empirical antibiotic therapy vs delayed initiation, more effective and safer?
18. In suspected sepsis or severe infection, is the use of molecular microbiological diagnostic techniques combined with blood cultures cost-effective?
19. In patients with SS receiving vasopressors, is maintaining a mean arterial pressure (MAP) ≥ 65 mmHg vs MAP < 65 mmHg, more effective and safer?
20. In suspected or confirmed SS, is early ICU admission vs delayed admission, more effective and safer?

PICO: Population/Patient, Intervention, Comparator, Outcomes; ED: emergency department; qSOFA: quick Sequential Organ Failure Assessment; SIRS: systemic inflammatory response syndrome; NEWS-2: National Early Warning Score 2; suPAR: soluble urokinase plasminogen activator receptor; proADM: proadrenomedullin.

PICO questions and recommendations

PICO Question 1

In adult patients aged < 65 years, is the qSOFA score vs SIRS criteria, NEWS-2, and other scales/models (qSOFA–lactate, qSOFA–procalcitonin, qSOFA–suPAR, qSOFA–proADM, SIRS–procalcitonin, SIRS–lactate), a better predictor of sepsis for initial assessment?

Recommendation

In adult patients aged < 65 years, qSOFA should not be used as the sole predictive tool for sepsis (for either diagnosis or prognosis). Sepsis should be suspected—

Table 4. Inclusion and exclusion criteria of the GT-LATINFURG Group for systematic and narrative reviews

INCLUSION CRITERIA:
– Patients older than 14 years evaluated in the ED with suspected or confirmed community-acquired infection, with or without sepsis criteria, defined according to either the 2001 Consensus Conference (Sepsis-2)[12] with ≥ 2 SIRS criteria[11], or the 2016 Consensus Conference (Sepsis-3)[6] with ≥ 2 qSOFA criteria.
– Clinical assessment, collection of blood samples for laboratory testing, as well as blood cultures and other complementary and microbiological studies must have been performed during the initial evaluation in the ED, always within the first 24 hours after hospital arrival.
– The indication for the interventions, measures, or variables analyzed in each research question must have been made in the ED setting.
– Studies must provide a clear description of patient groups with and without the intervention under study, as well as relevant demographic, epidemiological, and clinical variables.
EXCLUSION CRITERIA:
– Pediatric patients (≤ 14 years) or mixed populations (pediatric and adult).
– Patients evaluated or managed in other services or care settings (intensive/critical care units, postoperative units, inpatient wards, primary care) or in settings other than the ED, including mixed environments (ED + other services).
– Patients diagnosed with septic shock at the initial ED evaluation, or mixed populations including patients with both sepsis and septic shock, according to definitions and criteria from both the Sepsis-2 and Sepsis-3 Consensus Conferences.
– Possible nosocomial origin of the infectious process.
– Articles with low statistical power or a limited sample size (small number of episodes of bacterial infection/sepsis or of the selected dependent variable).
– Case–control studies, narrative reviews, case reports, editorials, commentaries or opinion pieces, letters to the editor, conference abstracts or proceedings, and poster presentations.

GT-LATINFURG: Latin American Study Group for the Improvement of Care of Patients in Emergency Departments, sponsored by SEMES and FLAME; ED: emergency department; SIRS: systemic inflammatory response syndrome; qSOFA: quick Sepsis-related Organ Failure Assessment.
Prepared by the authors.

and therefore the sepsis code activated and the recognition bundle initiated from triage—in any patient with suspected or confirmed infection who presents with qSOFA ≥ 2, or SIRS ≥ 2, or NEWS-2 ≥ 5 (or ≥ 3 points in a single variable). In addition, for the diagnosis of sepsis or severe infection, a PCT level ≥ 0.51 ng/mL strengthens the suspicion of bacterial infection, and a lactate level ≥ 2 mmol/L indicates a worse prognosis.

Background

Following publication of the Sepsis-3 definitions in 2016,[6] initial controversies have increased and the effectiveness of qSOFA as a useful rule for identifying patients with suspected sepsis in EDs, as well as its role as a replacement for classical sepsis criteria, has been questioned.[1-3] Since then, multiple studies—including SRs and meta-analyses—have evaluated the ability of qSOFA and other scales and models to detect sepsis,[30-35] such as SIRS[11] and NEWS-2.[18]

The 2021 SSC explicitly recommends not using qSOFA as the sole tool for sepsis detection when vs other scales or criteria such as SIRS, NEWS, or MEWS. This is a strong recommendation with moderate-quality evidence.[1]

Within Sepsis-3, qSOFA was identified as a predictor of poor prognosis in patients with known or suspected infection; however, no analyses were performed to support its use as a screening tool.[6,13,14] Furthermore, early SRs and meta-analyses showed that qSOFA ≥ 2 was more specific but less sensitive than meeting 2 of the 4 SIRS criteria for early identification of infection-induced organ dysfunction.[30-35] Only 25%–27% of patients with qSOFA ≥ 2 identified in the ED were ultimately found to have an infectious process.[1,3]

Subsequently, multiple meta-analyses have compared the accuracy of qSOFA and SIRS criteria in the initial assessment of patients with suspected infection.[3,30-35] Results have been heterogeneous, likely reflecting differences in the populations studied. Overall, findings consistently show lower sensitivity for qSOFA (25%–43%) vs SIRS (75%–88%) for the diagnosis of infection-related sepsis, potentially limiting qSOFA's ability to detect high-risk patients in the ED.[3,30-35] Conversely, for short-term mortality prediction, qSOFA shows low sensitivity (≈ 60%) and moderate specificity (≈ 77%), whereas SIRS demonstrates higher sensitivity (≈ 88%) but low specificity (≈ 25%). These data support the use of SIRS as a screening tool to identify patients with possible sepsis and to prompt initiation of treatment.[3,30-35]

In reality, neither SIRS nor qSOFA represents an ideal tool for ED use, and both have important limitations,[1-3] as do NEWS-2 and MEWS with respect to mortality prediction.[3,19]

In this context, EUCM specialists have long sought a definition or approach that provides optimal sensitivity and specificity for both early detection (diagnosis) and risk stratification and mortality prediction (prognosis), enabling rapid clinical decision-making in the ED.[2,3,10] Early definitions (Sepsis-1 and Sepsis-2) based diagnosis on the presence of a physiological response (SIRS) + suspected or confirmed infection.[11,12] These definitions proved highly sensitive but poorly specific, leading to the Sepsis-3 consensus,[13] which placed organ dysfunction at the core of the sepsis definition and emphasized mortality risk. Consequently, current ED practice shows wide variability in the use of sepsis definitions and scoring systems, with no clear consensus.[3,36] As of 2025, substantial controversy remains regarding the most appropriate criteria for defining and diagnosing sepsis in EDs across Latin American and European countries, contributing to marked variability in outcomes and estimates.[2,3,36]

In the search for improved diagnostic criteria, several proposals using variables readily available in EDs have been explored. For years, combinations of commonly used clinical scales (SIRS, qSOFA, NEWS-2, MEWS) have been proposed,[19,37-40] as well as their combination with well-established biomarkers (lactate and PCT)[41-47] and other highly promising biomarkers not yet routinely available in EDs, including midregional proadrenomedullin (MR-proADM), soluble urokinase plasminogen activator receptor (suPAR), presepsin, and interleukins 6 and 8.[48-57]

Summary of the evidence

Table 5 describes the characteristics of the 5 SRs and meta-analyses[39,58-61] included in the evaluation of PICO Question 1 that met the inclusion criteria described in Table 4. Additional eligible studies were also identified. Mellhammar *et al.*[63] reported that NEWS-2 outperformed qSOFA in detecting sepsis with organ dysfunction and predicting mortality. Similarly, Usman *et al.*[64] and Churpek *et al.*[35] confirmed the superiority of NEWS-2 over qSOFA for sepsis diagnosis and mortality prediction, respectively. Oduncu *et al.*[40] reported higher sensitivity for SIRS, higher specificity for qSOFA, and superior overall performance for NEWS-2.

A recently published SR and meta-analysis by Moncada-Gutiérrez *et al.*[45] (which only partially included ED populations) showed that adding lactate to qSOFA (LqSOFA) improved prediction of in-hospital mortality, with an area under the receiver operating characteristic curve (AUROC) of 0.807 (95% CI, 0.783–0.831), sensitivity of 61% (95% CI, 60–63), and specificity of 81% (95% CI, 80–81). Shah *et al.*[65] studied 933 critically ill patients (21% mortality; 56% ICU admission) and found that patients with SIRS ≥ 2 and PCT ≥ 2 ng/mL had significantly higher mortality (32% vs 16%) and ICU admission rates (76% vs 47%) vs patients with SIRS ≥ 2 and PCT < 2 ng/mL ($P < .0001$). In contrast, although similar trends were observed for qSOFA, no significant differences were found when adding PCT ≥ 2 ng/mL.

Two large prospective multicenter studies from the INFURG-SEMES group involving 4439 patients (30-day mortality, 10.3%) demonstrated that incorporating PCT and lactate improved the performance of SIRS and qSOFA for diagnosing bacterial infection and bacteremia, as well as predicting 30-day mortality. In the first study,[46] the model SIRS ≥ 2 + PCT > 0.5 ng/mL im-

proved microbiological confirmation and bacteremia diagnosis (AUROC, 0.890; 95% CI, 0.880–0.901; sensitivity, 79%; specificity, 85%). The best mortality prediction was achieved by adding lactate ≥ 2 mmol/L to qSOFA ≥ 2 (AUROC, 0.738; sensitivity, 60%; specificity, 91%). In the second study,[47] results were consistent with those reported by Seymour *et al.*,[13] showing that patients with qSOFA = 1 and lactate ≥ 2 mmol/L had similar in-hospital mortality to patients with qSOFA ≥ 2. Thus, qSOFA = 1 + lactate ≥ 2 mmol/L significantly improved predictive performance vs qSOFA = 1 alone and approached that of qSOFA ≥ 2. Thus, qSOFA = 1 plus lactate ≥ 2 mmol/L significantly improves the predictive performance achieved by qSOFA = 1 alone, with an AUROC of 0.66 (95% CI, 0.63–0.69), a sensitivity of 68% (95% CI, 61–75), and a specificity of 70% (95% CI, 67–73), reaching values very similar to those of qSOFA ≥ 2 (AUROC 0.66 vs 0.69; sensitivity 68% vs 51%; specificity 70% vs 85).[47]

Comments

Several SRs and meta-analyses have evaluated the ability of individual biomarkers to predict sepsis diagnosis, sometimes showing performance comparable to or exceeding that of qSOFA, SIRS, or NEWS-2. These include PCT,[66,67] presepsin,[53,57] MR-proADM,[57] suPAR,[56] and monocyte distribution width (MDW).[68,69]

Furthermore, recent studies on emerging biomarkers further support this approach. Rafael-González *et al.*[49] demonstrated that MR-proADM had superior predictive ability for poor clinical outcomes (progression to SS or ICU admission) and 30-day mortality vs PCT, lactate, CRP, and clinical scores. The combined model (MR-proADM ≥ 2.1 nmol/L + NEWS-2 ≥ 5) significantly improved prediction vs either component alone. Rubio *et al.*[55] concluded that suPAR had superior prognostic ability for 30-day mortality vs other biomarkers, and that combining qSOFA ≥ 2 with suPAR > 10 ng/mL enhanced qSOFA's predictive performance.

In summary, once these promising findings are validated in further studies—including those focused on specific subgroups such as immunocompromised patients—the most accurate initial assessment strategy for patients with suspected sepsis will likely involve combining rapid clinical prediction scales (qSOFA, SIRS, NEWS-2, and others) with emerging biomarkers (presepsin[53,57], MR-proADM[57], suPAR[56], MDW[68,69]). This approach has already been demonstrated for PCT and

Table 5. Characteristics of the systematic review and meta-analyses included in the review of PICO Question 1

Reference	Study design	Patients included	Objective	Main results	Authors' conclusions and comments
Jiang J, *et al.* 2018 [58]	SR and MA of prospective and retrospective studies	52,849	To compare the ability of qSOFA and SIRS to predict mortality	qSOFA ≥ 2: pooled RR 4.55 (95% CI, 3.38–6.14). SIRS ≥ 2: pooled RR 2.75 (95% CI, 1.96–3.86).	qSOFA ≥ 2 was more specific, whereas SIRS ≥ 2 was more sensitive. Both qSOFA and SIRS have limitations as standalone risk stratification tools for infected patients in the ED.
Ruan H, *et al.* 2022 [59]	SR and MA of 16 prospective studies	35,756	To compare the ability of qSOFA and SIRS to predict in-hospital mortality	qSOFA: sensitivity 0.43 (95% CI, 0.32–0.54), specificity 0.89 (95% CI, 0.84–0.93). SIRS: sensitivity 0.80 (95% CI, 0.73–0.86), specificity 0.39 (95% CI, 0.30–0.50). AUC: qSOFA 0.76 (95% CI, 0.72–0.80); SIRS 0.67 (95% CI, 0.62–0.72).	qSOFA showed higher specificity but lower sensitivity than SIRS for predicting in-hospital mortality in ED patients. However, SIRS cannot be completely replaced in the ED setting.
Wang C, *et al.* 2022 [60]	SR and MA of 26 prospective and retrospective studies	62,338	To compare the ability of qSOFA, SIRS, and NEWS to predict mortality	– qSOFA: highest specificity (0.82; 95% CI, 0.76–0.86) and lowest sensitivity (0.46; 95% CI, 0.39–0.53). – SIRS: highest sensitivity (0.82; 95% CI, 0.78–0.85) and lowest specificity (0.24; 95% CI, 0.19–0.29). – NEWS: intermediate sensitivity (0.73; 95% CI, 0.63–0.81) and specificity (0.52; 95% CI, 0.39–0.65). – qSOFA showed higher overall prognostic accuracy (AUC) than SIRS and NEWS.	qSOFA demonstrated better overall prognostic accuracy than SIRS and NEWS. However, no scoring system achieved optimal sensitivity and specificity for predicting mortality in patients with suspected sepsis.
Svendsen M, *et al.* 2023 [61]	SR of 5 prospective and retrospective studies	8,944	To compare the ability of qSOFA and SIRS to predict sepsis	SIRS showed higher sensitivity (56.4%–86.3%) than qSOFA (16.7%–48.6%). qSOFA showed higher specificity (89.1%–98%) than SIRS (18.8%–86.4%). Positive predictive value was higher for qSOFA; negative predictive values were similar.	qSOFA ≥ 2 was more specific, whereas SIRS ≥ 2 was more sensitive. qSOFA appears to be the most suitable screening tool for nursing staff for prognostic accuracy in sepsis detection in the ED.
Chua WL, *et al.* 2024 [39]	SR and MA of 10 prospective and retrospective studies	52,474	To compare the ability of qSOFA, SIRS, and NEWS to predict sepsis and in-hospital mortality	Sepsis diagnosis: – qSOFA: highest specificity 94% (95% CI, 86–98) and lowest sensitivity 37% (95% CI, 20–59). – SIRS: highest sensitivity 70% (95% CI, 49–85) and lowest specificity 62% (95% CI, 41–80). – NEWS: intermediate sensitivity 58% (95% CI, 47–68) and specificity 84% (95% CI, 69–93) In-hospital mortality: similar patterns observed.	No single scoring system demonstrated optimal sensitivity and specificity when used alone to predict sepsis or in-hospital mortality.

SR: systematic review; MA: meta-analysis; RR: relative risk; 95% CI, 95% confidence interval; qSOFA: quick Sequential Organ Failure Assessment; SIRS: Systemic Inflammatory Response Syndrome; NEWS-2: National Early Warning Score 2; ED: emergency department; AUC: area under the receiver operating characteristic curve; Se: sensitivity; Sp: specificity.

lactate in recent meta-analyses, significantly improving diagnostic and prognostic performance in EDs and even in prehospital emergency medical services.[48,70]

PICO Question 2

In patients aged ≥ 65 years, is the qSOFA score vs SIRS criteria, NEWS-2, and other scales/models (qSOFA–lactate, qSOFA–procalcitonin, qSOFA–suPAR, qSOFA–proADM, SIRS–procalcitonin, SIRS–lactate), a better predictor of sepsis for initial assessment?

Recommendation

In patients aged ≥ 65 years, qSOFA should not be used as the sole predictive tool for sepsis (for either diagnosis or prognosis). Sepsis should be suspected—and therefore the sepsis code activated and the recognition bundle initiated from triage—in any patient aged ≥ 65 years with suspected or confirmed infection who presents with qSOFA ≥ 2, or SIRS ≥ 2, or NEWS-2 ≥ 4 (or ≥ 3 points in a single variable), as well as a score ≥ 1 on the GYM scale.[74] In addition, for the diagnosis of sepsis or severe infection, a PCT level ≥ 0.51 ng/mL strengthens the suspicion of severe bacterial infection, and a lactate level ≥ 2 mmol/L indicates a worse prognosis.

Background

For patients aged ≥ 65 years, no specific indications were found within the Sepsis-3 definitions[6] or within the 2021 SSC guidelines.[1]

In addition to the limitations of qSOFA described in PICO Question 1, it is known that in frail subgroups such as patients older than 65 years—where clinical manifestations may be more confusing and underdiagnosis more pronounced[71,72]—the diagnostic performance of SIRS for sepsis and the prognostic performance of qSOFA for mortality are even worse.[3,73] SIRS is even less specific for infection in older adults, and it is assumed that cutoffs used for the general adult population may be suboptimal in the elderly.[71,72] In older adults, clinical signs of organ failure may be expressed with a less marked increase in respiratory rate, prolonged capillary refill time, poor peripheral perfusion, low urine output, or altered mental status.[71,72] These pathophysiological changes, together with immunosenescence, make detection and assessment of older patients with suspected sepsis particularly challenging.[3,71]

Summary of the evidence

No SR meeting the inclusion criteria (Table 4) was identified for this PICO question. Only a limited number of cohort studies provide results that have not been adequately validated.

González del Castillo *et al.*[74] proposed a new scale (GYM: Glasgow Coma Scale < 15; tachypnea > 20 breaths/min; Charlson comorbidity index ≥ 3) to predict 30-day mortality in patients aged ≥ 75 years presenting to the ED with infection. In a cohort of 293 patients (13% mortality), SIRS ≥ 2 yielded an AUROC of 0.58 (95% CI, 0.49–0.68), whereas GYM yielded an AUROC of 0.75 (95% CI, 0.66–0.84). Subsequently, the same group published another study[75] evaluating 30-day mortality prediction in older patients without severe dependency presenting to the ED with acute infection. SIRS ≥ 2 showed sensitivity of 65% (95% CI, 53–76) and specificity of 49% (95% CI, 46–52); qSOFA ≥ 2 showed sensitivity of 28% (95% CI, 18–40) and specificity of 94% (95% CI, 92–95); and GYM ≥ 1 showed sensitivity of 81% (95% CI, 69–89) and specificity of 45% (95% CI, 42–48). The AUROC was 0.73 (95% CI, 0.66–0.79) for GYM, 0.69 (95% CI, 0.61–0.76) for qSOFA, and 0.65 (95% CI, 0.59–0.72) for SIRS. Thus, GYM ≥ 1 was the most sensitive, while qSOFA ≥ 2 was the most specific. García-Lamberechts *et al.*[76] conducted a relevant multicenter study across 52 Spanish EDs including 6054 patients aged ≥ 65 years with infectious processes and a 30-day mortality of 16.4%. NEWS demonstrated the best point estimate (AUROC, 0.76; 95% CI, 0.72–0.81) vs qSOFA (AUROC, 0.70; 95% CI, 0.65–0.75) and GYM (AUROC, 0.72; 95% CI, 0.67–0.76), and no difference was observed between qSOFA and GYM. A GYM cutoff ≥ 1 was the most sensitive, whereas qSOFA ≥ 2 showed high specificity. NEWS showed the greatest predictive ability for 30-day mortality, with NEWS ≥ 4 yielding high sensitivity and NEWS ≥ 8 yielding high specificity.

