Sepsis and septic shock in geriatrics

Aurora Vitali,[1] Simone Dini,[2] Mariagiovanna Cozza,[3] Vincenzo Gianturco,[4] Mattia Brunori,[1] Liliana Mazza[5]

[1]Department of Medical Sciences, University of Ferrara; [2]Geriatrics Unit, Department of Geriatric Care, Orthogeriatrics and Rehabilitation, E.O. Ospedali Galliera, Genoa; [3]UOC Intermediate Care/Budrio Long-Term Care, Integration Department, AUSL Bologna; [4]Tor Vergata University, Coniugi Bernardini's Hospital, Palestrina, Rome; [5]Unit of Geriatrics, Department of Integration, Maggiore Hospital, AUSL Bologna, Italy

Abstract

Sepsis is a potentially life-threatening condition that poses diagnostic challenges, particularly in the older population. Clinical manifestations of sepsis in these individuals can be blurred and atypical, making detection and diagnosis difficult. Common symptoms such as fever may be absent; conversely, older patients may present with atypical signs such as delirium, altered mental status, falls, weakness, and urinary incontinence. This can lead to delayed diagnosis, which increases the risk of rapid progression to septic shock. To improve diagnostic accuracy, various laboratory biomarkers and clinical scores have been developed, such as the Sequential (Sepsis-related) Organ Failure Assessment Score (SOFA-score), quick SOFA (qSOFA), and geriatric-qSOFA. These tools aid in identifying sepsis and predicting mortality risk promptly. In terms of treatment, early intervention is crucial. Maintaining adequate tissue perfusion ("fluid resuscitation"), appropriate antibiotic therapy, and eventually vasopressor support are key components of sepsis management in older adults. Additionally, in frail and comorbid patients, priority must be given to supportive care aimed at enhancing quality of life. Tailored therapeutic interventions are crucial to improving outcomes in this vulnerable population.

Correspondence: Simone Dini, Geriatrics Unit, Department of Geriatric Care, Orthogeriatrics and Rehabilitation, E.O. Ospedali Galliera, Genoa, Italy.
Tel.: 3332053263.
E-mail: simone.dini@galliera.it

Key words: sepsis, frailty, antibiotic, septic shock.

Contributions: all the authors made a substantial intellectual contribution, read and approved the final version of the manuscript, and agreed to be accountable for all aspects of the work.

Conflict of interest: the authors declare no potential conflict of interest.

Ethics approval and consent to participate: not applicable.

Patient consent for publication: not applicable.

Funding: none.

Availability of data and materials: data available from the corresponding author upon request.

Received: 2 September 2024.
Accepted: 11 November 2024.

Licensee PAGEPress, Italy
Geriatric Care 2024; 10:11709
doi:10.4081/gc.2024.11709

Introduction

The Third International Consensus Definitions for Sepsis and Septic Shock defined sepsis as a life-threatening organ dysfunction caused by a deregulated host response to infection.[1] Septic shock is a form of sepsis characterized by persisting hypotension requiring vasopressors to maintain mean arterial pressure (MAP) equal to or greater than 65 mmHg and increased serum lactate (greater than 2 mmol/L) despite adequate volume resuscitation. The aim of this review is to discuss general issues of sepsis and to highlight specificities of the disease in older patients.

Epidemiology

Sepsis is one of the most frequent causes of hospitalization and a major cause of death in aged patients. It accounts for 20% of global deaths and is responsible for a high rate of morbidity, as those who survive frequently show long-term physical and cognitive impairment.[2] Rowe *et al*. showed that sepsis is a predictor of mortality upon admission to the intensive care unit (ICU).[3] In fact, the mortality rate in older adults admitted to the ICU was 1.8 times higher than in those admitted without sepsis.[4] Moreover, the mortality rate due to sepsis in old patients is 1.3-1.5 times higher than in younger patients, probably caused by elevated lactate levels, multi-organ failure such as respiratory and cardiac failure, and a longer length of stay.[4] Sepsis incidence is expected to rise according to the increase in the aged population and its impact on public health will be increasingly greater.[5]