Regarding lactate, Del Portal *et al.*[77] concluded that, in patients aged ≥ 65 years with infections, lactate ≥ 2 mmol/L is linearly associated with increased relative risk (RR) of in-hospital mortality (RR, 1.9–3.6) and 30-day mortality (RR, 1.7–2.6) vs patients with lactate < 2.0 mmol/L. Similarly, in a multicenter study including 739 patients aged ≥ 75 years, Yañez *et al.*[43] showed that adding lactate assessment to SIRS and qSOFA improved their ability to identify older patients with infection at risk of short-term death. AUROC for SIRS ≥ 2 (0.64; 95% CI, 0.59–0.69) and qSOFA ≥ 2 (0.69; 95% CI, 0.63–0.76) increased to 0.705 (95% CI, 0.65–0.76) and 0.755 (95% CI, 0.70–0.81), respectively, when lactate was added. Sensitivity for SIRS ≥ 2 (73.6%) and qSOFA ≥ 2 (58.2%) increased to 89% (SIRS ≥ 2 + lactate ≥ 2) and 79.1% (qSOFA ≥ 2 + lactate ≥ 2). However, adding the Charlson index did not improve performance.[43]

Other smaller, less generalizable studies have proposed additional models, such as the LIBPAS model[78] (lactate > 4 mmol/L, Barthel Index ≤ 60, and systolic blood pressure < 90 mmHg), which achieved an AUROC of 0.97 (95% CI, 0.95–0.99), and the INFURG-OLDER model,[79] which includes variables such as metastatic solid tumor, respiratory failure, renal failure, arterial hypotension, and decreased level of consciousness, with an AUROC of 0.78 (95% CI, 0.72–0.84).

Julián-Jiménez *et al.*[44] reported that MR-proADM had superior prognostic ability for 30-day mortality vs other biomarkers (lactate, CRP, PCT, suPAR). The combined model qSOFA ≥ 2 with MR-proADM > 2.07 nmol/L significantly improved the predictive ability of qSOFA, with an AUROC of 0.88 (95% CI, 0.75–1.00),

sensitivity of 69% (95% CI, 39–90), and specificity of 97% (95% CI, 92–99).

Comments

Based on the above, in patients aged ≥ 65 years it may be appropriate to adopt a more flexible approach and incorporate additional supportive tools, such as biomarkers or new scales, to improve the limited performance of qSOFA, SIRS, or NEWS-2. Further research is needed to validate these promising results in this subgroup, given their vulnerability and the limited available evidence.

PICO Question 3

Does the use of blood lactate vs not using it, improve the accuracy of prognostic prediction and the identification of poor clinical outcomes in the ED?

Recommendation

For all adult patients with suspected or confirmed severe infection or sepsis presenting to the ED, measurement of blood lactate concentration is recommended during the initial patient assessment (triage) and should be included as part of the "sepsis profile." In addition, for the diagnosis of sepsis, a lactate level ≥ 2 mmol/L predicts a worse prognosis.

Background

The 2021 SSC recommends measuring serum lactate concentration in adult patients with suspected sepsis. This is classified as a weak recommendation with low-quality evidence.[1]

The association between lactate concentration and in-hospital and short-term (30-day) mortality in adult patients with suspected infection and sepsis presenting to the ED has been well established for many years,[2,3,41] as it has in intensive care units and other clinical settings.[80-82] For this reason, lactate measurement is included in international recommendations and in the vast majority of clinical practice guidelines for initial patient assessment,[1,3,83] as well as in the definition of SS according to the Sepsis-3 criteria.[6,14] Although lactate has also been proposed as a tool for detecting sepsis in adult patients with clinical suspicion (but without confirmation), it is not sufficiently sensitive or specific when used alone to definitively rule in or rule out the diagnosis.[1-3,41]

Summary of the evidence

In a SR including 25 studies (6 involving patients with sepsis), Alshiakh *et al.*[84] suggested that even moderately elevated serum lactate concentrations may predict poor outcomes in patients evaluated in the ED for a variety of conditions. Therefore, early (during initial assessment) and serial determination of serum lactate levels is necessary and should become part of routine testing in the ED to predict outcomes and guide therapies that may benefit critically ill patients, including those with suspected or confirmed sepsis.

Other multicenter studies discussed in PICO Question 1,[46,47] narrative reviews,[41] and SRs and meta-analyses[48,85] have demonstrated that lactate, when combined with other biomarkers and qSOFA, improves prediction of mortality and poor clinical outcomes. Furthermore, all patients with lactate levels ≥ 2 mmol/L—given the increased relative risk of mortality and progression to SS—should be promptly evaluated and treated in the ED and should not be discharged.[2,3,41] The same approach should be applied to patients aged ≥ 65 years[77] and to those who do not present with systolic blood pressure ≤ 100 mmHg.[41,86]

Comments

The SSC 2021 notes that because blood lactate measurement may not be available in resource-limited settings, its use is classified as a weak recommendation in favor of serum lactate as an adjunctive test.[1] In the authors' opinion, this limitation should not discourage its recommendation; rather, it should serve as an incentive for EDs that do not currently offer this test to incorporate it into their diagnostic capabilities.[2,3] In this way, lactate measurement can be included both in the initial evaluation of patients with suspected sepsis and in subsequent monitoring in the ED or other hospital settings (ICU, inpatient wards, etc.).[2,3] The importance of proper sample collection and processing is also emphasized.

PICO Question 4

Does the use of procalcitonin vs not using it, improve the accuracy of diagnostic prediction of bacterial infection in EDs?

Recommendation

For adult patients with suspected or confirmed severe infection or sepsis presenting to the ED, measurement of serum PCT is recommended during the initial patient assessment (triage) and should be included as part of the laboratory "sepsis profile." In addition, a PCT level ≥ 0.25 ng/mL strengthens the suspicion of bacterial infection.

Background

Early and appropriate administration of antibiotic therapy (AT) and prompt diagnostic and therapeutic decision-making have a direct impact on survival in patients with severe bacterial infection.[1-3]

In Recommendation 16, the 2021 SSC suggests not using PCT in addition to clinical evaluation to decide when to initiate antimicrobial therapy vs clinical evaluation alone. This is classified as a weak recommendation with very low–quality evidence.[1] However, it is noteworthy that in Recommendation 31, for adult patients with an initial diagnosis of sepsis or SS in whom adequate source control has been achieved, the SSC 2021 does suggest using PCT in addition to clinical evaluation to guide decisions on when to discontinue antibiotics vs clinical evaluation alone. In this case, it is a

weak recommendation with low-quality evidence.[1] The references cited in SSC 2021 to support Recommendation 16 are not based on studies conducted in ED populations; therefore, none meet the inclusion criteria outlined in Table 4. Moreover, one of the arguments cited by the guideline authors for not recommending PCT as an adjunct to clinical evaluation is the absence of apparent benefit, unknown costs, and limited availability in some settings. Ultimately, SSC 2021 issued a weak recommendation with very low–quality evidence against using PCT to guide initiation of antibiotics in addition to clinical evaluation.[1] In contrast, evidence from studies conducted over the past 20 years in ED settings has been favorable toward the use of PCT as an adjunct to clinical assessment, clinical judgment, and other complementary tests, particularly in frail and vulnerable subgroups such as patients aged ≥ 65 years.[2,3,41,46,66,87]

Summary of the evidence

In this context, the GT-LATINFURG group recently published a SR analyzing the diagnostic accuracy of PCT for bacterial infection.[87] The primary endpoint was to evaluate the diagnostic accuracy of PCT in predicting bacterial infection among adult patients presenting to the ED with clinical suspicion of infection and to assess whether a specific PCT cutoff value could be identified as most clinically relevant for decision-making in EDs.[87] The SR identified a total of 21 studies (10 333 patients, including 4856 with bacterial infections [47%]) that met the inclusion criteria. Eight studies were rated as high quality, 8 as moderate quality, and 4 as low quality. The area under the receiver operating characteristic curve (AUROC) across studies ranged from 0.68 (95% CI, 0.61–0.72) to 0.99 (95% CI, 0.98–1.00). A PCT cutoff between 0.2 and 0.3 ng/mL was the most frequently used and proposed threshold, appearing in 12 of the included studies, with an estimated mean AUROC of 0.79. When only the five high-quality studies using a PCT cutoff of 0.2–0.3 ng/mL were considered, the estimated mean AUROC was 0.78, with a sensitivity of 69% and a specificity of 76%. This SR demonstrates that PCT has considerable diagnostic accuracy for bacterial infection and represents a useful tool for suspecting bacterial etiology in patients presenting to the ED with community-acquired infectious processes. Moreover, a PCT decision threshold > 0.25 ng/mL (0.2–0.3 ng/mL) has emerged as the most appropriate, extensively studied, and validated cutoff—always when used in combination with clinical judgment and other independent clinical variables. This approach may facilitate decisions regarding blood culture collection, additional microbiological testing, and diagnostic–therapeutic strategies, including the initiation of antimicrobial therapy.[87]

Since publication of the above SR[87], no additional studies fully meeting the inclusion criteria of Table 4 have been identified, although some have reinforced its findings. Zaki *et al.*[88] highlighted that PCT provides moderate accuracy in diagnosing sepsis and assessing severity, emphasizing its rapid turnaround and ability to distinguish bacterial from viral infections. In another SR, Chuang *et al.*[67] concluded that although PCT outperforms CRP for sepsis diagnosis (AUROC, 0.74; 95% CI, 0.62–0.84) and, at a cutoff > 0.54 ng/mL, yields a sensitivity of 70% and specificity of 67%, its discriminative capacity remains limited, underscoring the need for additional tools to improve sepsis diagnosis. Importantly, CRP cannot substitute for PCT in diagnosing bacterial infection.

Comments

In the authors' opinion, based on the current scientific evidence generated in ED settings, the recommendation to use PCT as an adjunctive tool in the initial evaluation of patients with suspected severe bacterial infection and sepsis should encourage EDs that do not currently offer this test to make it available to emergency physicians.[2,3,41] In this way, PCT can be incorporated both into the initial assessment of patients with suspected sepsis and into subsequent monitoring within the ED or other hospital settings (ICU, inpatient wards, etc.).[2,3]

Nevertheless, clinicians should be aware of situations in which false-negative results may occur (eg, early phases of infection, certain microorganisms, localized infections) and false-positive results may arise in conditions causing noninfectious SIRS (eg, severe trauma, burns, malaria, major surgery, shock, or certain malignancies).

In the future, other biomarkers[53,56,57] or multimarker models[41,48,49]—currently unavailable in most EDs—may outperform PCT. However, until these approaches are validated and shown to be effective, they cannot be recommended for widespread use.

PICO Question 5

In patients with a clinical diagnosis of infection and suspected bacteremia, does the use of procalcitonin vs not using it, improve the accuracy of diagnostic prediction of bacteremia in blood cultures obtained in the ED?

Recommendation

For adult patients with a clinical diagnosis of infection and suspected bacteremia presenting to the ED, measurement of serum PCT concentration is recommended. In addition, a PCT level ≥ 0.51 ng/mL strengthens the suspicion of bacterial infection with concomitant bacteremia.

Background

The 30-day mortality rate in patients with bacteremia is 2–3 times higher than in patients with the same infectious process without bacteremia. Therefore, early and appropriate administration of antibiotic therapy and prompt diagnostic and therapeutic decision-making have a direct impact on survival, and these patients are assumed to have severe bacterial infection.[1-3]

As discussed in PICO Question 4, the 2021 SSC suggests not using PCT in addition to clinical evaluation to decide when to initiate antibiotic therapy vs clinical evaluation alone. This is a weak recommendation with very low–quality evidence.[1] In contrast, studies conducted over recent years in ED settings support the use of PCT as an adjunctive tool for predicting bacteremia when combined with clinical assessment, clinical judgment, and other complementary tests.[2,3,41,46,90,91]

Summary of the evidence

The GT-LATINFURG group recently published a SR evaluating the diagnostic accuracy of PCT for predicting true bacteremia in adult patients presenting to the ED with clinical suspicion of infection, and to identify a clinically relevant PCT cutoff value to guide decision-making.[92]

The SR identified a total of 20 studies (18 120 blood cultures processed, with 2877 bacteremias [15.9%]) that met the inclusion criteria (Table 4). Ten studies were rated as high quality, 9 as moderate quality, and 1 as low quality. The AUROC across studies ranged from 0.68 (95% CI, 0.59–0.77) to 0.98 (95% CI, 0.97–0.99). A PCT cutoff > 0.5 ng/mL was the most frequently used threshold, appearing in ten studies, with an estimated mean AUROC of 0.83 (95% CI, 0.80–0.87). When only the six high-quality studies using a PCT cutoff > 0.5 ng/mL were considered, the mean AUROC was 0.89 (95% CI, 0.85–0.92), with sensitivity of 77.6% (95% CI, 72–83) and specificity of 78% (95% CI, 73–84). This SR demonstrates that PCT has substantial diagnostic accuracy for bacteremia and represents a useful tool for risk stratification. Moreover, a PCT level > 0.5 ng/mL is the most appropriate, extensively studied, and validated cutoff for predicting bacteremia—always when used in combination with clinical judgment and other independent patient- and process-related variables. In particular, a PCT level < 0.5 ng/mL may be reasonably used to rule out bacteremia. This approach facilitates decisions regarding blood culture collection and diagnostic–therapeutic strategies.

Since publication of this SR[92], no additional studies meeting the inclusion criteria of Table 4 have been identified, although several reports have reinforced its findings. Overall, these studies show PCT to be the biomarker with the highest predictive performance for bacteremia in the ED, outperforming CRP, presepsin, suPAR, and MR-proADM. However, when PCT is combined with presepsin or MR-proADM, the predictive ability of each biomarker improves further.[41,90,93,94]

Comments

In the authors' opinion and based on current scientific evidence generated in ED settings, the recommendation to use PCT as an adjunctive tool for predicting bacteremia is justified. Furthermore, when combined with other biomarkers or included as one of the variables in bacteremia prediction models, PCT may help optimize blood culture requests in the ED.[3,90-92]

PICO Question 6

In patients with a clinical diagnosis of infection and suspected bacteremia, does the use of other predictive models vs the Shapiro score/model, improve the ability to predict bacteremia in blood cultures obtained in the ED?

Recommendation

For adult patients with a clinical diagnosis of infection and suspected bacteremia presenting to the ED, the use of bacteremia prediction models (BPMs) 5MPB-Toledo and MPB-INFURG-SEMES is recommended. A score ≥ 5 using either the 5MPB-Toledo or the MPB-INFURG-SEMES model clearly strengthens the suspicion of bacterial infection with concomitant bacteremia.

Background

Indications for obtaining blood cultures in the ED and their diagnostic yield remain controversial. Suspicion and confirmation of bacteremia have major diagnostic and prognostic implications and necessitate immediate changes in key clinical decisions, including hospital admission vs discharge, blood culture collection, and prompt initiation of appropriate antimicrobial therapy.[1-3,91] Blood cultures are also obtained in the ED to ensure continuity of care, as subsequent management and outcomes depend on their results.[1-3]

Therefore, identifying an effective and broadly applicable bacteremia prediction model that avoids inappropriate discharges and unnecessary admissions is a major objective for many investigators.[91,92,96,97] These models or scores combine clinical, epidemiological, and laboratory variables—often including biomarkers of inflammatory response and infection—to significantly enhance predictive performance.[91,92,96,97] Until a few years ago, the bacteremia prediction model developed by Shapiro *et al.*[95] served as the reference standard in EDs worldwide.[91,92]

Summary of the evidence

The GT-LATINFURG group published a SR[98] to identify and compare the ability of bacteremia prediction models published since 2008 (the year of the Shapiro *et al.* model publication[95]) to predict bacteremia in ED settings, and to assess whether these models identify patient subgroups with high/very high or low/very low risk, as well as clinically relevant decision thresholds in the ED.

The SR identified a total of 20 studies (33 182 blood cultures processed, with 5074 bacteremias [15.3%]) that met the inclusion criteria (Table 4). Eleven studies were rated as high quality, 7 as moderate quality, and 2 as low quality. The AUROC of the Shapiro model ranged from 0.71 to 0.83, with sensitivity up to 98% and specificity between 26% and 69%. Among the 3 models with both internal and external validation and good methodological quality, the model by Lee *et al.*[99] achieved an AUROC of 0.81 with sensitivity of 68% and specificity of 81%; the 5MPB-Toledo model[96] achieved

an AUROC ranging from 0.906 (95% CI, 0.881–0.931) to 0.946 (95% CI, 0.933–0.960); and the MPB-INFURG-SEMES model[97] achieved an AUROC of 0.924 (95% CI, 0.914–0.934), with sensitivity of 96% (95% CI, 94–97) and specificity of 76% (95% CI, 74–78). The model by Lee *et al.*[99] was designed and validated exclusively in patients with pneumonia, whereas the 5MPB-Toledo[96] and MPB-INFURG-SEMES[97] models were developed and validated across multiple infectious processes and patient subgroups.[98]

Since publication of this SR[98], no additional studies meeting the inclusion criteria of Table 4 have been published, although some reports reinforce its findings. Kaal *et al.*[100] developed a predictive model highlighting the weight of PCT, consistent with the 5MPB-Toledo[96] and MPB-INFURG-SEMES models. A recent SR[101] showed that chills (one of the variables in MPB-INFURG-SEMES[97]) are highly specific (87%; 95% CI, 83–90) but poorly sensitive (37%; 95% CI, 29–45), indicating that clinical decisions should not rely on this variable alone.

Comments

Currently, the 5MPB-Toledo and MPB-INFURG-SEMES models represent useful tools for stratifying true bacteremia risk in patients presenting to the ED with various infectious processes. Both models use variables that are readily available during the initial patient assessment. Nonetheless, interpretation and use of these prediction models should always be combined with clinical judgment and other independent patient- and process-related variables. This approach facilitates decisions regarding blood culture collection and diagnostic–therapeutic strategies.[98]

PICO Question 7

Which patients should have blood cultures obtained in the ED, given the impact that microbiological isolation would have on prognosis, clinical course, and mortality?

Recommendation

For adult patients with suspected or confirmed severe infection or sepsis presenting to the ED, obtaining blood cultures (BCs) promptly is recommended in the various situations summarized in Tables 6, 7, and 8, and in particular: whenever the diagnosis of sepsis or SS is confirmed, serum PCT concentration is > 0.5 ng/mL, or a score ≥ 5 is obtained using either the 5MPB-Toledo or the MPB-INFURG-SEMES model.

Background

The 2021 SSC guidelines recommend obtaining cultures, including blood cultures, before initiating antimicrobial therapy in patients with suspected sepsis or SS, provided that this does not cause a substantial delay in treatment initiation (ie, < 45 minutes),[1] consistent with most international recommendations.[2,3,83]

However, as discussed in the background sections of PICO Questions 5 and 6, it remains neither clearly established nor universally agreed which patients should have blood cultures obtained in the ED, given the impact that microbiological isolation may have on prognosis, clinical course, and mortality.[3] In this regard, mortality among ED-origin bacteremia cases has been reported to range from 10% to 30% (2- to 3-fold higher than in patients with the same condition but without bacteremia).[1-3,102,103] Mortality is related to the severity of the clinical presentation, the type of primary source, and patient characteristics (eg, age, comorbidity, and other specific conditions).[3,102] Early identification in the ED of patients at risk for bacteremia is crucial: untreated bacteremia may progress to more severe stages such as SS and increase mortality. In this setting, immediate initiation of appropriate empiric antibiotic therapy is associated with improved prognosis.[3,102,104]

Summary of the evidence

GT-LATINFURG recently published a special review and opinion article[102] aimed at highlighting the relevance of the available scientific evidence, clarifying existing controversies, and determining which target adult population would benefit most from obtaining blood cultures in adults presenting to the ED with suspected sepsis or severe infection. In this context, "benefit" is defined not only as microbiological confirmation of bacteremia but also as the impact of that result on health outcomes and clinical course (prognosis, mortality, ICU admission, length of stay, appropriateness of antimicrobial therapy, and healthcare costs). Based on this analysis, the authors developed consensus recommendations regarding indications for blood cultures in ED settings. This review[102] was conducted in three phases as described in Phase 3 of the Methods section.

On the basis of accumulated evidence regarding the ability of newly proposed tools to predict bacteremia[92,98] and the diagnostic yield of blood cultures in ED settings, Table 6 proposes general recommendations for obtaining blood cultures in patients with severe infection and sepsis in the ED.[102] Table 7 provides specific recommendations according to the type of infectious process presenting to the ED.[102] Because the predictive performance of bacteremia prediction models (BPMs) in general populations may not be uniformly applicable to certain patient subgroups—requiring more detailed future analysis—Table 8 summarizes the utility of different BPMs for guiding blood culture collection in specific ED patient subgroups.[98,102,105]

After publication of this review, no additional SRs or studies meeting the inclusion criteria in Table 4 have been published, although some reports may reinforce its conclusions, such as the study by Muelas *et al.*,[105] which validates the utility of the MPB-INFURG-SEMES model in patients with solid tumors with and without neutropenia.