Pathophysiology

The pathogenesis is multifactorial, extremely complex, and not yet completely clear.[6] It is characterized by an imbalance between pro- and anti-inflammatory mechanisms, leading to circulatory and metabolic dysfunction. The excessive inflammatory response secondary to bloodstream infection (BSI) leads to dysfunction of the

vascular endothelium, loss of barrier integrity, uncontrolled activation of the coagulation cascade with microvascular thrombosis and tissue hypoperfusion, reduced tissue oxygenation, and subsequent organ failure. Vascular endothelial injury seems to be the major mechanism for the development of sepsis and multiorgan dysfunction. The endothelium plays an important role in regulating vascular tone, permeability, and the coagulation cascade, and its dysfunction can lead to microvascular thrombosis, disseminated intravascular coagulation, hypotension, and decreased tissue oxygenation. This leads to a humoral response and neuroendocrine abnormalities characterized by the overproduction of counter-regulatory hormones (cortisol, catecholamines, and glucagon) with the release of circulating metabolic substrates, followed by a "shut-down" of cell metabolism.[7] The loss of mitochondrial function with the accumulation of free oxygen radicals and the hyperproduction of lactic acid contribute to multi-organ dysfunction.[8]

Brain dysfunction: sepsis-associated brain dysfunction is a typical manifestation of sepsis due to direct neuronal damage by microbial agents and bacterial endotoxins, blood-brain barrier impairment with the presence of cytokines and pro-inflammatory factors, altered cerebral perfusion, endothelial vasculopathy, oxidative stress, and mitochondrial dysfunction.[9-11]

Cardiomyopathy: sepsis-induced cardiomyopathy is a consequence of hemodynamic stress and systemic inflammation that induces myocardial inflammation and microvascular dysfunction, leading to secondary heart failure.[12]

Myopathy: sepsis-induced myopathy is characterized by skeletal muscle weakness and atrophy, leading to failure to wean from a ventilator in critically ill patients. It is correlated with an increased risk of mortality and ICU length of stay. It is due to electrophysiological (muscle excitability) and histopathological (mitochondrial dysfunction, increased protein breakdown, inability to regenerate damaged or dysfunctional myofibers) abnormalities of the muscle.[13]

The organism's specific response to pathogenic *noxa*, however, depends on both the microorganism's own characteristics (pathogen load and microbial pathogenesis) and the patient's characteristics (genetic predisposition, comorbidity, innate immune response). The increases in pro-thrombotic factors (VIII, IX coagulation factors, fibrinogen) and pro-inflammatory cytokines that are associated with aging contribute to increased thrombotic risk and cell damage secondary to infection.[14] In particular, a crucial role is played by immunosenescence, which consists of the gradual decline of the immune system (especially T-cell function) and the persistent low-grade inflammation that is typical of older persons ("inflammaging").[15] Hence, the greater susceptibility and vulnerability of the old patient to sepsis. In this population, the shared common pathway between sepsis, aging, and inflammation, with a crucial function of neutrophilic aging, is the basis for the disruption of inflammatory burden, with the risk of persistent, recurring, secondary, and nosocomial infections, rates of hospital re-admissions and mortality.[16]

Diagnostic difficulties of sepsis in older people

Special attention may be made to avoid misdiagnosis of sepsis in older adults.

Clinical manifestations

Older patients often have multimorbidity and frailty, which makes the clinical picture of sepsis even more complex. The clinical manifestations of sepsis, especially in frail old individuals, may be blurred and atypical. The absence of fever, a peculiar sign of infection, is very common. Conversely, uncommon symptoms and signs such as delirium, altered mental status, dizziness, falls, anorexia, loss of appetite, weakness, and urinary incontinence may be present in the early stage of sepsis. Because of this aspecific pattern, the diagnosis and subsequent therapeutic approach may be delayed, increasing the risk of rapid progression to septic shock.[17] Moreover, not only can the risk of infection in older adults be increased by the presence of common comorbidities (*i.e.*, congestive heart failure, diabetes mellitus, chronic kidney disease, malignancies, and chronic obstructive lung diseases), but these can also alter the clinical pattern.

The unspecificity of presentations of sepsis in older patients makes a wide and personalized approach mandatory. In this context, the role of frailty appears relevant as it is associated with worse clinical outcomes, including mortality and home discharge.[18] Hence, a multidimensional approach, including frailty assessment (*i.e.*, adopting Clinical Frailty Scale) may be useful for a patient-tailored approach.[19]

Laboratory exams and biomarkers

Cultural examination of blood fluids may be administered according to the source of infection. Antibiograms are the key to the adaptation of antimicrobic therapy, as discussed below.

Regarding biochemical biomarkers, C-reactive protein (CRP), procalcitonin (PCT), presepsin, pentraxin, and interleukin (IL)-6 are some of the most studied sepsis laboratory biomarkers. More recently discovered biomarkers of glycocalyx damage and endothelial activation, such as syndecane and endocane, have been associated with clinical outcomes, including mortality, and can be used to guide treatment protocols.[20,21] CRP is an acute phase reactant secreted by hepatocytes, rising in any inflammatory response in response to pathogen or tissue damage. Due to its baseline increased value in aging-related disorders, it loses specificity in the older population.[22]

PCT is the precursor of calcitonin produced by thyroid C cells, whose plasmatic levels increase rapidly during bacterial infections.[23] PCT levels ≥2 ng/mL suggest a systemic bacterial infection;[24] higher levels are generally observed in Gram-negative BSI rather than Gram-positive or candidemia.[25] In the literature, PCT is considered a marker to guide antimicrobial treatment, and multiple serial PCT measurements are proposed to reduce antibiotic exposure.[26,27] PCT determination should not be used alone in older patients,[28] but it should be considered along with other biomarkers and according to clinical and microbiological assessment.[29,30] In a comprehensive geriatric assessment-based instrument, such as the Multidimensional Prognostic Index (MPI), the combination of PCT levels has increased the powerfulness of MPI in predicting mortality in older patients with community-acquired pneumonia (CAP).[31]

Other inflammatory markers can be considered in confirming the suspicion of sepsis. Presepsin, which is released from monocytes, presents higher levels proportionally to the severity of sepsis.[32] Adrenomedullin and pro-adrenomedullin are used for prognostication in septic patients with CAP and are associated with increased mortality in septic patients.[33,34] Soluble urokinase-type plasminogen activator receptor increases during inflammation, although it is inferior to PCT in differentiating non-infective SIRS.[35] In a recent retrospective study, serum levels of IL-6, IL-7, IL-15, and tumor necrosis factor-α were significantly higher in the non-survival group in aged patients with sepsis.[36]

Nonetheless, serum analysis and molecular diagnostic techniques are expensive, labor-intensive, resource-demanding, and time-consuming and require skilled personnel. In contrast, the microarray technique can identify microbes through surface-immobilized DNA and RNA probes.[37] However, the performance of biomarkers may be different in older patients. Therefore, a comprehen-

sive geriatric assessment associated with clinical judgment is always necessary.[38]

Scores

Clinical scores have been implemented to guide diagnostic suspicion and to evaluate prognosis in sepsis. The Sequential (Sepsis-related) Organ Failure Assessment (SOFA) Score represents the most validated tool. It grades the presence of respiratory, cardiovascular (MAP), neurological [Glasgow Coma Scale (GCS)], renal (creatinine serum level, renal output), hepatic (bilirubin serum level), and hematological (platelet count) dysfunction (Table 1). A score above 2 indicates an increased risk of mortality in a hospitalized population with suspected infection by approximately 10%. Quick SOFA (qSOFA) has recently been developed as a screening tool to obtain an even more timely diagnosis. It is based on only three variables: changes in pressure, consciousness, and respiratory rate. It is easy to perform and does not require the use of laboratory tests. Although its sensitivity is relatively low, a score greater than or equal to 2 should raise clinical suspicion of sepsis.[39] A variant of qSOFA is the geriatric-qSOFA, which appears more sensitive in predicting short-term mortality in hospitalized older patients with sepsis by assessing the presence of delirium according to the Diagnostic and Statistical Manual of Mental Disorders – 5th edition criteria other than GCS assessment (Table 2).[40]