Comments

There is no definitive and comprehensive ED-based evidence identifying the specific population or patient profile most likely to derive clinical outcome benefit

Table 6. General recommendations for obtaining blood cultures in patients with severe infection in hospital emergency departments

Decision Support Tools	Clinical situation			
	No sepsis*	Probable sepsis**	Confirmed sepsis***	SS Present****
Procalcitonin < 0.1 ng/mL	No	No[2]	Yes[1]	Yes[1]
Procalcitonin 0.1–0.5 ng/mL	Individualized assessment[2,3]	Individualized assessment[2,3]	Yes[1]	Yes[1]
Procalcitonin > 0.5 ng/mL	Yes[1]	Yes[1]	Yes[1]	Yes[1]
5MPB-Toledo score ≥ 5	Yes[1]	Yes[1]	Yes[1]	Yes[1]
MPB-INFURG-SEMES score ≥ 5	Yes[1]	Yes[1]	Yes[1]	Yes[1]

5MPB-Toledo: Toledo bacteremia prediction model. MPB-INFURG-SEMES: INFURG-SEMES bacteremia prediction model (References 96 and 97, respectively); SS: septic shock.
*No sepsis: No sepsis criteria according to either Sepsis-1 (≥ 2 SIRS criteria)[11] or Sepsis-3 (2–3 qSOFA criteria)[6].
**Probable sepsis: Cases in which sepsis is considered likely after a comprehensive evaluation and no reasonable alternative diagnosis is identified.
***Confirmed sepsis: Proven infection fulfilling Sepsis-2 or Sepsis-3 criteria.
****SS: Proven infection fulfilling SS criteria.
[1]Within the first hour (as soon as possible): together with the remaining elements of the "recognition/triage bundle", including sepsis laboratory profile (lactate–procalcitonin), blood cultures, antimicrobial therapy, fluid resuscitation, vasopressors if indicated, and identification and control of the infectious source.
[2]In cases where sepsis is only a possible diagnosis after comprehensive evaluation and no alternative diagnosis is reasonably suspected or confirmed, diagnostic efforts should be intensified before obtaining blood cultures and administering antibiotics. If no alternative diagnosis is identified and sepsis remains possible, antibiotic therapy should be started and blood cultures considered within the first 3 hours to prevent progression to SS, with individualized assessment of patient characteristics.
[3]Consider potential confounders: false positives, bacterial aggression < 6 hours, prior antibiotic use within the previous 72 hours, localized source of infection, type of infectious process, baseline clinical status, and patient epidemiology (e.g., neutropenia, immunosuppression).
Adapted from reference 102.

from the decision to obtain blood cultures when sepsis or severe infection is suspected. However, given the importance of this decision and the findings of the aforementioned review, prompt blood culture collection may be recommended in the situations specified in Tables 6, 7, and 8—explicitly when the diagnosis of sepsis or SS can be confirmed, serum PCT concentration is > 0.5 ng/mL, or a score ≥ 5 is obtained using either the 5MPB-Toledo or the MPB-INFURG-SEMES model.

PICO Question 8

Are molecular microbiological diagnostic techniques (MMDTs) used in conjunction with blood cultures more effective and safe?

Recommendation

For adult patients in the ED with a clinical diagnosis of infection and suspected bacteremia and sepsis, it is recommended—as a complement to blood cultures and other microbiological studies—to have access to molecular MMDTs as adjunctive tools to improve microbiological diagnosis and patient management.

Background

In the search strategy used to address this PICO question, the following outcomes regarding "safety and efficacy" were assessed: reduced mortality, improved clinical cure, improved microbiological eradication, reduced ICU admission, shorter length of stay, fewer days of antibiotic therapy, and fewer in-hospital complications.

For more than a decade, several SRs and meta-analyses have evaluated different MMDTs, primarily comparing them with blood cultures in terms of effectiveness, safety, and cost-effectiveness.[106-108] However, only a subset of included studies specifically involved ED patients and ED-derived samples.[106-108] Timbrook *et al.*[106], in a meta-analysis including 31 studies and 5920 samples, evaluated the FilmArray technique, which uses an automated polymerase chain reaction (PCR) platform as a rapid diagnostic system to identify multiple pathogens (bacteria, viruses, yeasts) in a single test within approximately 1 hour using sealed cartridges and syndromic panels. Results showed that MMDTs were associated with significantly reduced mortality (OR, 0.66; 95% CI, 0.54–0.80), a reduction in length of stay by 2.48 days, and improved therapeutic appropriateness, with a shorter time to effective therapy (reduced by 5.03 hours). Antón-Vázquez *et al.*[107], in a SR including 1638 patients from EDs, inpatient wards, and ICUs, compared MMDTs (FilmArray, Septifast, GeneXpert, and LAMP) with blood cultures in patients with sepsis. In subgroup analyses of RCTs including 564 participants (low-certainty evidence), MMDTs may improve time to appropriate antibiotic administration, reducing time to adequate therapy vs standard care (mean difference, 17.29 hours; 95% CI, 10.47–45.05). No significant differences were observed in mortality or length of stay. Peri *et al.*[108], in another meta-analysis with fewer cases (617), confirmed that MMDTs (including FilmArray) shorten the time to pathogen detection and to identification of resistance mechanisms.

The SSC 2021 recommends obtaining cultures, including blood cultures, before initiating antimicrobials in patients with suspected sepsis or SS, but does not explicitly address MMDTs.[1]

Summary of the evidence

Table 9 summarizes selected study characteristics, acknowledging substantial heterogeneity (type of MMDT used, study design, risk of bias, etc.).[109-115] Based on Table 9, the following may be stated:

1. Diagnostic yield and sensitivity of MMDTs vs blood cultures vary across studies; in some cases, MMDTs demonstrate comparable or even superior sensitivity.

Table 7. Specific recommendations for obtaining blood cultures according to the type of infectious process in the emergency department

In all infectious processes when sepsis criteria are confirmed*, regardless of the source of infection.
CAP: In cases requiring hospital admission or empirical coverage for methicillin-resistant *Staphylococcus aureus* or *Pseudomonas aeruginosa,* as well as in patients with previous infections caused by these pathogens, hospitalization within the last 90 days, or other risk factors for resistant organisms.
UTI: In cases of APN (not in uncomplicated lower UTIs), and in patients with renal failure, immunosuppression, those receiving hemodialysis, or with risk factors for resistant pathogens.
Skin and soft tissue infections: In cases of cellulitis when the patient has significant comorbidities, immunosuppression, or risk factors for resistant pathogens, and in other situations warranting hospital admission (e.g., older adults). Blood cultures are also recommended in all cases of suspected or confirmed pyomyositis, deep infections, or necrotizing infections.
In the following infectious syndromes: Cholangitis, liver abscesses, meningitis, discitis, epidural abscesses, septic arthritis, and endovascular infections, in which 3 pairs of blood cultures should be obtained.

*Sepsis criteria: Defined according to either classic Sepsis-1 criteria (two or more Systemic Inflammatory Response Syndrome [SIRS] criteria) or Sepsis-3 criteria (2 to 3 qSOFA criteria) (References 6, 11, 12).
CAP: community-acquired pneumonia; APN: acute pyelonephritis; UTI: urinary tract infection; qSOFA: quick Sequential Organ Failure Assessment.
Adapted from reference 102 and from Fabre V *et al.* Does This Patient Need Blood Cultures? A Scoping Review of Indications for Blood Cultures in Adult Nonneutropenic Inpatients. Clin Infect Dis. 2020;71:1339–1347.

Combining both techniques improves diagnostic yield in some studies, particularly for early pathogen detection. Moreover, MMDTs show very high sensitivity and specificity for pathogen identification and detection of resistance mechanisms and provide faster results, which may be crucial in the clinical management of sepsis.

2. With respect to turnaround time, MMDTs (eg, Septifast, T2Bacteria [Werfen]) consistently provide results faster than blood cultures for pathogen detection in patients with sepsis and bacteremia.

3. Regarding therapeutic appropriateness (optimization and treatment duration), MMDTs (eg, Septifast, FilmArray, GeneXpert, T2Bacteria) contribute to improved therapeutic appropriateness by optimizing antibiotic therapy, reducing treatment duration, and/or identifying resistance mechanisms more rapidly than blood cultures.

After completion of this review, no additional SRs or studies meeting the inclusion criteria in Table 4 were identified, although related publications exist. Candel *et al.*[116] (comprehensive review) and Rapszky *et al.*[117] (SR) compared conventional blood cultures with rapid multiplex molecular syndromic panels (≥ 3 pathogens; turnaround time < 6 hours) that allow simultaneous detection of multiple pathogens and genotypic resistance markers. These tools reduced time to diagnosis, inappropriate empiric therapy, and antibiotic duration, and may reduce length of stay, potentially leading to cost savings. Despite these advantages, such panels have limitations, including restricted availability, missed diagnoses when the causative agent or resistance determinants are not included in the panel, false-positive results, and codetections. Overall, they represent a major advance in infectious disease diagnosis and enable more precise and timely interventions. However, at present, these techniques cannot replace classical microbiological methods, although they may be useful as complementary tests that increase pathogen detection rates.

Comments

Although reviewed studies suggest meaningful benefits of MMDTs vs conventional microbiological methods in terms of sensitivity and speed, methodological limitations may affect results, including heterogeneity in patient profiles, clinical settings, and molecular techniques used. In addition, lack of inclusion of certain pathogens (common or clinically important in ED settings) in some panels may lead to discrepancies in detection. Finally, variability in the type of direct sample analyzed and the limited number of studies for each sample type and each MMDT preclude more definitive comparisons. Therefore, the available evidence supports implementing MMDTs as a valuable adjunct in the management of patients with sepsis in ED settings, as a complement to conventional microbiological studies. Nevertheless, addressing current limitations and conducting further research across different infectious processes and clinical contexts remains essential.

PICO Question 9

Does early empiric antibiotic therapy (< 3 hours from arrival at ED triage) vs no administration or delayed administration (≥ 3–6 hours), improve safety and effectiveness—ie, clinical course (by reducing progression to SS), short- and long-term mortality, complications, length of stay, and ICU admission?

Table 8. Utility of different predictive models for bacteremia in guiding blood culture collection in specific emergency department patient subgroups

Patients aged ≥ 65 years: 5PMB -Toledo and PMB-INFURG-SEMES (Reference 98). Comment: Although diagnostic performance is slightly lower in this age group, it is still considered very good and clinically applicable for both models.
Patients with solid malignancies: PMB-INFURG-SEMES (References 98, 105). Comment: This model shows very good performance in patients with solid tumors, both with and without metastases, as well as in those with chemotherapy-related neutropenia.
Immunocompromised patients: 5PMB -Toledo (Reference 98).

PMB: predictive model of bacteremia.
In patients with neutropenia or immunosuppression, the decision to obtain blood cultures should be individualized according to disease severity. Predictive models of bacteremia should be used as supportive tools to aid clinical decision-making rather than as stand-alone criteria.
Adapted from reference 102.

Table 9. Characteristics of the studies selected in the review of PICO Question 8

Reference	Study design	Patients included (n)	Objective (technique)	Results, conclusions, and authors' comments
Idelevich EA, *et al.* 2015 [109]	Single-center RCT	150	Compare BC and SeptiFast in patients with sepsis	**MMDT improved antibiotic appropriateness,** shortening the time to optimal antibiotic therapy to 21.4 h (95% CI, 16.2–46.3) compared with 47.5 h in the control group (95% CI, 7.3–59.2). **Higher sensitivity test.** TMDM was positive in 30.7% of patients, accounting for 26.5% of samples, whereas BCs were positive in 40.0% of patients, representing 36.0% of samples. The overall agreement between both tests was 70.4%. In 55.2% of TMDM-positive samples, the same microorganism was identified by blood culture. **Faster test.** Time to pathogen detection was 5.3 h with TMDM vs 51.3 h to blood culture positivity.
Shengchen D, *et al.* 2019 [110]	Single-center RCT	800	Compare BC and FilmArray in patients with respiratory infections	**MMDTs reduced length of stay** (8 days [95% CI, 7–11] vs 9 days [95% CI, 7–12]), re*duced duration of antibiotic therapy* (7 vs 8 days), and improved antibiotic appropriateness. **Higher early de-escalation rates** (within 72 h: 7.7% vs 3.4%; 72 h–7 days: 29.8% vs 22.8%). **MMDTs were more cost-effective,** reducing IV antibiotic and hospitalization costs.
Burdino E, *et al.* 2014 [111]	Single-center cohort	1.024	Compare BC and SeptiFast in patients with sepsis	**MMDTs showed higher sensitivity** (18%) vs BC alone (15.4%). Combining both techniques increased overall diagnostic yield to 22%.
Avolio M, *et al.* 2010 [112]	Single-center RCT	252	Compare BC and SeptiFast in patients with sepsis	**MMDTs increased BC sensitivity:** MMDTs detected pathogens in 7% of BC-negative patients, raising sensitivity from 21% to 28%. **Faster turnaround** time with MMDTs (15 h [95% CI, 6–30] vs 36 h [95% CI, 48–72] for BC).
Hettwer S, *et al.* 2012 [113]	Single-center retrospective observational	211	Compare BC and SeptiFast in patients with sepsis	**MMDTs did not reduce mortality** (12.6% BC-guided vs 15.6% MMDT-guided) or length of stay (16.9 ± 15.1 vs 16.6 ± 14.1 days). Sensitivity was lower for MMDTs (37.8%) than BC (43%). MMDTs were less effective for detecting coagulase-negative staphylococci but more accurate for Gram-negative bacilli. **MMDTs provided faster results.**
Ziegler I, *et al.* 2016 [114]	Prospective cohort	696	Compare BC and Magicplex for bacteremia detection in sepsis	**MMDTs were more sensitive:** 46% positive with any method; 18% BC-positive vs 38% MMDT-positive. Using BC as gold standard, MMDT sensitivity 47%, specificity 66%, PPV 23%, NPV 87%. Coagulase-negative staphylococci and uncommon community pathogens were frequent in MMDT-positive/BC-negative samples.
Voigt C, *et al.* 2020 [115]	Prospective observational	137	Compare BC and T2Bacteria (Werfen) for bacteremia detection in sepsis	**MMDTs increased sensitivity,** with 100% positive agreement and 98.4% negative agreement vs BC. Detected 25% more infection-related positives. **Faster identification** (56.6 h earlier than BC). **MMDTs improved antibiotic adequacy** and shortened time to targeted therapy.

MMDTs: molecular microbiological diagnostic techniques; RCT: randomized controlled trial; BC: blood cultures; AB: antibiotic; h: hours.

Recommendation

For adult patients with a clinical diagnosis of infection and suspected bacteremia and sepsis presenting to the ED, early antimicrobial therapy is recommended, preferably within the first 3 hours (in practice, as soon as possible—once the diagnosis can be confirmed, or when suspicion persists and no alternative diagnosis is identified). Delaying antibiotic administration by each additional hour has been associated with a trend toward higher short-term mortality, increased long-term mortality, and a higher likelihood of progression to SS.

Background

Currently, in the absence of randomized clinical trials evaluating the benefits of early antimicrobial therapy in ED patients with sepsis, the evidence published in recent years has been inconsistent,[1-3,104,118,119] and substantial controversy remains regarding the recommended time window (within 1 hour, 3 hours, 6 hours, or longer) for empiric or targeted antibiotic administration in the ED, depending on the level of suspicion and clinical severity.[1-3,104] Nevertheless, early and appropriate antibiotic therapy has long been associated with shorter hospital length of stay, reduced ICU admission, and lower mortality.[118,119]

Accordingly, international guidelines—and specifically the 2021 SSC—recommend antibiotic administration within 1 hour for adults with possible, probable, or confirmed SS, as well as for patients "with a high likelihood of sepsis but without shock."[1] In contrast, when sepsis is possible but not confirmed, SSC 2021 recommends continuing diagnostic evaluation to confirm bacterial infection and, within the subsequent 3 hours, deciding either to administer antibiotics or to continue close observation ("weak recommendations with very low-quality evidence").[1] Other guidelines, such as Dutch guidelines, do not specify a strict time window (eg, 1 hour), but do recommend initiating antibiotics immediately in cases of sepsis and SS and emphasize that EDs should prioritize reducing time-to-antibiotics as much as possible.[121]

In this context, it appears reasonable to assume that early empiric antibiotic therapy—defined here as administration within < 3 hours of ED triage—in patients

Table 10. Recommendations on the timing of antibiotic therapy administration in patients with severe infection and sepsis in the emergency department

Clinical Situation	Confirmed sepsis	Probable sepsis	Possible sepsis
Shock present	Within the first hour (as soon as possible)[1]	Within the first hour (as soon as possible)[1]	Within the first hour (as soon as possible)[1]
No shock criteria	Within the first 3 hours (as soon as possible while attempting to confirm the diagnosis)[2]	Within the first 3 hours (as soon as possible while attempting to confirm the diagnosis)[2]	Preferably within the first 3 hours (after confirming the diagnosis)[3]

[1]Within the first hour (as soon as possible): together with the other measures of the "post-recognition or triage bundle," including obtaining the sepsis profile (lactate–procalcitonin), blood cultures, fluid resuscitation, vasopressors if indicated, and identification and control of the infectious source.
[2]Probable sepsis after comprehensive evaluation: when no alternative diagnosis is suspected, antibiotics should always be administered within the first 3 hours, except in cases of suspected severe infection, where administration within the first hour is recommended. These situations include suspected bacteremia, significant comorbidity (Charlson Comorbidity Index ≥ 3), extreme ages (older adults and neonates), specific foci such as meningitis or necrotizing skin and soft tissue infections, immunosuppression, neutropenia, transplant recipients, and similar high-risk conditions.
[3]Possible sepsis only: when sepsis remains merely a possibility after comprehensive evaluation and no reasonable alternative diagnosis is identified, efforts should be intensified to actively search for other diagnoses using all available emergency department resources. If no alternative diagnosis is found and sepsis remains possible, antibiotic therapy is recommended within the first 3 hours to prevent progression to SS, with individualized assessment based on patient characteristics and clinical context.
Adapted from reference 104.

with severe infection or sepsis is associated with a better prognosis (fewer complications and lower mortality).[1-3,118] However, systematically minimizing time-to-antibiotics for all suspected cases may cause harm.[3,120] In addition to unnecessary antibiotic exposure in patients without bacterial infection, potential harms include adverse drug reactions (eg, allergic or hypersensitivity reactions), renal or hepatic injury, thrombocytopenia, *Clostridioides difficile* infection, antimicrobial resistance, and increased costs.[3,118]

Summary of the evidence

GT-LATINFURG published a SR[104] comparing whether early antibiotics (< 3 hours from ED triage) vs delayed antibiotics (> 3–6 hours) in adult ED patients with severe infection or sepsis is safer and more effective, improving clinical course by reducing progression to SS and reducing short- and long-term mortality.

Seven studies meeting the inclusion criteria (Table 4) were included, comprising 118 349 patients; 74 141 (62.6%) received early AT.[104] Three studies were rated high quality, three moderate, and 1, low. Populations were heterogeneous, with early antibiotic administration ranging from 56% to 85%. None included patients diagnosed with SS, but they did include varying proportions classified as severe sepsis or hypotension responsive to initial fluid resuscitation.[104]

Among the 3 high-quality studies: one study showed a nonsignificant trend toward higher mortality when antibiotics were administered > 6 hours after triage vs < 1 hour (HR, 2.25; 95% CI, 0.91–5.59; $P = .08$). A second study reported an adjusted odds ratio (aOR) for in-hospital mortality of 1.09 per hour of delay from triage (95% CI, 1.05–1.13; $P = .024$). A third study found that each additional hour to antibiotic initiation was associated with a 10% increase (95% CI, 5%–14%; $P < .001$) in the probability of death at 360 days. Additionally, another study included in the review showed that time (in hours) to first antibiotic administration was associated with progression to SS (OR, 1.03; 95% CI, 1.02–1.04; $P < .001$).[104]

Based on the accumulated evidence, Table 10 presents recommendations regarding timing of antibiotic therapy in ED patients with severe infection and sepsis.