Clinical scores present some limits and controversies. The use of platelet count in SOFA could not provide a full picture of coagulopathy. Similarly, the assessment of central nervous system function could be difficult in some patients, particularly those receiving mechanical ventilation. Delta SOFA alone has a poor discriminating ability between survivors and non-survivors.[41]

A negative qSOFA screen with laboratory signs of multi-organ failure should not deviate clinicians from the suspicion of sepsis. In older patients, the predictive value of the qSOFA has been little studied, mainly in ICU wards,[42] with the performance of qSOFA score changing across studies. Nevertheless, in a population of aged patients admitted to an intermediate care unit, SOFA and qSOFA showed relatively high negative predictive values for the risk of in-hospital death.[43] In a 90+ age group, qSOFA≥ 2 and BSI originating outside the urinary tract (intra-abdominal or respiratory tract) were strong independent predictors of in-hospital mortality, as were thrombocytopenia, inappropriate antibiotics, and hospital-acquired infection.[44]

In any case, since these scores include measures of organ dysfunction, in old patients, they may be an epiphenomenon of exacerbation of pre-existing (potentially underdiagnosed) comorbidities, predicting deaths due to the latter and not for the sepsis itself.[45] Thus, the identification of frailty and comorbidities remains a key point in the diagnosis and management of sepsis in older adults.[46]

Management and treatment

Treatment for sepsis should begin as soon as possible. Two are the cornerstones: fluids and antimicrobial therapy.

For what concerns fluids, the mainstay of treatment is the maintenance of adequate tissue perfusion with a MAP of 65 mmHg or higher, and in some cases, 70-75 mmHg, especially in patients with known hypertension. Infusion of crystalloid fluids with a minimum of 30 mL/kg within the first 3 hours is indicated, ensuring that the volume load does not precipitate diastolic cardiac dysfunction.[47,48] In the case of large fluid infusions, the use of albumin may be considered, although there is no evidence that its use has an impact on survival within 90 days.[49] In hypotension refractory to intravenous fluid therapy, the first-line treatment is the use of vasopressors with norepinephrine, and vasopressin infusion may be associated with it. There is less evidence regarding the administration of dopamine, which has only been recommended at low dosages (not exceeding 5 γ/kg).[50]

As for antimicrobial therapy, empirical broad-spectrum antibiotic therapy should be administered promptly, preferably within the first hour or, in any case, within the first 3 hours of diagnosis. The choice of the first-line antibiotic therapy depends on the source of infection (respiratory tract infections, urinary tract infections, and bacteremia account for more than 80% of the causes of sepsis) and consequently on the pathogens most frequently responsible, according to local epidemiology (*Staphylococci*, *Streptococci, and Pseudomonas* for airway infections, and *Escherichia coli*, *Proteus*, *Klebsiella*, *Enterobacter* for urinary infections) and clinical risk fac-

Table 1. Sequential Sepsis-related Organ Failure Assessment Score.

	0	1	2	3	4
P/F	≥400	<400	<300	<200*	<100*
Platelets	≥150	<150	<100	<50	<20
Bilirubin	<1.2	1.2-1.9	2.0-5.9	6-11.9	>12
MAP	≥70	<70	Dopamine <5** or dobutamine	Dopamine 5.1-15 or E**≤0.1 or norepinephrine** ≤0.1	Dopamine >15 or epinephrine** >0.1 or norepinephrine >0.1
GCS	15	13-14	10-12	06-09	<6
Creatinine	<1.2	1.2-1.9	2.0-3.4	3.5-4.9	>5.0
Urine output				<500	<200

P/F, PaO_2/FiO_2 ratio; MAP, maintain mean arterial pressure; GCS, Glasgow Coma Scale;*with respitatory support; **dopamine, dobutamine, epinephrine (E), norepinephrine.