After publication of the GT-LATINFURG SR, a subsequent SR and meta-analysis by Tang *et al.*[122] evaluated the association between delayed antibiotics and mortality in patients with sepsis and SS (18 of 29 included studies were conducted in ED settings). Vs antibiotics administered within the first hour, each hour of delay increased in-hospital mortality (OR, 1.041; 95% CI, 1.021–1.062), and antibiotic administration after 1 hour increased in-hospital mortality (OR, 1.205; 95% CI, 1.123–1.293). When antibiotics were administered beyond the third hour vs early administration, the OR for in-hospital mortality was 1.297 (95% CI, 1.011–1.664). However, no significant association was found for 28-day, 90-day, or 1-year mortality

Comments

In cases of severe infection (suspected bacteremia or confirmed/possible sepsis) without meeting criteria for SS, early antibiotic administration can be recommended—primarily within the first 3 hours (in practice, as soon as possible once infection is confirmed or suspicion remains and no alternative diagnosis emerges). Evidence supports a trend toward higher in-hospital, short-term, and long-term mortality, as well as a higher probability of progression to SS, with each hour of delay in antibiotic administration.

PICO Question 10

In suspected or confirmed sepsis, is 0.9% saline vs balanced crystalloids/Ringer lactate/colloids/albumin/gelatins, safer and more effective?

Recommendation

For adult patients with a clinical diagnosis of severe infection and sepsis presenting to the ED who show signs of hypoperfusion or have sepsis-related hypotension, immediate resuscitation with balanced solutions (eg, Ringer lactate) is recommended rather than 0.9% saline for initial ED resuscitation. Current evidence indicates that balanced solutions are associated with a lower incidence of adverse renal events and lower mortality vs 0.9% saline. Although fluid choice should be individualized according to each patient's clinical characteris-

Table 11. Characteristics of randomized clinical trials comparing 0.9% saline with balanced solutions

Study (Author, year [Ref])	Study type	No. of patients (setting)	Intervention (balanced solutions)	Control (0.9% saline)	Primary outcome	Secondary Outcome
SMART Semler *et al.*, 2018 (126)	RCT	15,802 (ICU)	Balanced crystalloids	0.9% saline	Lower rate of major adverse kidney events (14.3% vs 15.4%, *P* = .01, favoring intervention)	Reduced in-hospital mortality (10.3% vs 11.1%, *P* = .04, favoring intervention)
SALT-ED Self *et al.*, 2018 (127)	RCT	13,347 (ED)	Balanced crystalloids	0.9% saline	Improved renal outcomes (13.5% vs 14.6%, *P* = .02, favoring intervention)	Reduced 30-day mortality (1.1% vs 1.3%, *P* = .05, favoring intervention)
CHEST Myburgh *et al.*, 2012 (128)	RCT	7,000 (ICU)	Hydroxyethyl starch	0.9% saline	No significant difference in 90-day mortality (17.0% vs 16.3%, *P* = .26)	Higher incidence of renal dysfunction with starch (7.0% vs 5.8%, *P* = .03, against intervention)
ALBIOS Caironi *et al.*, 2014 (129)	RCT	1,818 (ICU)	Albumin + 0.9% saline	0.9% saline alone	No significant difference in 28-day mortality (31.8% vs 32.0%, *P* = .94)	Non-significant trend toward lower 90-day mortality (41.1% vs 44.2%, *P* = .09, favoring intervention)

RCT: randomized controlled trial; ICU: intensive care unit; ED: emergency department.
Prepared by the authors.

tics and the specific clinical context, prioritizing balanced solutions is recommended, particularly in patients with renal risk factors or those requiring aggressive resuscitation.

Background

Timely and effective fluid resuscitation is crucial for stabilizing sepsis- and SS–induced tissue hypoperfusion in the ED.[1-3,83,123-125] The SSC 2021 recommends that initial sepsis resuscitation begin immediately ("best practice statement") and that, in patients with sepsis-induced hypoperfusion or SS, at least 30 mL/kg of crystalloids be administered early, within the first 3 hours of resuscitation ("weak recommendation with low-quality evidence"). It also recommends maintaining a low threshold to initiate resuscitation in patients in whom sepsis is not proven but is suspected.[1]

Traditionally, 0.9% saline has been the fluid of choice because of availability and low cost.[123] However, recent research has questioned its safety profile: its high chloride content may induce hyperchloremic acidosis, promote renal vasoconstriction, and contribute to acute kidney dysfunction, which is associated with higher mortality. Consequently, balanced crystalloids have gained popularity as preferred fluids because their lower chloride content more closely reflects physiologic human levels.[123-125] Balanced solutions such as Ringer lactate and Plasma-Lyte have an electrolyte composition closer to plasma and often include anions such as lactate, acetate, or gluconate that act as buffers to prevent acidosis. This supports a more stable acid–base balance, which is particularly relevant in septic patients who are prone to lactic acidosis.[123-125] From a physiological standpoint, administering large volumes of 0.9% saline can increase capillary hydrostatic pressure and worsen tissue edema, including pulmonary edema. This may complicate oxygenation and prolong hospitalization. In contrast, balanced solutions appear to be associated with less extravascular fluid accumulation. Nonetheless, it is important to note that certain balanced solutions contain potassium, which may pose risk in patients with hyperkalemia or severe renal failure; therefore, fluid selection should be individualized.[123-125]

Summary of the evidence identified

In the review produced by GT-LATINFURG, several relevant studies were identified, including randomized clinical trials, meta-analyses, and SRs, although most were not conducted in ED settings. Table 11 presents a selection of those considered most relevant.

Among recent multicenter studies and SRs/meta-analyses showing that balanced solutions are associated with a lower rate of acute kidney injury and lower in-hospital mortality vs 0.9% saline is the SMART trial.[126] SMART was a randomized clinical trial conducted in 3 ICUs including 15 802 adults who were randomized to receive either 0.9% saline or balanced crystalloids (lactated Ringer or Plasma-Lyte A). In the balanced-crystalloid group, the composite outcome occurred less frequently, including death (10.3% vs 11.1%), need for renal replacement therapy (2.5% vs 2.9%), and persistent renal dysfunction vs the saline group.

Similarly, the SALT-ED trial[127] (another randomized clinical trial) demonstrated comparable benefits in non-critically ill ED patients. This study compared balanced crystalloids (lactated Ringer or Plasma-Lyte A) with saline in adults treated in the ED who were subsequently hospitalized outside the ICU. A total of 13 347 patients were included; the median crystalloid volume administered in the ED was 1079 mL. Patients who received balanced crystalloids had a lower incidence of major adverse kidney events within 30 days (4.7% vs 5.6%; adjusted OR, 0.82 [95% CI, 0.70–0.95]; *P* = .01).

By contrast, colloids such as starches are associated with a higher risk of kidney failure and mortality in ICU patients, as shown in the CHEST trial.[128] Gelatins, although less studied, have not demonstrated clear advantages and are associated with potential adverse reactions. Albumin, according to the ALBIOS trial,[129] may have a role in patients with severe sepsis; however, albumin replacement + crystalloids vs crystalloids alone, did not improve 28- or 90-day survival.

In a meta-analysis by Xu *et al.*,[130] among patients with severe sepsis or SS, albumin use was associated with a significant reduction in mortality vs crystalloids (RR, 0.82 [95% CI, 0.70–0.97]). Conversely, Zarychanski *et al.*,[131] in a SR and meta-analysis, found that hydroxyethyl starch was associated with a significant increase in mortality risk and acute kidney injury. The clinical use of hydroxyethyl starch for acute volume resuscitation is not justified because of serious safety concerns.

Finally, over the past year, the European Society of Intensive Care Medicine published clinical practice guidelines on fluid therapy in critically ill adults.[132,133] In those guidelines, Recommendation 2 states: "We suggest the use of crystalloids rather than volume expansion with albumin in critically ill adult patients with sepsis" (conditional recommendation; moderate certainty of evidence). In Recommendation 8, they state: "We suggest the use of balanced crystalloids rather than isotonic saline for volume expansion in critically ill adult patients with sepsis" (conditional recommendation; low certainty of evidence).

Comments

For adult patients with a clinical diagnosis of severe infection and sepsis presenting to the ED who have sepsis-related hypotension or signs of hypoperfusion, immediate resuscitation is recommended. Current evidence supports the use of balanced solutions (eg, lactated Ringer) rather than 0.9% saline, because balanced solutions are associated with a lower rate of adverse events—particularly renal events—and lower mortality in patients with sepsis.[123-139,132] However, fluid selection should always be individualized according to each patient's clinical characteristics and the specific clinical context. In this setting, prioritizing balanced solutions is recommended, especially in patients with renal risk factors or those requiring aggressive resuscitation.[123-129,132]

PICO Question 11

In suspected or confirmed SS, is 0.9% saline vs balanced crystalloids/lactated Ringer/colloids/albumin/gelatins, safer and more effective?

Recommendation

For adult patients with a clinical diagnosis of SS presenting to the ED, immediate use of balanced solutions (eg, lactated Ringer) rather than 0.9% saline is recommended for initial resuscitation. Current evidence indicates that balanced solutions are associated with fewer adverse events and lower mortality vs 0.9% saline. Although fluid selection should be individualized according to patient characteristics and the specific clinical setting, prioritizing balanced solutions is recommended, especially in patients with renal risk factors or those requiring aggressive resuscitation.

Background

As discussed in the previous PICO question, immediate fluid resuscitation is crucial for stabilizing SS–induced tissue hypoperfusion and hypotension.[83,123-125,132,133] Although fluid choice should be individualized, balanced solutions are recommended as the preferred option when SS is diagnosed in the ED.[1,123-125,132,133]

The SSC 2021[1] recommends that initial sepsis resuscitation begin immediately ("best practice statement") and that, in patients with sepsis-induced hypoperfusion or SS, at least 30 mL/kg of crystalloids be administered early, within the first 3 hours of resuscitation ("weak recommendation with low-quality evidence").[1]

Once the resuscitation fluid is selected and after the initial phase, fluid administration should be guided by careful assessment of intravascular volume status and organ perfusion.[1,132,133] Dynamic measures have demonstrated better accuracy in predicting fluid responsiveness than static measures (heart rate, central venous pressure, and systolic blood pressure). Dynamic measures include passive leg raise with cardiac output measurement, response to fluid boluses, stroke volume variation, pulse pressure variation, and inferior vena cava collapsibility/distensibility—often supported by echocardiography, which is now considered indispensable in ED settings.[1,132]

When advanced hemodynamic monitoring is unavailable, alternative markers of organ perfusion can be used to evaluate the effectiveness and safety of volume administration, including extremity temperature, skin mottling, and capillary refill time; these have been validated and shown to be reproducible indicators of tissue perfusion.[1]

In addition, SSC 2021[1] suggests guiding resuscitation in adults with sepsis and SS using lactate (eg, lactate clearance) (weak recommendation; low-quality evidence) and using capillary refill time to guide resuscitation as an adjunct to other measures (weak recommendation; low-quality evidence).[1]

Summary of the evidence identified

Table 11 includes several studies considered most relevant and that include patients with SS. The evidence discussed in PICO Question 10 also applies to this question, including the SMART trial,[126] SALT-ED,[127] CHEST,[128] and ALBIOS.[129]

In the recent European Society of Intensive Care Medicine guidelines on fluid therapy in critically ill adults,[132,133] Recommendation 2 states: "We suggest the use of balanced crystalloids rather than isotonic saline for volume expansion in critically ill adult patients with sepsis,"[132] and the subsequent recommendations specify:[133]

1. In adults with sepsis or SS requiring fluid resuscitation for circulatory failure, administering up to 30 mL/kg of IV crystalloids during the initial phase is suggested (when hemodynamic monitoring is not yet available, generally within the first 3 hours), with adjustments based on clinical context and frequent reassessment (conditional recommendation; very low certainty of evidence).[133]

2. In adults with sepsis or SS requiring fluid resuscitation for circulatory failure, no recommendation can

be made for or against a systematically restrictive or liberal fluid strategy (no recommendation; moderate evidence of no effect).[133]

Comments

For adult patients with a clinical diagnosis of SS presenting to the ED, immediate use of balanced solutions (eg, lactated Ringer) rather than 0.9% saline is recommended for initial resuscitation. Although fluid choice should be individualized, prioritizing balanced crystalloids is recommended, particularly in patients with renal risk factors or those requiring aggressive resuscitation.[123-125] After the initial resuscitation stage, during the stabilization phase, dynamic measures provide better accuracy for assessing fluid responsiveness, ideally combined with lactate monitoring, echocardiography, and/or capillary refill time, depending on available resources.[1,132,133]

PICO Question 12

In suspected or confirmed SS requiring vasopressor therapy, is norepinephrine (NE) vs dopamine/epinephrine/vasopressin/others safer and more effective?

Recommendation

For adult patients with a clinical diagnosis of SS presenting to the ED, early use of NE is recommended as the first-line vasopressor for initial resuscitation. Evidence regarding inotrope use in the ED is limited. Therefore, initial use of NE is suggested, and high-quality randomized clinical trials are needed to confirm the effectiveness of vasopressors in ED settings.

Background

SS is a hyperdynamic state characterized by increased cardiac output and low systemic vascular resistance.[1,6,134] Prolonged peripheral vasodilation and elevated cardiac index in sepsis may lead to cardiac dysfunction or may mask underlying myocardial depression.[1,6,134]

After other measures are implemented and once tissue hypoperfusion or hypotension is identified, intravenous fluids are generally administered first, followed by vasopressor infusion when the blood pressure target is not achieved after optimization of intravascular volume.[1,135]

The 2021[1] SSC provides a strong recommendation for NE as the first-line vasopressor of choice, supported by evidence from multiple randomized clinical trials and SRs/meta-analyses. Vs other vasopressors (dopamine, vasopressin, epinephrine, selepressin, or angiotensin II), this strong recommendation is supported by high-quality evidence for dopamine comparisons, moderate-quality evidencefor vasopressin, and low or very low–quality evidence for the remaining agents.[1]

In adults with SS and cardiac dysfunction with persistent hypoperfusion despite adequate volume status and blood pressure, SSC 2021 suggests adding dobutamine to NE or using epinephrine alone.[1]

Thus, there is little controversy regarding NE as the vasopressor of choice. However, uncertainty remains regarding the optimal timing of NE initiation. Specifically, it is necessary to define whether ED administration should be early/immediate or deferred until after complete fluid resuscitation without hemodynamic normalization.[1,135,136] SSC 2021 issues a strong recommendation to start NE within the first hour of sepsis identification if the patient remains hypotensive during or after fluid administration.[1]

Summary of the evidence identified

GT-LATINFURG conducted a SR following PRISMA guidance[13] and the inclusion criteria in Table 4. This review was recently published by García *et al.*[137] Although 720 articles were initially identified, only 1 study met inclusion criteria: the CENSER randomized clinical trial[138] by Permpikul *et al.,* which enrolled 310 adults with sepsis and hypotension in the ED. The aim was to evaluate whether early low-dose NE increases shock control at 6 hours vs standard care (placebo). Shock was considered controlled if a MAP $\geq$ 65 mm Hg and urine output $\geq$ 0.5 mL/kg/h were achieved for 2 consecutive hours, or if serum lactate decreased by $\geq$ 10% from baseline at 6 hours after diagnosis. Time from ED arrival to NE administration was significantly shorter in the early NE group (median, 93 vs 192 minutes; $P < .001$). Shock control at 6 hours was higher in the early NE group (118/155 [76.1%] vs 75/155 [48.4%]; $P < .001$). Although 28-day mortality did not differ significantly (only a trend) and no significant differences were observed for other complications, early NE was associated with a lower rate of cardiogenic pulmonary edema (22/155 [14.4%] vs 43/155 [27.7%]; RR, 0.51 [95% CI, 0.41–0.81]; $P = .003$) and fewer new-onset arrhythmias (17/155 [11%] vs 31/155 [20%]; RR, 0.55 [95% CI, 0.32–0.95]; $P = .007$).

After completion of the GT-LATINFURG SR, Shi *et al.* published a SR and meta-analysis[139] examining early vs late NE initiation in adults with SS. Early initiation was associated with lower ICU mortality, less fluid volume administered at 6 hours, faster achievement of MAP targets, and more ventilator-free days. Across the 10 included studies, early NE reduced mortality in randomized clinical trials (OR, 0.49 [95% CI, 0.25–0.96]; $P = .04$). From the ED perspective, subgroup analyses suggested reduced mortality when NE was started within the first hour and lactate was $\leq$ 3 mmol/L—an ED-relevant scenario.

Comments

Overall, high-quality ED-specific evidence remains limited regarding the magnitude of benefit in patients with suspected or confirmed SS requiring vasopressor initiation. In centers where NE is not available in the ED, dopamine or epinephrine may be considered as alternatives; however, the primary recommendation in such settings is to ensure access to NE.

Accordingly, for adult patients with a clinical diagnosis of SS presenting to the ED, early NE is recom-

Table 12. Characteristics of systematic review or systematic review –meta-analyses comparing the efficacy and safety of vasopressor administration via central venous catheters vs peripheral venous catheters

Author, year (Ref.)	Design (No. of patients)	Objective	Results	Conclusions and authors' comments
Tian DH *et al.*, 2020 (141)	SR including 7 studies (1,382 patients)	To evaluate the frequency of complications associated with vasopressor administration via PVCs.	– NE was the most frequently administered drug (702 patients), followed by phenylephrine (546) and dopamine (108). – Mean infusion duration: 22 h (95% CI, 8–36 h). – Extravasation occurred in 3.4% (95% CI, 2.5–4.7) of patients; all cases were successfully managed conservatively or with vasodilators. – No cases of tissue necrosis or limb ischemia were reported.	No study met all validity criteria. When vasopressors are administered via PVCs for a limited time under close monitoring, extravasation appears to be infrequent and unlikely to cause serious complications.
Owen VS *et al.*, 2021 (144)	SR–MA including 11 adult studies (873 patients from EDs)	To analyze the rate of local adverse events associated with vasopressor administration via PVCs across different clinical settings.	– Pooled rate of adverse events related to intravenous vasopressor administration via PVCs was 1.8% (95% CI, 0.1–4.8). – Subgroup analyses (ICU, ED, other settings) showed no significant differences based on clinical environment.	The rate of adverse events was low. However, further research is required to evaluate specific effects in ED settings and according to catheter size, type, vasopressor dose, and patient characteristics to better assess the safety of vasopressor administration via PVCs.
Tran QK *et al.*, 2020 (145)	SR including 9 studies (2 conducted in EDs; 1,835 patients)	To assess the prevalence of complications related to vasopressor infusion through PVCs.	– A total of 122 complications (7%) were reported; 117 (96%) were minor. – Random-effects meta-analysis showed a pooled complication prevalence of 8% (95% CI, 3–21). – Studies reporting infusion safety protocols showed a lower prevalence of complications.	The prevalence of complications directly attributable to vasopressor infusion via PVCs was low, and even lower in studies implementing safety protocols. Further studies are needed to confirm these findings.

SR: systematic review; MA: meta-analysis; CVC: central venous catheter; PVC: peripheral venous catheter; NE: norepinephrine; h: hours; CI: confidence interval.
Prepared by the authors.

mended as the first-line vasopressor for initial resuscitation.

PICO Question 13

In suspected or confirmed SS requiring vasopressors, is peripheral venous vs central venous catheter administration, effective and safe?

Recommendation

For adult patients with a clinical diagnosis of SS presenting to the ED, it is suggested that for immediate vasopressor administration (in this case, NE), peripheral venous catheters (PVCs; large-bore, placed proximally to the antecubital fossa) represent a valid alternative within the first hours of SS until central venous access is established. Although some evidence supports this approach, evidence remains limited, and high-quality studies are needed to confirm its safety and efficacy.

Background

Traditionally, vasopressors have been administered almost exclusively through central venous catheters (CVCs) due to concerns about adverse effects when given through PVCs, such as extravasation, limb ischemia, and tissue necrosis.[136,140] CVC placement requires specialized training, can be time-consuming, and may delay early vasopressor initiation; it also carries its own insertion- and maintenance-related complications.[136,141] Therefore, because obtaining a CVC in the ED or prehospital emergency medical services may delay treatment and worsen outcomes, PVC vasopressor infusion may provide an effective short-term alternative to enable early initiation.[141-143]

SSC 2021 considers PVC use appropriate (proximal to the antecubital fossa and for a short duration) for vasopressor administration when central venous access cannot be immediately established.[1]

Summary of the evidence identified

GT-LATINFURG conducted a SR following PRISMA guidance.[13] The protocol was registered in PROSPERO (CRD42024500207). Most included studies were conducted in ICU or mixed settings; when available, ED adult subgroups were included. Ultimately, the review included 3 SRs/meta-analyses,[141,144,145] a post hoc analysis of a randomized clinical trial,[146] a randomized clinical trial,[147] 4 retrospective observational cohort studies,[148-151] and 1 prospective observational cohort study.[152] Table 12 illustrates the characteristics and findings of the SRs/meta-analyses.

Furthermore, in a post hoc analysis of the ARISE trial,[146] which assessed whether starting vasopressors via PVC vs CVC in ED patients with early SS was associated with earlier completion of some care processes, no mortality differences were observed. Conversely, in a resource-limited setting protocol that incorporated early antibiotics and NE via PVC in adults with sepsis and hypotension (most HIV-positive), in-hospital mortality increased vs usual care.[147] Similarly, in another resource-limited study including 64 patients, extravasation incidence rate with PVC vasopressors was low even with prolonged use, suggesting peripheral infusions may be acceptable when CVC placement barriers exist.[148] In 3 additional small retrospective studies using PVCs for vasopressors (primarily NE), extravasation and ischemic complications were very low or absent and did not significantly affect mortality.[149-151] Finally, in a

small prospective study (55 patients), complication rates associated with PVC vasopressors were low and did not result in significant morbidity.[152]

Comments

In ED settings, for adult patients with SS requiring immediate vasopressor therapy (NE as first option), large-bore PVCs placed proximally to the antecubital fossa may be considered an acceptable short-term alternative during the first hours of SS until CVC access is secured. However, evidence remains limited, and high-quality studies are needed to confirm safety and efficacy.

PICO Question 14

In patients with suspected or confirmed SS who require vasopressor therapy, is early vasopressor administration vs delayed administration safer and more effective?

Recommendation

For adult patients with a clinical diagnosis of SS in the ED, early vasopressor administration is suggested. Current evidence indicates that rapid vasopressor initiation, together with initial fluid resuscitation, is associated with improved shock control and a trend toward lower mortality. However, the decision should be individualized based on the patient's clinical condition and available hemodynamic monitoring.

Background

SS is a critical clinical condition characterized by persistent hypotension and inadequate tissue perfusion despite appropriate fluid administration.[1-3,133,153] Rapid restoration of blood pressure and tissue perfusion is essential to prevent multiorgan dysfunction and reduce mortality. Early vasopressor administration, such as norepinephrine, may help rapidly achieve hemodynamic targets, minimize the duration of hypotension, and improve clinical outcomes.[133,138,153]

The physiological rationale for early vasopressor initiation is that volume expansion with crystalloids, while essential, may be insufficient to restore blood pressure in cases of severe vasodilation. Vasopressors act directly on adrenergic receptors to increase systemic vascular resistance, thereby improving perfusion pressure without requiring excessive fluid volumes. In contrast, delayed administration extends hypoperfusion, delays blood pressure recovery, and may lead to the need for large fluid volumes, which are associated with complications such as pulmonary edema and abdominal compartment syndrome.[133,138,139,153] Moreover, initiating vasopressors during fluid resuscitation (rather than after) enables a balanced approach that avoids both hypovolemia and volume overload.[153] Some recent studies suggest that early NE may contribute to a lower incidence of pulmonary edema, shorter duration of mechanical ventilation, and reduced ICU length of stay. Conversely, delaying vasopressors may increase the risk of cardiovascular complications, endothelial injury, and an exaggerated inflammatory response.[133,138,139,153]

As detailed in PICO Question 12, recent randomized clinical trials and SRs/meta-analyses consistently show that, even when absolute mortality does not differ significantly across all studies, early NE is associated with faster shock reversal, shorter hospitalization, and reduced need for prolonged vasopressor support. These outcomes are clinically meaningful because faster recovery may translate into lower hospital costs and better quality of life among survivors. Thus, early vasopressor administration in SS not only supports hemodynamic recovery but also serves as an integrated strategy to minimize complications related to prolonged hypoperfusion and excessive fluid exposure. Nevertheless, decisions should be individualized, taking into account comorbidities, available monitoring, and the initial response to fluid resuscitation.[1,138,139,153]

SSC 2021 provides a strong recommendation to start NE within the first hour of sepsis identification if the patient is hypotensive during or after fluid administration,[1] consistent with prior discussion in PICO Question 12 and aligned with recent reviews.[153]

Summary of the evidence identified

GT-LATINFURG conducted a SR following PRISMA guidance[13] and the Table 4 inclusion criteria. Table 13 summarizes characteristics and key findings of several of the most relevant identified articles.

After completion of the GT-LATINFURG SR, Shi *et al.* published a SR and meta-analysis[139] showing reduced ICU mortality, lower fluid volume administered at 6 hours, faster time to achieve target MAP, and more ventilator-free days with early norepinephrine. Across the 10 included studies, early NE reduced mortality in randomized clinical trials (OR, 0.49 [95% CI, 0.25–0.96]; $P = .04$). In ED-relevant subgroup analyses, mortality reduction was observed when early NE was started within the first hour and lactate was ≤ 3 mmol/L (a scenario that may occur frequently in ED settings). More recently, Ma *et al.* published another SR and meta-analysis[156] including 11 studies (6661 patients) with substantial heterogeneity. Findings suggested that early vasopressor initiation—particularly 1 to 3 hours after SS diagnosis—may be associated with lower short-term mortality in certain subgroups, though results should be interpreted cautiously. The authors emphasized the need for more standardized research to define the optimal timing of vasopressor initiation and maximize survival in SS.

Comments

In ED patients with SS, early vasopressor administration is suggested—potentially within the first hour after starting fluid resuscitation, individualized to each case. Current evidence supports that rapid vasopressor initiation alongside initial fluid resuscitation is associated with earlier shock control and a clear trend toward reduced mortality. However, decisions should always be individualized based on the patient's clinical status and available hemodynamic monitoring.

Table 13. Characteristics of selected relevant studies (randomized controlled trial and cohort studies) on early vs delayed vasopressor administration

Study (Author, year – Ref.)	Study type	No. of patients	Intervention (early vasopressors)	Control (delayed vasopressors)	Primary outcome	Secondary outcome
CENSER Permpikul *et al.*, 2019 (138)	RCT	310	Early NE	Standard NE	Higher shock reversal at 6 hours (76.1% vs 48.4%, *P* < .001)	Non-statistically significant trend toward lower 28-day mortality (15.5% vs 21.9%, *P* = .15)
Bai *et al.*, 2014 (154)	Retrospective cohort study	213	Vasopressor initiation ≤ 1 hour	Initiation > 1 hour	Lower 28-day mortality (23.7% vs 33.3%, *P* = .04)	Shorter duration of hypotension (3.1 vs 5.4 hours, *P* = .01)
Beck *et al.*, 2014 (155)	Retrospective cohort study	6.514	Vasopressors initiated ≤ 1 hour from diagnosis	Vasopressors initiated > 1 hour	Lower in-hospital mortality (29% vs 42%, *P* = 0.03)	Less organ dysfunction (SOFA score 7 vs 9, *P* = .02)
Ospina-Tascón *et al.*, 2020 (143)	Prospective cohort study	337	Early NE	Delayed norepinephrine	Higher 28-day survival (76% vs 65%, *P* = .02)	Lower incidence of acute kidney injury (13% vs 23%, *P* = .01)

RCT: randomized controlled trial; NE: norepinephrine; SOFA: Sequential Organ Failure Assessment.

PICO Question 15

Does early source identification and control (< 6 hours) vs no source control or delayed source control (> 12 hours), improve safety and efficacy by improving clinical course (preventing progression to SS), mortality, complications, length of stay, or ICU admission?

Recommendation

For patients presenting to the ED with suspected or confirmed sepsis in whom an anatomic source is identified, implementing any indicated source-control intervention as soon as possible—ideally early (within 6 hours)—is recommended. Source control performed after ED evaluation is associated with lower short-term mortality (30–60 days). Source-control–amenable infections include intra-abdominal abscesses, gastrointestinal perforation, ischemic bowel or volvulus, cholangitis, cholecystitis, pyelonephritis with obstruction or abscess, necrotizing soft-tissue infection, other deep-space infections (eg, empyema or septic arthritis), and infections related to implanted devices. These sources should be identified and addressed promptly, and when feasible, within 6 hours of ED evaluation.

Background

Early and appropriate antimicrobial therapy and timely diagnostic-therapeutic decisions (eg, ordering ancillary tests, obtaining blood cultures and other microbiologic samples, determining the intensity of hemodynamic support, and the need for admission), as well as—specifically—abscess drainage, debridement of infected necrotic tissue, removal of potentially infected devices, or definitive control of an ongoing source of microbial contamination, directly affect survival in patients with severe bacterial infection.[1,3,157-159] In addition to the core international "bundle" measures to be implemented as early as possible in the ED (lactate measurement, blood cultures, broad-spectrum antibiotics, fluid resuscitation, and early vasopressors when indicated), an exhaustive evaluation should be performed to determine whether a specific anatomic source is present that can be identified and controlled.[1,3,78]

The term "source control" encompasses physical interventions that reduce the inoculum and modify local factors that promote microbial growth or impair host defenses.[157-159] This may include drainage of an abscess, debridement of infected necrotic tissue, removal of an infected device, or definitive control of an ongoing site of contamination.[157-160] Readily treatable sources include those listed above.[157-160]

Current practice emphasizes selecting the least invasive option that can achieve effective source control.[157-160] The SSC 2021 guidelines include, as best-practice statements, the need to rapidly suspect and identify—and then confirm or rule out—a specific anatomic diagnosis requiring immediate source control, and to implement any indicated source-control intervention as soon as logistically feasible in the given institution.[1]

Summary of the evidence identified

GT-LATINFURG published a SR[161] comparing early source identification and control (< 6 hours) in adults presenting to the ED with severe infection or sepsis vs no source control or delayed source control (> 12 hours), assessing clinical course, mortality, complications, length of stay, and ICU admission.

The SR included 2 high-quality studies meeting the Table 4 inclusion criteria, totaling 2404 patients; among them, 678 (28.2%) underwent a source-control intervention.[161] In the first study,[162] 28-day mortality was lower among patients who underwent source control (12.3% vs 22.5%; *P* < .001), with an adjusted hazard ratio of 0.538 (95% CI, 0.389–0.744; *P* < .001). In the second study,[163] the time from first evaluation and hemodynamic stabilization to surgical initiation was associated with 60-day survival, with an OR of 0.31 (95% CI, 0.19–0.45; *P* < .0001). Notably, for each additional hour of delay, an adjusted OR of 0.29 (95% CI, 0.16–0.47; *P* < .0001) was reported. Survival at 60 days was 98% when intervention occurred within 2 hours; 78% when performed between 2–4 hours; 55% between 4–6 hours; and 0% when performed after 6 hours.

Although multiple prior publications have supported the need for source control within the first 6 hours after identification,[159,160] they were not SR/meta-analyses. In this SR, evidence was limited by sample size and study count, but findings were consistent with international guidance and reports from other clinical contexts.[157,158,164-166]

Comments

For ED patients with infections amenable to source control (eg, intra-abdominal abscess, GI perforation, ischemic bowel/volvulus, cholangitis, cholecystitis, pyelonephritis with obstruction or abscess, necrotizing soft-tissue infection, empyema, septic arthritis, and implanted-device infections), these sources should be identified and source-control interventions initiated as early as possible, and when feasible, within 6 hours of ED evaluation.[157-166] This recommendation complements the core sepsis bundle measures to be implemented promptly in the ED (lactate measurement, blood cultures, broad-spectrum antibiotics, fluid resuscitation, and early vasopressors when indicated).[1,3,83] A thorough evaluation is necessary to determine whether a specific anatomic source is present and amenable to timely control.[1,3,83]

PICO Question 16

In suspected sepsis, is the use of a multidisciplinary sepsis team or "sepsis code," vs no such program, safer and more effective?

Recommendation

ED clinicians should be integrated into multidisciplinary sepsis teams and, together with other specialists (eg, intensivists, infectious disease physicians, internists, microbiologists), should lead the execution of a sepsis code to activate—from triage or the first patient assessment—the "time-zero recognition bundle" aimed at detecting sepsis early, preventing progression, and providing timely care for severe infection and sepsis in the ED.

Background, summary of evidence, and comments

Sepsis is a time-dependent condition; earlier recognition and treatment are associated with better outcomes.[1-3,158] Delays in treatment initiation are linked to worse prognosis and higher mortality. To improve early detection and outcomes, multidisciplinary sepsis response teams activated through a "sepsis code" have been promoted.[1-3,158,167,168] The 4 pillars of a sepsis code are continuing education, early detection, rapid response, and multidisciplinary care.[167]

SSC 2021 recommends implementing a sepsis performance-improvement program, including sepsis screening for high-risk patients with acute illness and standardized operating procedures for treatment.[1]

The concept of a sepsis code has emerged as a comprehensive, dynamic care protocol in which early identification of suspected patients is the key element. Early detection enables etiologic diagnosis, immediate initiation of both targeted and supportive therapy, and monitoring of the response to this syndrome.[167,168] The sepsis code aims to deliver a rapid, coordinated, and efficient response when sepsis is suspected. However, for this approach to be effective, it must incorporate not only early disease recognition but also a multimodal, multidisciplinary strategy involving professionals from different disciplines caring for patients across all hospital areas, with particularly high prevalence in the ED (> 60% of sepsis diagnoses occur in the ED).[1-3,158,167,168]

The primary goal of the sepsis code is to reduce mortality and to promote a paradigm shift in sepsis care at the clinical, organizational, and educational levels.[167-169]

In recent years, several Spanish experiences have demonstrated a substantial impact on improving care for septic patients throughout the hospital, most notably in the ED and ICU.[158,167-169] According to a recent study, in > 65% of Spanish hospitals, when sepsis is suspected, a protocol is activated and a multidisciplinary team makes rapid, coordinated decisions to initiate early treatment. This not only improves survival and resource utilization, but also reduces long-term complications and improves quality of life among sepsis survivors.[158,167-169]

When ED physicians are integrated into the sepsis team and protocols are implemented, adherence to recommended bundles improves, while ICU admission rates, hospital length of stay, and mortality decrease.[170-172] Bundles are fundamental to ensure that sepsis management is systematic, rapid, and coordinated, thereby increasing the likelihood of survival and improving outcomes in sepsis and SS. In addition, bundles help minimize variability in care by ensuring that all patients receive the same level of care regardless of illness severity.[1,167-169,173]

By integrating a multimodal, multidisciplinary approach, the sepsis code provides a comprehensive response that significantly improves clinical outcomes and optimizes the use of hospital resources. The core elements are early identification, rapid treatment, and teamwork—factors that can determine life or death for patients with sepsis.

Accordingly, in the authors' view, ED physicians should be integrated into their institutions' multidisciplinary teams and, together with other specialists, should lead execution of the sepsis code to activate—starting at triage or the first patient assessment—the ED "time-zero recognition bundle," thereby detecting severe infection and sepsis, preventing progression, and delivering timely care.

PICO Question 17

In suspected/confirmed SS, is early empiric antibiotic therapy vs non-early initiation, safer and more effective?

Table 14. PICO questions and final recommendations of the document in suspected or confirmed severe infection, sepsis, and septic shock in the emergency department

PICO question	Recommendation
1. In adults < 65 years of age, is the qSOFA scale vs SIRS criteria, NEWS-2, and other scales/models, a better predictor of sepsis for initial assessment?	qSOFA should not be used as the sole predictive tool for sepsis. Sepsis should be suspected (and therefore the sepsis code activated and the recognition bundle initiated from triage) in any patient presenting with qSOFA ≥ 2 and/or SIRS ≥ 2 and/or NEWS-2 ≥ 5 (or ≥ 3 points in a single variable).
2. In patients ≥ 65 years of age, is the qSOFA scale vs SIRS criteria, NEWS-2, and other scales/models, a better predictor of sepsis for initial assessment?	qSOFA should not be used as the sole predictive tool for sepsis (for either diagnosis or prognosis). Sepsis should be suspected (and therefore the sepsis code activated and the recognition bundle initiated from triage) in any patient ≥ 65 years presenting with qSOFA ≥ 2 and/or SIRS ≥ 2 and/or NEWS-2 ≥ 4 (or ≥ 3 points in a single variable), as well as ≥ 1 point on the GYM scale.
3. Does the use of blood lactate vs non-use, improve prognostic prediction and identification of poor clinical outcomes?	Blood lactate concentration should be measured at first patient contact (triage) and included in the "sepsis profile." For the diagnosis of sepsis or severe infection, a lactate ≥ 2 mmol/L indicates a worse prognosis.
4. Does the use of PCT vs non-use, improve the diagnostic accuracy for bacterial infection?	PCT concentration should be measured at first patient contact (triage) and included in the "sepsis profile." A PCT ≥ 0.25 ng/mL reinforces the suspicion of bacterial infection.
5. In patients with suspected bacteremia, does the use of PCT vs non-use, improve the prediction of bacteremia in blood cultures obtained in the ED?	Serum PCT concentration should be measured. A PCT ≥ 0.51 ng/mL reinforces the suspicion of bacterial infection with concomitant bacteremia.
6. In patients with suspected bacteremia, does the use of other predictive models vs the Shapiro model, improve the prediction of bacteremia in ED blood cultures?	Bacteremia prediction models 5MPB-Toledo and MPB-INFURG-SEMES should be used. A score ≥ 5 on either model clearly reinforces the suspicion of bacterial infection with concomitant bacteremia.
7. Which patients should have blood cultures drawn in the ED, given the prognostic and mortality impact of microbiological isolation?	Blood cultures should be obtained immediately whenever sepsis or SS is confirmed, when PCT concentration is > 0.5 ng/mL, or when a score ≥ 5 is obtained using either the 5MPB-Toledo or MPB-INFURG-SEMES models.
8. Is the use of molecular MMDT combined with blood cultures more effective and safe?	In adult patients with suspected bacteremia and sepsis in the ED, and as a complement to blood cultures, the availability of MMDT is recommended as a supportive tool to improve microbiological diagnosis and patient management.
9. Is early empirical antibiotic therapy (< 3 hours from ED triage) vs no or delayed administration (≥ 3–6 hours), safer and more effective?	In adult patients with suspected bacteremia and sepsis, early administration of antimicrobial therapy is recommended, preferably within the first 3 hours (in practice, as soon as possible once suspicion is confirmed or maintained without an alternative diagnosis).
10. In suspected or confirmed sepsis, is saline solution vs balanced crystalloids more effective and safe?	In adult patients with signs of hypoperfusion or sepsis-related hypotension, immediate use of balanced solutions (such as Ringer lactate) instead of 0.9% saline is recommended for initial resuscitation in the ED.

(Continued)

Recommendation

For adult patients with a clinical diagnosis of SS, immediate administration of appropriate antimicrobial therapy is recommended within the first hour of arrival to the ED (ie, as soon as possible once venous access is obtained and blood cultures are drawn—without allowing culture collection to delay antibiotic administration), because mortality increases with each hour of delay in antibiotic therapy.

Background, summary of evidence, and comments

Although PICO Question 9 noted ongoing controversy regarding ideal antibiotic timing in possible, probable, or confirmed sepsis, there has been no such controversy for decades when sepsis-related hypotension or SS is present.[118-120,122,174,175] In the study by Kumar *et al.*,[174] each hour of delay in antibiotic administration during the first 6 hours after onset of recurrent/persistent hypotension in SS was associated with a mean 7.6% decrease in survival. Moreover, by the second hour after hypotension onset, in-hospital mortality increased significantly vs receipt of therapy within the first hour (OR, 1.67 [95% CI, 1.12–2.48]).[174] Sherwin *et al.*[175] similarly concluded that patients with SS who received appropriate antibiotics within the first hour after ED diagnosis derived the greatest mortality reduction.

Consistent with this, SSC 2021[1] recommends antibiotic administration within 1 hour in adults with possible, probable, or confirmed SS; this is a strong recommendation based on low-quality evidence.[1]

Regarding the GT-LATINFURG SR,[104] Table 10 summarizes recommendations on antibiotic timing in ED patients with SS. Even when shock is only possible or probably due to infection, the recommendation remains to administer antibiotics within the first hour (ie, as soon as feasible).

PICO Question 18

In suspected sepsis/severe infection, are molecular microbiologic diagnostic techniques used alongside blood cultures more cost-effective?