Table 2. Geriatric quick-Sequential Sepsis-related Organ Failure Assessment Score.

	Variables			
Hypotension	SBP>100 mmHg	**0**	SBP≤100 mmHg	**1**
Tachypnea	R/R<22 breaths per min	**0**	R/R≥22 breaths per min	**1**
Mental status	Absence of delirium	**0**	Presence of delirium	**1**

Range score: 0-3. SBP, systolic blood pressure; R/R, respiratory rate.

tors.[51] As soon as any antibiogram on cultural examination may be disposable, antibiotic therapy has to be reconsidered to make it targeted toward the etiological agent of infection. Efforts may be made to reduce antimicrobic resistance, which is frequent in older patients. In this sense, an approach aimed at antimicrobial stewardship promotes the appropriate use of antibiotic drugs.[52]

Treatment should be personalized according to the patient's characteristics and comorbidities. For example, concerning frequent concomitant adrenal insufficiency in older adults, corticosteroids may be considered for those unresponsive to the above-mentioned treatments. Transfusions are indicated with hemoglobin values of 7-8 g/dL. Fluids should be tailored considering the state of hemodynamic compensation, as in the case of pre-existing heart failure. Potential drug interactions should also be considered.

Any treatment needs to be periodically reassessed depending on clinical, laboratory, and microbiological data. In frail and comorbid patients with reduced chances of recovery and reduced life expectancy, it is necessary to consider the proportionality of care, avoid aggressive and invasive treatments, and focus on supportive care aimed at improving the residual quality of life. Decisions need to be made in agreement with the patient's family members, who are involved in the entire decision-making and care process of illness.[17]

Conclusions

Sepsis represents a life-threatening condition that is time-dependent and requires the appropriate clinical evaluation and targeted therapeutic intervention in older patients right from hospital admission. While clinical scores can help guide promptly to diagnosis, a global evaluation of older patients, in terms of comprehensive geriatric assessment, remains crucial for the correct interpretation of symptoms and patient-tailored standard of care.