Recommendation

For adult patients with a clinical diagnosis of infection and suspected bacteremia and sepsis in the ED, use of MMDTs is recommended—when available—as an ad-

Table 14. PICO questions and final recommendations of the document in suspected or confirmed severe infection, sepsis, and septic shock in the emergency department (Continued)

PICO question	Recommendation
11. In the diagnosis of SS, is saline solution vs balanced crystalloids more effective and safe?	In adult patients with SS in the ED, immediate use of balanced solutions (such as Ringer lactate) instead of 0.9% saline is recommended for initial resuscitation.
12. In suspected or confirmed SS with an indication to initiate vasopressor therapy, is NE vs dopamine/epinephrine/vasopressin/others more effective and safe?	Early use of NE is recommended as the first-line vasopressor for initial resuscitation.
13. In patients with suspected or confirmed SS and an indication for vasopressor therapy, is administration through a peripheral venous catheter vs a central venous catheter effective and safe?	For immediate vasopressor administration (in this case NE), peripheral venous catheters (large-bore and placed proximal to the antecubital fossa) are suggested as a valid alternative during the first hours of SS until central venous access is obtained.
14. In suspected or confirmed SS with an indication for vasopressor therapy, is early administration vs delayed administration more effective and safe?	Early initiation of vasopressors is suggested, as combined with initial fluid resuscitation it is associated with improved shock control and a trend toward reduced mortality. The decision should be individualized based on patient characteristics and available hemodynamic monitoring.
15. Is early detection and source control (< 6 hours) vs no source control or delayed source control (> 6–12 hours) more effective and safe?	In patients with sepsis in whom an infectious source is identified, any source control intervention should be implemented as soon as possible, preferably early (within 6 hours).
16. In suspected sepsis, is the use of a multidisciplinary sepsis team or "sepsis code" vs non-use more effective and safe?	ED physicians are recommended to integrate into multidisciplinary sepsis teams and, together with other specialists, lead the execution of the Sepsis Code to activate the "time-zero or recognition bundle" from triage in order to detect, prevent progression, and manage patients with severe infection and sepsis.
17. In suspected or confirmed SS, is early empirical antibiotic therapy vs delayed initiation more effective and safe?	Immediate administration of appropriate antimicrobial therapy within the first hour from ED arrival is recommended (in practice, as soon as possible once venous access and blood cultures are obtained, without delaying antibiotic administration).
18. In suspected sepsis or severe infection, is the use of molecular microbiological diagnostic techniques combined with blood cultures cost-effective?	In adult patients with suspected bacteremia and sepsis in the ED, and as a complement to blood cultures, molecular microbiological diagnostic techniques should be used when available to improve microbiological diagnosis and patient management, as they are cost-effective in several clinical scenarios (e.g., when no antimicrobial stewardship team is available).
19. In suspected or confirmed SS requiring vasopressors, is a mean arterial pressure (MAP) > 65 mmHg vs MAP < 65 mmHg more effective and safe?	In adult patients with SS requiring vasopressor therapy, achieving and maintaining a MAP ≥ 65 mmHg as early as possible is recommended.
20. In suspected or confirmed SS, is early admission to the intensive care unit vs delayed admission more effective and safe?	In adult patients with sepsis and SS requiring ICU admission, early transfer is recommended (as soon as possible once the sepsis code has been activated and the "time-zero recognition and early management" measures have been initiated).

PICO: Population/Patient, Intervention, Comparator, Outcomes; ED: emergency department; qSOFA: quick Sepsis-related Organ Failure Assessment; SIRS: systemic inflammatory response syndrome; GYM: 30-day mortality prediction scale in older patients (Glasgow Coma Scale < 15, respiratory rate > 20, and Charlson Comorbidity Index ≥ 3); NEWS-2: National Early Warning Score 2; PCT: procalcitonin; MMDT/TMDM: molecular microbiological diagnostic techniques; PROA: antimicrobial stewardship program; SS: septic shock; MMDT: molecular microbiological diagnostic techniques; NE: norepinephrine.

junct to blood cultures to improve microbiologic diagnosis and patient management, because these approaches appear cost-effective in multiple clinical scenarios (eg, settings without a sepsis team, infectious diseases committee, or an antimicrobial stewardship program).

Background, summary of evidence, and comments

As discussed in PICO Question 8, and in the authors' view, existing evidence supports implementation of MMDTs as a valuable adjunct to blood cultures in ED sepsis care. However, it remains important to define which clinical contexts (ie, infectious syndromes) may derive the greatest effectiveness and efficiency. Candel *et al.*[116] and Rapszky *et al.*[117] (SRs discussed under PICO Question 8) reported that these tools can shorten time to diagnosis, reduce inappropriate empiric therapy and antibiotic duration, and reduce hospital length of stay—changes that may translate into cost savings. Overall, they represent a meaningful advance in infectious diseases diagnostics by enabling more timely and precise interventions, while noting that MMDTs cannot currently replace blood cultures.

Regarding cost-effectiveness, Shengchen *et al.*[110] also suggested that MMDT implementation may yield significant benefits in treatment duration, hospital stay, and other costs among patients with lower respiratory tract infections. Finally, 2 reviews[176,177] specifically evaluating cost-benefit of incorporating MMDTs alongside blood cultures in ED settings concluded that, in sepsis management, these tools are promising for improving efficacy and safety outcomes and may be cost-effective across several clinical scenarios (eg, where no sepsis team, infectious diseases commission, or stewardship program is available).

PICO Question 19

In patients with suspected or confirmed SS who start vasopressors, is targeting a MAP > 65 mm Hg vs < 65 mm Hg, safer and more effective?

Recommendation

For adult patients with a clinical diagnosis of SS who require vasopressors, achieve a MAP ≥ 65 mm Hg early and maintain it.

Background, summary of the evidence found, and comments

MAP plays a fundamental role in determining systemic perfusion pressure, which in turn influences venous return and cardiac output. Increasing MAP generally increases tissue blood flow and enhances tissue oxygen delivery, which may help normalize blood lactate concentrations to < 2 mmol/L as an indirect monitoring measure.[1,133] Although some organs, such as the brain and kidneys, can autoregulate their own blood flow, a MAP < 60 mm Hg is associated with reduced organ perfusion and may therefore contribute to organ dysfunction.[1,132,133] In this regard, it is important to recall the definitions of sepsis and SS presented in the glossary of terms (Supplementary Table 2, https://revistaemergencias.org/extra/5189.pdf).

However, it is unknown whether the MAP target of 65 mm Hg—used by consensus to identify patients with SS—is beneficial for all patients with SS seen in the ED. This uncertainty reflects interpatient variability in functional reserve, comorbidities (eg, cardiac disease, hypertension, chronic kidney disease), and prior treatments, all of which may influence sepsis pathophysiology, host response, and therefore individualized therapeutic requirements.[1,2]

In this context, the 2021 SSC recommends an initial MAP target of 65 mm Hg (rather than higher MAP targets) in adults with SS receiving vasopressors; this is a strong recommendation supported by moderate-quality evidence.[1]

Following the methodology described (PRISMA[13] and the inclusion criteria in Table 4), the GT-LATINFURG designed and conducted a SR, as for the other PICO questions. During eligibility assessment, 11 full-text articles were retrieved, including 2 SRs[178,179] and 2 SR–meta-analyses;[180,181] however, all were conducted in ICU settings. Higher targets (eg, MAP 80–85 mm Hg) did not improve mortality and, in some subgroups, may be associated with worse outcomes.[1] Therefore, for patients with SS who require vasopressors, the goal should be to promptly achieve and maintain a MAP ≥ 65 mm Hg.

In summary, because no eligible study specifically addressed this question in an ED population, further high-quality studies designed for ED patients are needed.

PICO Question 20

In suspected or confirmed SS, is early ICU admission vs non-early admission safer and more effective?

Recommendation

For adult patients with a clinical diagnosis of sepsis or SS who require ICU admission, a prompt transfer is recommended (ie, as soon as possible once the sepsis code has been activated and "time-zero" recognition and early-management measures have been initiated in the ED, and as soon as the patient's condition and logistics allow).

Background, summary of the evidence found, and comments

Sepsis may progress to SS and, in some cases, death. Among ED patients with sepsis who are initially hemodynamically stable, 17.8% progress to SS within the subsequent 72 hours, with 30-day mortality increasing from 3.1% to 13.1%.[168] Therefore, identifying this subgroup is essential to ensure immediate treatment and a faster transfer to the ICU.[168] This is closely linked to compliance with SSC bundles established over time for ED care at 6 hours, 3 hours, or within the first hour.[1,83,182,183]

Delayed ICU admission of patients with sepsis and SS from the ED is associated with poorer bundle compliance, which in turn is associated with increased mortality and longer ICU and hospital length of stay.[1] Evidence regarding the optimal timing of ICU transfer largely comes from observational studies and registry databases; for example, an ICU mortality increase of 1.5% has been reported for each hour of delay from ED to ICU transfer.[1,184] Similarly, another multicenter observational study including more than 50,000 patients found higher mortality when ED length of stay exceeded 6 hours (17% vs 12.9%; $P < .001$). Among hospital survivors, delayed ICU admission was associated with longer hospitalization, higher mortality, and higher rates of mechanical ventilation and central venous catheterization.[185]

The SSC 2021 suggests admitting adults with sepsis or SS who require ICU care within the first 6 hours (weak recommendation, low-quality evidence).[1]

In the GT-LATINFURG review, only observational studies similar to those above were identified. For instance, Zhang *et al.* studied 1,997 patients and found that vs the length of the ED stay < 6 hours, staying 12–24 hours (OR, 1.82; 95% CI, 1.28–2.58) or > 24 hours (OR, 1.79; 95% CI, 1.27–2.52) was associated with a higher risk of death.[186]

Accordingly, for patients with sepsis or SS who require ICU admission, transfer should occur as soon as possible, alongside initiation of time-zero bundle measures and activation of the sepsis code.

Discussion and conclusions

Once the 20 PICO questions considered by the authors regarding the care of patients with severe infection, sepsis, and SS in EDs have been reviewed and discussed, together with the consensus recommendations for each of them (Tables 3 and 14) and those previously issued by the GT-LATINFURG in other CDs,[2,3] Table 15 summarizes the steps in the management of the pa-

Table 15. Time-zero bundle for early detection and early management: Steps in the approach to the patient with sepsis in the emergency departments

1. Immediate suspicion and detection of the patient with possible sepsis
A. Early recognition at triage and during the initial medical history.
B. Physical examination and assessment of hemodynamic, respiratory, and neurological status: Blood pressure (BP), heart rate (HR), respiratory rate (RR), temperature, oxygen saturation (SpO_2) by pulse oximetry, level of consciousness (Glasgow Coma Scale), capillary blood glucose, and urine output.
2. Activation of the Sepsis Code if any of the following criteria are met: qSOFA ≥ 2 or SRIS ≥ 2 or NEWS-2 ≥ 5 or qSOFA 1 + lactate ≥ 2 mmol/L. Scales and criteria are described in the main text of the document (Tables 1 and 2 and the Introduction).
3. Diagnostic confirmation and acquisition of complementary studies: Sepsis laboratory profile (Supplementary Table 2), blood cultures (Tables 6, 7, and 8), and other microbiological and complementary diagnostic tests.
4.
A. Selection and immediate or early administration of appropriate antimicrobial therapy: Based on the clinical situation and the degree of suspicion or confirmation of sepsis (Table 10).
B. Initiation of individualized resuscitation: Clinical, respiratory, and hemodynamic stabilization. Early/immediate fluid resuscitation with balanced crystalloids (Ringer lactate), individualized according to patient status, and early initiation of vasopressors (NE), via central or peripheral access as appropriate. Target mean arterial pressure (MAP) ≥ 65 mmHg. Monitoring preferably using dynamic parameters and/or echocardiography.
5. Confirmation and early initiation of source control when indicated (e.g., surgery, drainage): Radiology, interventional radiology, and surgical consultation as required.
6. Prognostic assessment and disposition planning: Assessment of organ dysfunction using the SOFA score (Table 1), lactate monitoring, and decision regarding patient disposition. In cases of SS, early transfer to the ICU.

Note: Once suspicion is established (Step 1), the remaining bundle measures should be performed consecutively or simultaneously, depending on disease severity and individualized clinical assessment.
qSOFA: quick Sepsis-related Organ Failure Assessment; SIRS: systemic inflammatory response syndrome; NE: norepinephrine; NEWS-2: National Early Warning Score 2; ICU: intensive care unit; SS: septic shock.

tient with sepsis in the ED [the so-called "time-zero detection and early care bundle"], which are also graphically depicted in Figure 1. Figure 3 shows the ED management algorithm in cases of suspected sepsis. Figure 3 is available as Supplementary data at: https://revistaemergencias.org/extra/5189.pdf.

Of note, as a limitation of the development of this CD, that according to the AGREE II evaluation tool,[28] neither the perspectives of the target population (patients and the general public) were included nor was a procedure defined for future updates of this CD. Therefore, following AGREE II items 5 and 17, respectively, it would not achieve the maximum possible score.

These recommendations should be modulated and adapted according to local characteristics and the resources available in each setting, but always with the same objective: to overcome existing gaps, barriers, and controversies as much as possible to improve the care of patients with severe infection and sepsis in EDs. In addition, there is an evident need to generate high-quality evidence that addresses questions still under debate, such as the optimal timing of antibiotic administration, the effective incorporation of molecular microbiological diagnostic techniques, alarm systems, and artificial intelligence.

Finally, it is crucial to participate in and agree upon the implementation of all these measures within a multidisciplinary hospital team (sepsis code: intensive care, hospital wards, infectious diseases and microbiology, surgical services, etc.), as well as to ensure appropriate transfer and continuity of care to the ICU and conventional hospitalization, allowing the coordinated continuation of the care and measures initiated in the ED.

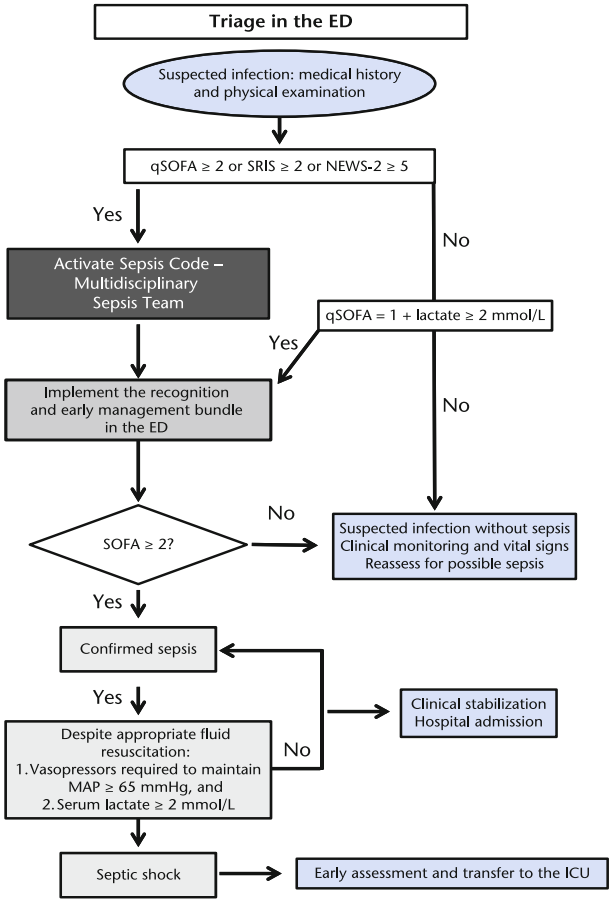

Figure 3. Management algorithm for suspected sepsis.
qSOFA: quick Sequential Organ Failure Assessment; SIRS: systemic inflammatory response syndrome; NEWS-2: National Early Warning Score; SOFA: Sequential Organ Failure Assessment; MAP: mean arterial pressure; ICU: intensive care unit; ED: emergency department.

Scientific endorsements: The Latin American Federation of Emergency Medicine (FLAME), on behalf of the scientific societies and associations of its member countries, and the Spanish Society of Emergency Medicine (SEMES) have reviewed, granted scientific endorsement, and adhere to the contents of this CD.

Conflict of Interest Disclosures: None reported.

Funding: The authors declare the non-existence of funding related to this article.

Ethical Responsibilities: All authors have confirmed the maintenance of confidentiality and respect for patients' rights in the author's responsibilities document, publication agreement and assignment of rights to EMERGENCIAS.

Article not commissioned by the Editorial Board and with external peer review.

Appendix 1: Other members of the Sepsis–Severe Infection Working Group of GT-LATINFURG who reviewed and accepted the contents of the CD: Brazilian Association of Emergency Medicine (ABRAMADE): Helio Penna Guimarães, María Camila Lunardi, Fernando Soares Varela Luiz, Ian Ward Abdalla Maia, Ana María de Rocha Freitas, Uri Adrian Prync Flato. Colombian Association of Emergency and Emergency Medicine Specialists (ACEM): Fabian Andrés Rosas Romero, Luis Felipe Duque Sierra, Luis Eduardo Vargas Téllez. Costa Rican Association of Emergency Physicians (ASOCOME): Oscar Esteban Buitrago Carazo, Javier Chavarría Campos, Alejandro Moyá Álvarez. Nicaraguan Association of Emergency Medicine (ANME): Carolina Ulloa González. Salvadoran Association of Emergencies (ASAE): Carlos Enrique Alberto Orellana Jiménez. Argentine Society of Emergencies (SAE): Darío Eduardo García, Marcelo Rodrigo Rodríguez, Regina Gualco, Nazareno Galvanisi, Edgardo Menéndez, Gonzalo Camargo, Matías José Fosco. Chilean Society of Emergency Medicine (SOCHIMU): Luis Ignacio Enberg Gaete, Allan Mix Vidal, Ulises González-Bascuñán, Pablo René Aguilera Fuenzalida. Dominican Society of Emergencies (SODOEM): Hayro González. Ecuadorian Society of Emergency and Disaster Medicine (SEMED): Nelson Rodrigo Laica Saliema, Rafael Salazar. Spanish Society of Emergency Medicine (SEMES): Agustín Julián-Jiménez, Juan González del Castillo, Francisco Javier Candel González, Ángel Estella, Julio Javier Gamazo del Río, Ferrán Llopis Roca, Raúl López Izquierdo, Rafael Rubio Díaz, Gema Delgado Cárdenas, Rocío Lorenzo Álvarez, Neus Robert Boter, Manuel José Vázquez Lima, Rigoberto del Río, Alejandro Martín Quirós, Victoria Gutiérrez Bueno, Miranda Sánchez Trujillo, Marco Antonio Esquivias Campos, Eric Jorge García Lamberechts, Edgar Lazcano Jakimczuk. Mexican Society of Emergency Medicine (SMME.AC): Graciela Merinos-Sánchez, Diego Armando Santillán-Santos, Luis Antonio Gorordo-Delsol, Jesús Daniel López Tapia, Javier Saavedra Uribe, Luis Daniel Sánchez Arreola. Paraguayan Society of Emergency Medicine (SPEM): Clarisa Da Costa, Ariel José Fretes. Peruvian Society of Emergency and Disaster Medicine (SPMED): Luis Honorio, Luis Melchor Loro Chero. Venezuelan Society of Emergency and Disaster Medicine (SVMED): Mercedes Vivas, Diego Grajales López.

Appendix 2: External experts outside GT-LATINFURG who reviewed and accepted the contents of the CD: Latin American Association for Cooperation in Emergency Medicine and Disasters (ALACED): Luis Eduardo Vargas Téllez. Panamanian Association of Emergency Medicine (ASPAME): José Miguel Sánchez. Bolivian Society of Emergency Medicine (SOBOEM): Patricia Torrico Bautista, Oliver Bernal Flores. Uruguayan Society of Emergency Physicians (SUE): Blauco Fabricio Rodríguez Andrada. Australasian College for Emergency Medicine (ACEM): Anthony Cross. Mexican Association of Emergency and Disaster Medicine (AMUDEM): Ricardo Bañuelos Huerta, Fabián Chable Chan, Sergio Germán Burgos Salcedo. Peruvian Society of Intensive Care Medicine and Peruvian Society of Pediatrics: Raffo Escalante-Kanashiro. Emergency Committee of the Spanish Society of Laboratory Medicine (SEMEDLAB): Luis García de Guadiana-Romualdo. Universidad Autónoma de Bucaramanga, Colombia: Paul Anthony Camacho López. Edgardo Rebagliati Martins Hospital, Peru: Jessica Milagros Calcino Cuela. Sepsis Code, Spain: Marcio Borges Sa.