References

1. Singer M, Deutschman CS, Seymour CW, et al. The third international consensus definitions for sepsis and septic shock (sepsis-3). JAMA 2016;315:801-10.
2. Rudd KE, Johnson SC, Agesa KM, 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.
3. Remelli F, Fogagnolo A, Zurlo A, et al. Prognostic factors in older patients admitted in ICU with diagnosis of abdominal sepsis (sepsis-3 criteria). JGG 2020;68:152-8.
4. Rowe T, Araujo KL, Van Ness PH, et al. Outcomes of older adults with sepsis at admission to an intensive care unit. Open Forum Infect Dis 2016;3:ofw010.
5. Fleischmann C, Scherag A, Adhikari NK, et al. Assessment of global incidence and mortality of hospital-treated sepsis. Current estimates and limitations. Am J Respir Crit Care Med 2016;193:259-72.
6. Nasa P, Juneja D, Singh O. Severe sepsis and septic shock in the elderly: an overview. World J Crit Care Med 2012;1:23-30.
7. Vincent JL, De Backer D. Circulatory Shock N Engl J Med 2013;369:1726-34.
8. Preau S, Vodovar D, Jung B et al. Energetic dysfunction in sepsis: a narrative review. Ann Intensive Care 2021;11:104.
9. Chung HY, Wickel J, Brunkhorst FM, et al. Sepsis-associated encephalopathy: from delirium to dementia? J Clin Med 2020;9:703.
10. Czempik PF, Pluta MP, Krzych ŁJ. Sepsis-associated brain dysfunction: a review of current literature. Int J Environ Res Public Health 2020;17:5852.
11. Mazeraud A, Righy C, Bouchereau E, et al. Septic-associated encephalopathy: a comprehensive review. Neurotherapeutics 2020;17:392-403.
12. Carbone F, Liberale L, Preda A, et al. Septic cardiomyopathy: from pathophysiology to the clinical setting. Cells 2022; 11:2833.
13. Mankowski RT, Laitano O, Clanton TL, et al. Pathophysiology and treatment strategies of acute myopathy and muscle wasting after sepsis. J Clin Med 2021;10:1874.
14. Iba T, Umemura Y, Wada H, et al. Roles of coagulation abnormalities and microthrombosis in sepsis: pathophysiology, diagnosis, and treatment. Arch Med Res 2021;52:788-97.
15. Soysal P, Stubbs B, Lucato P, et al. Inflammation and frailty in the elderly: a systematic review and meta-analysis. Ageing Res Rev 2016;31:1-8.
16. Ramoni D, Tirandi A, Montecucco F, Liberale L. Sepsis in elderly patients: the role of neutrophils in pathophysiology and therapy. Intern Emerg Med 2024;19:901-17.
17. Clifford KM, Dy-Boarman EA, Haase KK, et al. Challenges with diagnosing and managing sepsis in older adults. Expert Rev Anti Infect Ther 2016;14:231-41.
18. Lee HY, Lee J, Jung YS, et al. Preexisting clinical frailty is associated with worse clinical outcomes in patients with sepsis. Crit Care Med 2022;50:780-90.
19. Church S, Rogers E, Rockwood K, Theou O. A scoping review of the clinical frailty scale. BMC Geriatr 2020;20:393.
20. Von Groote T, Meersch-Dini M. Biomarkers for the prediction and judgement of sepsis and sepsis complications: a step towards precision medicine? J Clin Med 2022;11:5782.
21. Sullivan RC, Rockstrom MD, Schmidt EP, et al. Endothelial glycocalyx degradation during sepsis: causes and consequences. Matrix Biol Plus 2021;12:100094.
22. Tang Y, Fung E, Xu A, Lan HY. C-reactive protein and ageing. Clin Exp Pharmacol Physiol 2017;44:9-14.
23. Lo Buglio A, Bellanti F, Talia M, et al. Reliability of serum procalcitonin concentration for the diagnosis of sepsis in elderly patient with chronic kidney disease. JGG 2016;64:49-54.
24. Thomas-Rüddel DO, Poidinger B, Kott M, et al. Influence of pathogen and focus of infection on procalcitonin values in sepsis patients with bacteremia or candidemia. Crit Care 2018;22:128.
25. Hatzistilianou M. Diagnostic and prognostic role of procalcitonin in infections. ScientificWorldJournal 2010;10:1941-6.
26. Wirz Y, Meier MA, Bouadma L, et al. Effect of procalcitonin-guided antibiotic treatment on clinical outcomes in intensive care unit patients with infection and sepsis patients: a patient-level meta-analysis of randomized trials. Crit Care 2018;22:191.
27. Heilmann E, Gregoriano C, Annane D, et al. Duration of antibiotic treatment using procalcitonin-guided treatment algorithms in older patients: a patient-level meta-analysis from randomized controlled trials. Age Ageing 2021;50:1546-56.
28. Falcone M, Bauer M, Ferrer R, et al. Biomarkers for risk stratification and antibiotic stewardship in elderly patients. Aging Clin Exp Res 2023;35:925-35.
29. Zhao Y, Li C. Diagnostic value of a combination of biomarkers in patients with sepsis and severe sepsis in emergency department. Zhonghua Wei Zhong Bing Ji Jiu Yi Xue 2014;26:153-8. [Article in Chinese].
30. Ahuja N, Mishra A, Gupta R, Ray S. Biomarkers in sepsis-looking for the holy grail or chasing a mirage! World J Crit Care Med 2023;12:188-203.
31. Pilotto A, Dini S, Daragjati J, et al. Combined use of the multidimensional prognostic index (MPI) and procalcitonin serum