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. Intensive Care Med. 2021;47:1181-247.
2 Julián-Jiménez A, Supino M, López Tapia JD, Ulloa González C, Vargas Téllez LE, González del Castillo J, et al. Puntos clave y controversias sobre la sepsis en los servicios de urgencias: propuestas de mejora para Latinoamérica. Emergencias. 2019;31:123-35.
3 Julián-Jiménez A, Gorordo-Delsol LA, Merinos-Sánchez G, Santillán-Santos DA, Rosas Romero FA, Sánchez Arreola D, et al. Declaración de Guadalajara: una visión constructiva desde el servicio de urgencias a partir de la Surviving Sepsis Campaign 2021. Emergencias. 2023;35:53-64.
4 Rudd KE, Johnson SC, Agesa KM, Shackelford KA, Tsoi D, Kievlan DR, et al. Global, regional, and national sepsis incidence and mortality, 1990-2017: analysis for the Global Burden of Disease Study. Lancet. 2020;395:200-11.
5 Bauer M, Gerlach H, Vogelmann T, Preissing F, Stiefel J, Adam D. Mortality in sepsis and septic shock in Europe, North America and Australia between 2009 and 2019–results from a systematic review and meta-analysis. Crit Care. 2020;24:239.
6 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.
7 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.
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 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.
10 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.
11 Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. Chest. 1992;101:1644-55.
12 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.
13 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;3155:762-74.
14 Freund Y, Lemachatti N, Krastinova E, Van Laer M, Claessens YE, Avondo A, et al; French Society of Emergency Medicine Collaborators Group. Prognostic Accuracy of Sepsis-3 Criteria for In-Hospital Mortality Among Patients With Suspected Infection Presenting to the Emergency Department. JAMA. 2017;317:301-8.
15 Vincent JL, Moreno R, Takala J, Willatts S, De Mendonça A, Bruining H, et al; Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. Intensive Care Med. 1996;22:707-10.
16 Hunt A. Sepsis: an overview of the signs, symptoms, diagnosis, treatment and pathophysiology. Emerg Nurse. 2019;27:32-41.
17 Holub M, Závada J. Clinical aspects of sepsis. Contrib Microbiol. 2011;17:12-30.
18 Royal College of Physicians. National Early Warning Score (NEWS) 2: Standardizing the assessment of acute-illness severity in the NHS. Updated report of a working party. Londres: RCP; 2017.
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 hospitalarias. Revisión sistemática y metanálisis. Emergencias. 2021;33:374-81.
20 Kim HJ, Ko RE, Lim SY, Park S, Suh GY, Lee YJ. Sepsis Alert Systems, Mortality, and Adherence in Emergency Departments: A Systematic Review and Meta-Analysis. JAMA Netw Open. 2024;7:e2422823.
21 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.
22 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.
23 Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. BMJ. 2021;372:71.
24 Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017;358:j4008.
25 Cook DA, Reed DA. Appraising the Quality of Medical Education

Research Methods: The Medical Education Research Study Quality Instrument and the Newcastle-Ottawa Scale-Education. Acad Med. 2015;90:1067-76.
26 Sterne JAC, Savovic J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:l4898.
27 Igelström E, Campbell M, Craig P, Katikireddi SV. Cochrane's risk of bias tool for non-randomized studies (ROBINS-I) is frequently misapplied: A methodological systematic review. J Clin Epidemiol. 2021;140:22-32.
28 AGREE II: Advancing guideline development, reporting and evaluation in healthcare. [internet]. (Consultado 28 Agosto 2025). Disponible en: https://www.agreetrust.org/resource-centre/agree-ii/agree-ii-publications/
29 Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al; GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336:924-6.
30 Serafim R, Gomes JA, Salluh J, 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.
31 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.
32 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.
33 Herwanto V, Shetty A, Nalos M, Chakraborty M, McLean A, Eslick GD, et al. Accuracy of quick se- quential 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.
34 Song JU, Sin CK, Park HK, Shim SR, Lee J. Performance of the quick Sequential (sepsis-related) Organ Failure Assessment score as a prognostic tool in infected patients outside the intensive care unit: A systematic review and meta-analysis. Crit Care. 2018;22:28.
35 Churpek MM, Snyder A, Han X, Sokol S, Pettit N, Howell MD, et al. Quick Sepsis-related Organ Failure Assessment, Systemic Inflammatory Response Syndrome, and Early Warning Scores for Detecting Clinical Deterioration in Infected Patients outside the Intensive Care Unit. Am J Respir Crit Care Med. 2017;195:906-11.
36 Bolanaki M, Lisab K, Mikkelc B, Rond D, Kireng G, Frankj H, et al. Current sepsis management practices in European emergency departments: the ISG-emergency department European Survey. Eur J Emerg Med. 2025; 32:368-76.
37 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.
38 Green SL, Smith MTD, Cairns C, Clarke DL, Bruce J, Bekker W, et al. The Combined SIRS + qSOFA (qSIRS) Score is More Accurate Than qSOFA Alone in Predicting Mortality in Patients with Surgical Sepsis in an LMIC Emergency Department. World J Surg. 2020;44:21-9.
39 Chua WL, Rusli KDB, Aitken LM. Early warning scores for sepsis identification and prediction of in-hospital mortality in adults with sepsis: A systematic review and meta-analysis. J Clin Nurs. 2024;33:2005-18.
40 Oduncu AF, Kıyan GS, Yalçınlı S. Comparison of qSOFA, SIRS, and NEWS scoring systems for diagnosis, mortality, and morbidity of sepsis in emergency department. Am J Emerg Med. 2021;48:54-9.
41 Julián-Jiménez A, Candel-González FJ, González Del Castillo J. Usefulness of inflammation and infection biomarkers in the Emergency Department. Enferm Infecc Microbiol Clin. 2014;32:177-90.
42 Vincent JL, Bogossian E, Menozzi M. The Future of Biomarkers. Crit Care Clin. 2020;36:177-87.
43 Yañez MC, Salido Mota M, Fuentes Ferrer M, Julián-Jiménez A, Piñera P, Llopis F, et al. Comparison of different strategies for short-term death prediction in the infected older patient. Rev Esp Quimioter. 2019;32:156-64.
44 Julián-Jiménez A, Yañez MC, González-Del Castillo J, Salido-Mota M, Mora-Ordoñez B, Arranz-Nieto MJ, et al. Prognostic power of biomarkers for short-term mortality in the elderly patients seen in Emergency Departments due to infections. Enferm Infecc Microbiol Clin. 2019;37:11-8.
45 Moncada-Gutiérrez D, Vásquez-Tirado GA, Meregildo-Rodríguez ED, Quispe-Castañeda CV, Cuadra-Campos M, Abanto-Montalván PH, et al. Lactate-enhanced-qSOFA (LqSOFA) score as a predictor of in-hospital mortality in patients with sepsis: systematic review and meta-analysis. Eur J Trauma Emerg Surg. 2025;51:33.
46 Rubio-Díaz R, Julián-Jiménez A, González Del Castillo J, García-Lamberechts EJ, Huarte Sanz I, Navarro Bustos C, et al. Ability of lactate, procalcitonin, and criteria defining sepsis to predict 30-day mortality, bacteremia, and microbiologically confirmed infection in patients with infection suspicion treated in emergency departments. Emergencias. 2022;34:181-9.
47 Julián-Jiménez A, Rubio-Díaz R, González Del Castillo J, García-Lamberechts EJ, Huarte Sanz I, Navarro Bustos C, et al. Ability of qSOFA1-lactate to predict 30-day mortality in patients seen for infection in the Emergency Department]. Rev Esp Quimioter. 2023;36:408-15.
48 Tong-Minh K, Welten I, Endeman H, Hagenaars T, Ramakers C, Gommers D, et al. Predicting mortality in adult patients with sepsis in the emergency department by using combinations of biomarkers and clinical scoring systems: a systematic review. BMC Emerg Med. 2021;21:70.
49 de Rafael-González E, Cabañas-Morafraile J, Serrano-Martín L, Julián-Jiménez A, Torres-Fernández M, Chaves-Prieto E, et al. Ability of mid-regional proadrenomedullin (MR-proADM) to predict poor clinical outcome and stratify prognosis in adult patients seen for suspected infection in the Emergency Department. Rev Esp Quimioter. 2025;38:319-34.
50 Graziadio S, O'Leary RA, Stocken DD, Power M, Allen AJ, Simpson AJ, et al. Can mid-regional pro-adrenomedullin (MR-proADM) increase the prognostic accuracy of NEWS in predicting deterioration in patients admitted to hospital with mild to moderately severe illness? A prospective single-centre observational study. BMJ Open. 2019;8:e020337.
51 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.
52 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.
53 Peng K, Zhang X, Li Q, Luo Z. Presepsin as a diagnostic biomarker for sepsis across neonates, children, and adults: A meta-analysis. Biomol Biomed. 2025. doi: 10.17305/bb.2025.12909.
54 Herrero-Puente P, Eugen-Olsen J, Ferreras Amez JM, Gamazo Del Río J, Prieto-García B, de Las Heras-Vallelado A, et al. Value of the soluble urokinase-type plasminogen activator receptor as a predictor of prognosis in patients attended in hospital emergency departments. Emergencias. 2024;36:17-24.
55 Rubio Díaz R, de Rafael González E, Martín Torres E, Valera Núñez E, López Martos AM, Melguizo Melguizo D, et al. Prognostic power of soluble urokinase plasminogen activator receptor (suPAR) for short-term mortality in patients seen in Emergency Departments due to infections]. Rev Esp Quimioter. 2022;35:50-62.
56 Huang Q, Xiong H, Yan P, Shuai T, Liu J, Zhu L, et al. The Diagnostic and Prognostic Value of suPAR in Patients with Sepsis: A Systematic Review and Meta-Analysis. Shock. 2020;53:416-25.
57 Liang J, Cai Y, Shao Y. Comparison of presepsin and Mid-regional pro-adrenomedullin in the diagnosis of sepsis or septic shock: a systematic review and meta-analysis. BMC Infect Dis. 2023;23:288.
58 Jiang J, Yang J, Mei J, Jin Y, Lu Y. Head-to-head comparison of qSOFA and SIRS criteria in predicting the mortality of infected patients in the emergency department: a meta-analysis. Scand J Trauma Resusc Emerg Med. 2018;26:56.
59 Ruan H, Ke D, Liao D. Prognostic Accuracy of qSOFA and SIRS for Mortality in the Emergency Department: A Meta-Analysis and Systematic Review of Prospective Studies. Emerg Med Int. 2022;2022:1802707.
60 Wang C, Xu R, Zeng Y, Zhao Y, Hu X. A comparison of qSOFA, SIRS and NEWS in predicting the accuracy of mortality in patients with suspected sepsis: A meta-analysis. PLoS One. 2022;17:e0266755.
61 Svendsen M, Steindal SA, Hamilton Larsen M, Trygg Solberg M. Comparison of the systematic Inflammatory response syndrome and the quick sequential organ failure assessment for prognostic accuracy in detecting sepsis in the emergency department: A systematic review. Int Emerg Nurs. 2023;66:101242.
62 Qiu X, Lei YP, Zhou RX. SIRS, SOFA, qSOFA, and NEWS in the diagnosis of sepsis and prediction of adverse outcomes: a systematic review and meta-analysis. Expert Rev Anti Infect Ther. 2023;21:891-900.
63 Mellhammar L, Linder A, Tverring J, Christensson B, Boyd JH, Sendi P, et al. NEWS2 is Superior to qSOFA in Detecting Sepsis with Organ Dysfunction in the Emergency Department. J Clin Med. 2019;8:1128.

64 Usman OA, Usman AA, Ward MA. Comparison of SIRS, qSOFA, and NEWS for the early identification of sepsis in the Emergency Department. Am J Emerg Med. 2019;37:1490-7.
65 Shah P, Keswani S, Yamaguchi L, Shetty K, Benge E, Gheriani AG, et al. The Effect of Adding Procalcitonin to the Systemic Inflammatory Response Syndrome (Sirs) and Quick Sepsis-Related Organ Failure Assessment (qSOFA) Scoring System in Predicting Sepsis Mortality. Cureus. 2022;14:e31740.
66 Manrique Abril F, Mendez Fandiño Y, Herrera-Amaya G, Rodriguez J, Manrique-Abril R. Procalcitonin test for diagnosis of sepsis or septic shock: systematic review of literature and metanalysis. Infection. 2019;23:133-42.
67 Chuang CL, Yeh HT, Niu KY, Chen CB, Seak CJ, Yen CC. Diagnostic performances of procalcitonin and C-reactive protein for sepsis: a systematic review and meta-analysis. Eur J Emerg Med. 2025;32:248-58.
68 Eisinger GJ, Hosler Q, Crouser ED, Herman DD. Diagnostic Performance of Monocyte Distribution Width for the Detection of Sepsis: A Systematic Review and Meta-Analysis. J Am Coll Emerg Physicians Open. 2025;6:100073.
69 Esposito JE, D'Amato M, Parruti G, Polilli E. Monocyte Distribution Width for Sepsis Diagnosis in the Emergency Department and Intensive Care Unit: A Systematic Review and Meta-Analysis. Int J Mol Sci. 2025;26:7444.
70 Díaz-González S, Martín-Conty JL, del Pozo Vegas C, López-Izquierdo R, Martín-Rodríguez F, Sanz-García A. Impacto de los biomarcadores en el punto de atención sobre la capacidad predictiva de las escalas de alerta temprana en cuidados prehospitalarios: revisión sistemática y metanálisis. Emergencias. 2025;37:281-92.
71 Martín S, Pérez A, Aldecoa C. Sepsis and Immunosenescence in the Elderly Patient: A Review. Front Med (Lausanne). 2017;4:20.
72 Opal SM, Girard TD, Ely EW. The immunopathogenesis of sepsis in elderly patients. Clin Infect Dis. 2005;41 Supl 7:S504-12.
73 Estella A, Gamazo-Del Rio J, Álvarez-Manzanares J, Julián-Jiménez A, González Del Castillo J. Prognostic accuracy of qSOFA according to the site of infection in older patient attended in Emergency Department. Eur J Intern Med. 2018;50:e13-e15.
74 González Del Castillo J, Escobar-Curbelo L, Martínez-Ortíz de Zárate M, Llopis-Roca F, García-Lamberechts J, Moreno-Cuervo Á, et al; Representing the Infectious Disease Group of Spanish Emergency Medicine Society. GYM score: 30-day mortality predictive model in elderly patients attended in the emergency department with infection. Eur J Emerg Med. 2017;24:183-8.
75 González Del Castillo J, Julián-Jiménez A, González-Martínez F, Álvarez-Manzanares J, Piñera P, Navarro-Bustos C, et al. Prognostic accuracy of SIRS criteria, qSOFA score and GYM score for 30-day-mortality in older non-severely dependent infected patients attended in the emergency department. Eur J Clin Microbiol Infect Dis. 2017;36:2361-9.
76 García-Lamberechts EJ, Fuentes Ferrer M, Fernández-Alonso C, Burillo-Putze G, Aguiló S, Alquezar-Arbé A,et al. Predictive usefulness of qSOFA, NEWS and GYM scores in the elderly patient: EDEN-5 study. Enferm Infecc Microbiol Clin. 2024;42:468-77.
77 Del Portal DA, Shofer F, Mikkelsen ME, Dorsey PJ, Gaieski DF, Goya lM, et al. Emergency department lactate is associated with mortality in older adults admitted with and without infections. Acad Emerg Med. 2010;17:260-8.
78 Julián-Jiménez A, González del Castillo J, Martínez Ortiz M, Arranz-Nieto MJ, González Martínez F, Piñera-Salmerón P, et al. Short-term prognostic factors in the elderly patients seen in emergency departments due to infections. Enferm Infecc Microbiol Clin. 2017;35:214-9.
79 García-Lamberechts EJ, Martín-Sánchez FJ, Julián-Jiménez A, Llopis F, Martínez-Ortiz de Zarate M, Arranz-Nieto MJ, et al. Infection and systemic inflammatory response syndrome in older patients in the emergency department: a 30-day risk model. Emergencias. 2018;30:241-6.
80.-Borthwick HA, Brunt LK, Mitchem KL, Chaloner C. Does lactate measurement performed on admission predict clinical outcome on the intensive care unit? A concise systematic review. Ann Clin Biochem. 2012;49:391-4.
81 Liu G, An Y, Yi X. Early lactate levels for prediction of mortality in patients with sepsis or septic shock: A meta-anal- ysis. Int J Exp Med. 2017;10:37-47.
82 Khodashahi R, Sarjamee S. Early lactate area scores and serial blood lactate levels as prognostic markers for patients with septic shock: a systematic review. Infect Dis (Lond). 2020;52:451-63.
83 Levy MM, Evans LE, Rhodes A: The surviving sepsis campaign bundle: 2018 update. Crit Care Med. 2018; 46:997-1000.
84 Alshiakh SM. Role of serum lactate as prognostic marker of mortality among emergency department patients with multiple conditions: A systematic review. SAGE Open Med. 2023;11:20503121221136401.
85 Gill A, Ackermann K, Hughes C, Lam V, Li L. Does lactate enhance the prognostic accuracy of the quick Sequential Organ Failure Assessment for adult patients with sepsis? A systematic review. BMJ Open. 2022;12:e060455.
86 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.
87 Julián-Jiménez A, García de Guadiana-Romualdo L, Merinos-Sánchez G, García DE. Diagnostic accuracy of procalcitonin for bacterial infection in the Emergency Department: a systematic review. Rev Clin Esp (Barc). 2024;224:400-16.
88 Zaki HA, Bensliman S, Bashir K, Iftikhar H, Fayed MH, Salem W, et al. Accuracy of procalcitonin for diagnosing sepsis in adult patients admitted to the emergency department: a systematic review and meta-analysis. Syst Rev. 2024;13:37.
89 Cabañas Morafraile J, de Rafael González E, Serrano Martín L, Rubio Díaz R, Torres Fernández M, Heredero Gálvez E, et al. Diagnostic power of LIAISON MeMed VB® for bacterial infection in adults patients seen in Emergency Departments due to infections. Rev Esp Quimioter. 2024;37:486-97.
90 Julián-Jiménez A, Candel González FJ, González-Del Castillo J. Uselfulness of biomarkers to predict bacteremia in patients with infection in the emergency department. Rev Esp Quimioter. 2017;30:245-56.
91 Julián-Jiménez A, Rubio-Díaz R, González-Del Castillo J, Candel González FJ, New predictive models of bacteremia in the emergency department: a step forward. Rev Esp Quimioter. 2022;35:344-56.
92 Julián-Jiménez A, García DE, Merinos-Sánchez G, García de Guadiana-Romualdo L, González Del Castillo J. Diagnostic accuracy of procalcitonin for bacteremia in the emergency department: a systematic review. Rev Esp Quimioter. 2024;37:29-42.
93 Yañez Palma MC, Roman F, Llopis-Roca F, Fragiel M, Julián Jiménez A, Martín-Sánchez FJ, et al. Utility of the medial region of pro-adrenomodulin for the detection of true bacteremia in elderly patients treated in the emergency department for suspected infection. Rev Esp Quimioter. 2024;37:78-87.
94 Xiao H, Zhang H, Wang G, Wang Y, Tan Z, Sun X, et al. Comparison among Presepsin, Procalcitonin, and C-Reactive Protein in predicting blood culture positivity and pathogen in sepsis patients. Shock. 2024;61:387-394.
95 Shapiro NI, Wolfe RE, Wright SB, Moore R, Bates DW. Who needs a blood culture? A prospectively derived and validated prediction rule. J Emerg Med. 2008;35:255-64.
96 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.
97 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.
98 Julián-Jiménez A, García DE, García de Guadiana-Romualdo L, Merinos-Sánchez G, Candel González FJ. Models to predict bacteremia in the emergency department: a systematic review. Emergencias. 2024;36:48-62.
99 Lee J, Hwang SS, Kim K, Jo YH, Lee JH, Kim J, et al. Bacteraemia prediction model using a common clinical test in patients with community-acquired pneumonia. Am J Emerg Med. 2014;32:700-4.
100 Kaal AG, Meziyerh S, van Burgel N, Dane M, Kolfschoten NE, Mahajan P, et al. Procalcitonin for safe reduction of unnecessary blood cultures in the emergency department: Development and validation of a prediction model. J Infect. 2024;89:106251.
101 Aita T, Nakagawa H, Takahashi S, Naganuma T, Anan K, Banno M, et al. Utility of shaking chills as a diagnostic sign for bacteremia in adults: a systematic review and meta-analysis. BMC Med. 2024;22:240.
102 Gamazo Del Río JJ, López Izquierdo R, Delgado Cárdenas G, Estella Á, García DE, Julián-Jiménez A. Adult patients in the emergency department with sepsis or suspected serious infection: Which patients should have blood cultures ordered? Emergencias. 2025;37:131-40.
103 Rubio Díaz R, Nieto Rojas I, Julián-Jiménez A. Importancia de los resultados de los hemocultivos: especial atención para los solicitados desde los Servicios de Urgencias. Rev Esp Quimioter. 2020;33:459-61.
104 Rodrigo Rodríguez M, Llopis Roca F, Rubio Díaz R, García DE, Julián-Jiménez A. Early empirical antibiotherapy in patients attended for suspected sepsis in emergency departments: a systematic review. Emergencias. 2025;37:44-55.
105 Muelas González M, Torner Marchesi E, Peláez Díaz G, Ramos Aranguez M, Cabañas Morafraile J, López Forero W, et al. Usefulness of the MPB-INFURG-SEMES model to predict bacteremia in the patient with solid tumor in the Emergency Department. Rev Esp Quimioter. 2024;37:257-65.