levels in predicting 1-month mortality risk in older patients hospitalized with community-acquired pneumonia (CAP): a prospective study. Aging Clin Exp Res 2018;30:193-7.
32. Liu B, Chen YX, Yin Q, et al. Diagnostic value and prognostic evaluation of Presepsin for sepsis in an emergency department. Crit Care 2013;17:R244.
33. Christ-Crain M, Morgenthaler NG, Stolz D, et al. Pro-adrenomedullin to predict severity and outcome in community-acquired pneumonia [ISRCTN04176397]. Crit Care 2006; 10:R96.
34 Li Q, Wang BS, Yang L, et al. Assessment of adrenomedullin and proadrenomedullin as predictors of mortality in septic patients: a systematic review and meta-analysis. Med Intensiva 2018;42:416-24.
35. Huang Q, Xiong H, Yan P, et al. The diagnostic and prognostic value of suPAR in patients with sepsis: a systematic review and meta-analysis. Shock 2020;53:416-25.
36. Zhao J, Zhang Y, Wang JY, et al. Correlation analyses between serum interleukin-7, interleukin-15 and lactate provide insights into their potential roles in the regulation of inflammation in elderly septic patients. Biomark Insights 2024;19: 11772719241275525.
37. Kumar NR, Balraj TA, Shivashankar KK, et al. Inflammaging in multidrug-resistant sepsis of geriatric ICU patients and healthcare challenges. Geriatrics 2024;9:45.
38. Ibarz M, Haas LEM, Ceccato A, Artigas A. The critically ill older patient with sepsis: a narrative review. Ann Intensive Care 2024;14:6.
39. Liu C, Suo S, Luo L, et al. SOFA score in relation to sepsis: clinical implications in diagnosis, treatment, and prognostic assessment. Comput Math Methods Med 2022;2022:7870434. Retraction in: Comput Math Methods Med 2023;2023:9856196.
40. Remelli F, Castellucci F, Vitali A, et al. Predictive value of geriatric-quickSOFA in hospitalized older people with sepsis. BMC Geriatr 2021;21:241.
41. Moreno R, Rhodes A, Piquilloud L, et al. The sequential organ failure assessment (SOFA) score: has the time come for an update? Crit Care 2023;27:15.
42. Bastoni D, Ticinesi A, Lauretani F, et al. Application of the sepsis-3 consensus criteria in a geriatric acute care unit: a prospective study. J Clin Med 2019;8:359.
43. Minne L, Abu-Hanna A, de Jonge E. Evaluation of SOFA-based models for predicting mortality in the ICU: a systematic review. Crit Care 2008;12:R161.
44. Falsetti L, Martino M, Zaccone V, et al. SOFA and qSOFA usefulness for in-hospital death prediction of elderly patients admitted for suspected infection in internal medicine. Infection 2020;48:879-87.
45. Ramos-Rincón JM, Fernández-Gil A, Merino E, et al. The quick sepsis-related organ failure assessment (qSOFA) is a good predictor of in-hospital mortality in very elderly patients with bloodstream infections: a retrospective observational study. Sci Rep 2019;9:15075.
46. Goodacre S, Fuller G, Conroy S, Hendrikse C. Diagnosis and management of sepsis in the older adult. BMJ 2023;382: e075585.
47. Evans L, Rhodes A, Alhazzani W, et al. surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. Intensive Care Med 2021;47:1181-247.
48. Brown RM, Semler MW. Fluid management in sepsis. J Intensive Care Med 2019;34:364-73.
49. Caironi P, Tognoni G, Masson S, et al; ALBIOS study investigators. Albumin replacement in patients with severe sepsis or septic shock. N Engl J Med 2014;370:1412-21.
50. Lesur O, Delile E, Asfar P, et al. Hemodynamic support in the early phase of septic shock: a review of challenges and unanswered questions. Ann Intensive Care 2018;8:102.
51. IDSA Sepsis Task Force. Infectious Diseases Society of America (IDSA) POSITION STATEMENT: why IDSA did not endorse the surviving sepsis campaign guidelines. Clin Infect Dis 2018;66:1631-5.
52. Sulis G, Sayood S, Katukoori S, et al. Exposure to World Health Organization's AWaRe antibiotics and isolation of multidrug resistant bacteria: a systematic review and meta-analysis. Clin Microbiol Infect 2022;28:1193-202.