106 Timbrook TT, Morton JB, McConeghy KW, Caffrey AR, Mylonakis E, LaPlante KL. The Effect of Molecular Rapid Diagnostic Testing on Clinical Outcomes in Bloodstream Infections: A Systematic Review and Meta-analysis. Clin Infect Dis. 2017;64:15-23.
107 Anton-Vazquez V, Hine P, Krishna S, Chaplin M, Planche T. Rapid versus standard antimicrobial susceptibility testing to guide treatment of bloodstream infection. Cochrane Database Syst Rev. 2021;5:CD013235.
108 Peri AM, Ling W, Furuya-Kanamori L, Harris PNA, Paterson DL. Performance of BioFire Blood Culture Identification 2 Panel (BCID2) for the detection of bloodstream pathogens and their associated resistance markers: a systematic review and meta-analysis of diagnostic test accuracy studies. BMC Infect Dis. 2022;22:794.
109 Idelevich EA, Silling G, Niederbracht Y, Penner H, Sauerland MC, Tafelski S, et al. Impact of multiplex PCR on antimicrobial treatment in febrile neutropenia: a randomized controlled study. Med Microbiol Immunol. 2015;204:585-92.
110 Shengchen D, Gu X, Fan G, Sun R, Wang Y, Yu D, et al. Evaluation of a molecular point-of-care testing for viral and atypical pathogens on intravenous antibiotic duration in hospitalized adults with lower respiratory tract infection: a randomized clinical trial. Clin Microbiol Infect. 2019;25:1415-21.
111 Burdino E, Ruggiero T, Allice T, Milia MG, Gregori G, Milano R, et al. Combination of conventional blood cultures and the SeptiFast molecular test in patients with suspected sepsis for the identification of bloodstream pathogens. Diagn Microbiol Infect Dis. 2014;79:287-92.
112 Avolio M, Diamante P, Zamparo S, Modolo ML, Grosso S, Zigante P, et al. Molecular identification of bloodstream pathogens in patients presenting to the emergency department with suspected sepsis. Shock. 2010;34:27-30.
113 Hettwer S, Wilhelm J, Schürmann M, Ebelt H, Hammer D, Amoury M, et al. Microbial diagnostics in patients with presumed severe infection in the emergency department. Med Klin Intensivmed Notfmed. 2012;107:53-62.
114 Ziegler I, Fagerström A, Strålin K, Mölling P. Evaluation of a Commercial Multiplex PCR Assay for Detection of Pathogen DNA in Blood from Patients with Suspected Sepsis. PLoS One. 2016;11:e0167883.
115 Voigt C, Silbert S, Widen RH, Marturano JE, Lowery TJ, Ashcraft D, et al. The T2Bacteria Assay Is a Sensitive and Rapid Detector of Bacteremia That Can Be Initiated in the Emergency Department and Has Potential to Favorably Influence Subsequent Therapy. J Emerg Med. 2020;58:785-96.
116 Candel FJ, Salavert M, Cantón R, Del Pozo JL, Galán-Sánchez F, Navarro D, et al. The role of rapid multiplex molecular syndromic panels in the clinical management of infections in critically ill patients: an experts-opinion document. Crit Care. 2024;28:440.
117 Rapszky GA, Do To UN, Kiss VE, Kói T, Walter A, Gergő D, et al. Rapid molecular assays versus blood culture for bloodstream infections: a systematic review and meta-analysis. EClinicalMedicine. 2025;79:103028.
118 González-Castillo J, Candel FJ, Julián-Jiménez A. Antibióticos y el factor tiempo en la infección en urgencias. Enferm Infecc Microbiol Clin. 2013;31:173-80.
119 Bassetti M, Rello J, Blasi F, Goossens H, Sotgiu G, Tavoschi L, et al. Systematic review of the impact of appropriate versus inappropriate initial antibiotic therapy on outcomes of patients with severe bacterial infections. Int J Antimicrob Agents. 2020;56:106184.
120 Asner SA, Desgranges F, Schrijver IT, Calandra T. Impact of the timeliness of antibiotic therapy on the outcome of patients with sepsis and septic shock. J Infect. 2021;82:125-34.
121 Sieswerda E, Bax HI, Hoogerwerf JJ, de Boer MGJ, Boermeester M, Bonten MJM, et al. The 2021 Dutch Working Party on Antibiotic Policy (SWAB) guidelines for empirical antibacterial therapy of sepsis in adults. BMC Infect Dis. 2022;22:687.
122 Tang F, Yuan H, Li X, Qiao L. Effect of delayed antibiotic use on mortality outcomes in patients with sepsis or septic shock: A systematic review and meta-analysis. Int Immunopharmacol. 2024;129:111616.
123 Del Río-Carbajo L, Nieto-Del Olmo J, Fernández-Ugidos P, Vidal-Cortés P. Resuscitation strategy for patients with sepsis and septic shock. Med Intensiva. 2022;46(Supl 1):60-71.
124 Zampieri FG, Bagshaw SM, Semler MW. Fluid Therapy for Critically Ill Adults With Sepsis: A Review. JAMA. 2023;329:1967-80.
125 Pérez-Díaz MS, Solares-Zendejas R. Avances contemporáneos de la fluidoterapia en la sepsis y el choque séptico, una revisión narrativa. Rev Educ Investig Emer. 2025;7:186-96.
126 Semler MW, Self WH, Wanderer JP, Ehrenfeld JM, Wang L, Byrne DW, et al; SMART Investigators and the Pragmatic Critical Care Research Group. Balanced Crystalloids versus Saline in Critically Ill Adults. N Engl J Med. 2018;378:829-39.
127 Self WH, Semler MW, Wanderer JP, Wang L, Byrne DW, Collins SP, et al; SALT-ED Investigators. Balanced Crystalloids versus Saline in Noncritically Ill Adults. N Engl J Med. 2018;378:819-28.
128 Myburgh JA, Finfer S, Bellomo R, Billot L, Cass A, Gattas D, et al; CHEST Investigators; Australian and New Zealand Intensive Care Society Clinical Trials Group. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. N Engl J Med. 2012;367:1901-11.
129 Caironi P, Tognoni G, Masson S, Fumagalli R, Pesenti A, Romero M, et al; ALBIOS Study Investigators. Albumin replacement in patients with severe sepsis or septic shock. N Engl J Med. 2014;370:1412-21.
130 Xu JY, Chen QH, Xie JF, Pan C, Liu SQ, Huang LW, et al. Comparison of the effects of albumin and crystalloid on mortality in adult patients with severe sepsis and septic shock: a meta-analysis of randomized clinical trials. Crit Care. 2014;18:702.
131 Zarychanski R, Abou-Setta AM, Turgeon AF, Houston BL, McIntyre L, Marshall JC, et al. Association of hydroxyethyl starch administration with mortality and acute kidney injury in critically ill patients requiring volume resuscitation: a systematic review and meta-analysis. JAMA. 2013;309:678-88.
132 Arabi YM, Belley-Cote E, Carsetti A, De Backer D, Donadello K, Juffermans NP, et al. European Society of Intensive Care Medicine clinical practice guideline on fluid therapy in adult critically ill patients. Part 1: the choice of resuscitation fluids. Intensive Care Med. 2024;50:813-31.
133 Mekontso Dessap A, AlShamsi F, Belletti A, De Backer D, Delaney A, Møller MH, et al. European Society of Intensive Care Medicine (ESICM) 2025 clinical practice guideline on fluid therapy in adult critically ill patients: part 2-the volume of resuscitation fluids. Intensive Care Med. 2025;51:461-77.
134 Font MD, Thyagarajan B, Khanna AK. Sepsis and Septic Shock-Basics of diagnosis, pathophysiology and clinical decision making. Med Clin North Am. 2020;104:573-85.
135 Chawla LS, Ostermann M, Forni L, Tidmarsh GF. Broad spectrum vasopressors: a new approach to the initial management of septic shock? Crit Care. 2019;23:124.
136 Martínez-Sedas GD. Uso de aminas: guía de uso en urgencias y prehospital. Rev Educ Investig Emer. 2023;5:111-9.
137 García DE, Julián-Jiménez A, López-Izquierdo R, Gualco R, González-Bascuñán U, Fosco MJ, et al. Eficacia y seguridad del uso de inotrópicos en el servicio de urgencias: revisión sistemática. Rev Educ Investig Emer. 2025;7:1-10.
138 Permpikul C, Tongyoo S, Viarasilpa T, Trainarongsakul T, Chakorn T, Udompanturak S. Early Use of Norepinephrine in Septic Shock Resuscitation (CENSER). A Randomized Trial. Am J Respir Crit Care Med. 2019;199:1097-105.
139 Shi R, Braïk R, Monnet X, Gu WJ, Ospina-Tascon G, Permpikul, et al. Early norepinephrine for patients with septic shock: an updated systematic review and meta-analysis with trial sequential analysis. Crit Care. 2025;29:182.
140 Loubani OM, Green RS. A systematic review of extravasation and local tissue injury from administration of vasopressors through peripheral intravenous catheters and central venous catheters. J Crit Care. 2015;30:653.e9-17.
141 Tian DH, Smyth C, Keijzers G, Macdonald S, Peake S, Udy A. Safety of peripheral administration of vasopressor medications: a systematic review. Emerg Med Australas. 2020;32:220-7.
142 Ablordeppey EA, Drewry AM, Beyer AB, Theodoro DL, Fowler SA, Fuller BM, et al. Diagnostic Accuracy of Central Venous Catheter Confirmation by Bedside Ultrasound Versus Chest Radiography in Critically Ill Patients: A Systematic Review and Meta-Analysis. Crit Care Med. 2017;45:715-24.
143 Ospina-Tascón GA, Hernandez G, Alvarez 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.
144 Owen VS, Rosgen BK, Cherak SJ, Ferland A, Stelfox HT, Fiest KM, et al. Adverse events associated with administration of vasopressor medications through a peripheral intravenous catheter: a systematic review and meta-analysis. Crit Care. 2021;25:146.
145 Tran QK, Mester G, Bzhilyanskaya V, Afridi LZ, Andhavarapu S, Alam Z, et al. Complication of vasopressor infusion through peripheral venous catheter: A systematic review and meta-analysis. Am J Emerg Med. 2020;38:2434-43.
146 Delaney A, Finnis M, Bellomo R, Udy A, Jones D, Keijzers G, et al. Initiation of vasopressor infusions via peripheral versus central access in patients with early septic shock: A retrospective cohort study. Emerg Med Australas. 2020;32:210-9.
147 Andrews B, Semler MW, Muchemwa L, Kelly P, Lakhi S, Heimburger DC, et al. Effect of an Early Resuscitation Protocol on In-hospital Mortality Among Adults With Sepsis and Hypotension: A Randomized Clinical Trial. JAMA. 2017;318:1233-40.
148 Marques CG, Mwemerashyaka L, Martin K, Tang O, Uwamahoro C,

Ndebwanimana V, et al. Utilisation of peripheral vasopressor medications and extravasation events among critically ill patients in Rwanda: A prospective cohort study. Afr J Emerg Med. 2022;12:154-9.
149 Kilian S, Surrey A, McCarron W, Mueller K, Wessman BT. Vasopressor Administration via Peripheral Intravenous Access for Emergency Department Stabilization in Septic Shock Patients. Indian J Crit Care Med. 2022;26:811-5.
150 Nguyen TT, Surrey A, Barmaan B, Miller S, Oswalt A, Evans D, et al. Utilization and extravasation of peripheral norepinephrine in the emergency department. Am J Emerg Med. 2021;39:55-9.
151 Putland M, Kerr D, Kelly AM. Adverse events associated with the use of intravenous epinephrine in emergency department patients presenting with severe asthma. Ann Emerg Med. 2006;47:559-63.
152 Medlej K, Kazzi AA, El Hajj Chehade A, Saad Eldine M, Chami A, Bachir R, et al. Complications from Administration of Vasopressors Through Peripheral Venous Catheters: An Observational Study. J Emerg Med. 2018;54:47-53.
153 Mergoum AM, Rhone AR, Larson NJ, Dries DJ, Blondeau B, Rogers FB. A Guide to the Use of Vasopressors and Inotropes for Patients in Shock. J Intensive Care Med. 2025;40:726-38.
154 Bai X, Yu W, Ji W, Lin Z, Tan S, Duan K, et al. Early versus delayed administration of norepinephrine in patients with septic shock. Crit Care. 2014;18:532.
155 Beck V, Chateau D, Bryson GL, Pisipati A, Zanotti S, Parrillo JE, et al. Timing of vasopressor initiation and mortality in septic shock: a cohort study. Crit Care. 2014;18:R97.
156 Ma CH, Healy J, Kinteh E, Ma CC, Tzeng CT, Chou EH, et al. Extremely early initiation of vasopressors might not decrease short-term mortality for adults with septic shock: a systematic review and meta-analysis. Ann Intensive Care. 2025;15:18.
157 Marshall JC, Maier RV, Jimenez M, Dellinger EP. Source control in the management of severe sepsis and septic shock: an evidence-based review. Crit Care Med. 2004; 32(Supl 11): S513-26.
158 Candel FJ, Borges Sá M, Belda S, Bou G, Del Pozo JL, Estrada O, et al. Current aspects in sepsis approach. Turning things around. Rev Esp Quimioter. 2018;31:298-315.
159 Nguyen HB, Rivers EP, Abrahamian FM, Moran GJ, Abraham E, Trzeciak S, et al; Emergency Department Sepsis Education Program and Strategies to Improve Survival (ED-SEPSIS) Working Group. Severe sepsis and septic shock: review of the literature and emergency department management guidelines. Ann Emerg Med. 2006;48:28-54.
160 Coccolini F, Sartelli M, Sawyer R, Rasa K, Viaggi B, Abu-Zidan F, et al. Source control in emergency general surgery: WSES, GAIS, SIS-E, SIS-A guidelines. World J Emerg Surg. 2023;18:41.
161 Julián-Jiménez A, Lorenzo Álvarez R, Gutiérrez Bueno V, Sánchez Trujillo M, Eduardo García D. Early source control of infection in patients seen in the emergency department: a systematic review. Rev Esp Quimioter. 2024;37:323-33.
162 Kim H, Chung SP, Choi SH, Kang GH, Shin TG, Kim K, et al; Korean Shock Society (KoSS) Investigators. Impact of timing to source control in patients with septic shock: A prospective multi-center observational study. J Crit Care. 2019;53:176-82.
163 Azuhata T, Kinoshita K, Kawano D, Komatsu T, Sakurai A, Chiba Y, et al. Time from admission to initiation of surgery for source control is a critical determinant of survival in patients with gastrointestinal perforation with associated septic shock. Crit Care. 2014;18:R87.
164 Oliver ZP, Perkins J. Source Identification and Source Control. Emerg Med Clin North Am. 2017;35:43-58.
165 De Waele JJ, Girardis M, Martin-Loeches I. Source control in the management of sepsis and septic shock. Intensive Care Med. 2022;48:1799-802.
166 Sartelli M, Chichom-Mefire A, Labricciosa FM, Hardcastle T, Abu-Zidan FM, Adesunkanmi AK, et al. The management of intra-abdominal infections from a global perspective: 2017 WSES guidelines for management of intra-abdominal infections. World J Emerg Surg. 2017;12:29.
167 Borges Sa M. Código Sepsis, En: Candel FJ, González del Castillo J y Julián-Jiménez A, editores. Patología Infecciosa en Urgencias. Madrid: Estratagema; 2025. pp.96-100.
168 Borges Sa M, Hidalgo J, Perez-Fernandez J, editors. THE SEPSIS CODEX. First. St Louis: ELSEVIER; 2023.
169 Giglio A, Aranda M, Ferre A, Borges M. Adult Code Sepsis: A Narrative Review of its Implementation and Impact. J Intensive Care Med. 2024 doi: 10.1177/08850666241293034.
170 Ferreras Amez JM, Arribas Entrala B, Sarrat Torres MA, García Noain A, Caudevilla Martínez A, Colás Oros C, et al. Before-after study of the effect of implementing a sepsis code for emergency departments in the community of Aragon. Emergencias. 2017;29:154-60.
171 Méndez R, Figuerola A, Chicot M, Barrios A, Pascual N, Ramasco F, et al. Sepsis Code: dodging mortality in a tertiary hospital. Rev Esp Quimioter. 2022;35:43-9.
172 Robert Boter N, Mòdol Deltell JM, Casas Garcia I, Rocamora Blanch G, Lladós Beltran G, Carreres Molas A. Activation of a code sepsis in the emergency department is associated with a decrease in mortality. Med Clin (Barc). 2019;152:255-60.
173 Palencia Herrejón E, González Del Castillo J, Ramasco Rueda F, Candel FJ, Sánchez Artola B, von Wernitz Teleki A, et al. Consensus document for sepsis code implementation and development in the Community of Madrid. Rev Esp Quimioter. 2019;32:400-9.
174 Kumar A, Roberts D, Wood KE, Light B, Parrillo JE, Sharma S, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med. 2006;34:1589-96.
175 Sherwin R, Winters ME, Vilke GM, Wardi G. Does Early and Appropriate Antibiotic Administration Improve Mortality in Emergency Department Patients with Severe Sepsis or Septic Shock? J Emerg Med. 2017;53:588-95.
176 Pliakos EE, Andreatos N, Shehadeh F, Ziakas PD, Mylonakis E. The Cost-Effectiveness of Rapid Diagnostic Testing for the Diagnosis of Bloodstream Infections with or without Antimicrobial Stewardship. Clin Microbiol Rev. 2018;31:e00095-17.
177 Zacharioudakis IM, Zervou FN, Shehadeh F, Mylonakis E. Cost-effectiveness of molecular diagnostic assays for the therapy of severe sepsis and septic shock in the emergency department. PLoS One. 2019;14:e0217508.
178 D'Aragon F, Belley-Cote EP, Meade MO, Lauzier F, Adhikari NK, Briel M, et al; Canadian Critical Care Trials Group. Blood pressure targets for vasopressor therapy: a systematic review. Shock. 2015;43:530-9.
179 Hylands M, Moller MH, Asfar P, Toma A, Frenette AJ, Beaudoin N, et al. A systematic review of vasopressor blood pressure targets in critically ill adults with hypotension. Can J Anaesth. 2017;64:703-15.
180 Yoshimoto H, Fukui S, Higashio K, Endo A, Takasu A, Yamakawa K. Optimal target blood pressure in critically ill adult patients with vasodilatory shock: A systematic review and meta-analysis. Front Physiol. 2022;13:962670.
181 Sarkar S, Singh S, Rout A. Mean Arterial Pressure Goal in Critically Ill Patients: A Meta-Analysis of Randomized Controlled Trials. J Clin Med Res. 2022;14:196-201.
182 Hidalgo JL, Kumar VK, Akech SO, Myatra SN, Jacob ST, Kortz T, et al. The Sepsis Chain of Survival: A Comprehensive Framework for Improving Sepsis Outcomes. Crit Care Med. 2025. doi: 10.1097/CCM.0000000000006796.
183 Bolanaki M, Kurland L, Brabrand M, Daniels R, Govender K, Hanses F, et al. Current sepsis management practices in European emergency departments: the ISG-emergency department European Survey. Eur J Emerg Med. 2025;32:368-76.
184 Harris S, Singer M, Sanderson C, Grieve R, Harrison D, Rowan K. Impact on mortality of prompt admission to critical care for deteriorating ward patients: an instrumental variable analysis using critical care bed strain. Intensive Care Med. 2018;44:606-15.
185 Klein Klouwenberg PM, Cremer OL, van Vught LA, Ong DS, Frencken JF, Schultz MJ, et al. Likelihood of infection in patients with presumed sepsis at the time of intensive care unit admission: a cohort study. Crit Care. 2015;19:319.
186 Zhang Z, Bokhari F, Guo Y, Goyal H. Prolonged length of stay in the emergency department and increased risk of hospital mortality in patients with sepsis requiring ICU admission. Emerg Med J. 2019;36:82-7.