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**Review Article**

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# *Geriatric Sepsis in the COVID-19 Era: Challenges in Diagnosis and Management*

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## ABSTRACT

*The elderly or geriatric patients represent a significant portion of emergency department (ED) admissions. Factors affecting poor outcome in these patients suspected or diagnosed with sepsis include shock, hyperlactatemia, and organ failure. Atypical presentations should be emphasized in the training of triage and ED personnel due to difficulties and pitfalls in diagnostic processes for sepsis. The vital organ functions of the elderly, who are among the highest risk groups in the management of sepsis, may deteriorate rapidly with very few precursors, and aggressive methods should be used rapidly when necessary. Interactions of drug doses in the elderly, problems in excretion and differences in metabolism should be considered in treatment regimens. Healthcare workers should try to eliminate colonization risks such as vascular catheterization, unnecessary vascular access and urinary catheters should be removed.*
*In the long term after recovery from sepsis, heart failure, peripheral vascular disease, dementia, and diabetes are the most common entities recorded in the literature. This review was intended to provide an overview of the overall management and give some practical tips for this fragile group of patients in the post-pandemic era.*

**Key words:** *Geriatric sepsis, Sepsis, Septic shock, COVID-19, Diagnosis, Management*

## INTRODUCTION

The world average life expectancy has increased from 58 years in the 1970s to 68 in the 2000s [1]. The elderly or geriatric patients represent a significant portion of emergency department (ED) admissions. The age limit for the "elderly" is not fully finalized either. While Western medicine seems unanimous that 65 is the limit for being elderly, socioeconomic and cultural variation is significant. For example, the United Nations defines **a**n older person as a person over 60 years of age [2]. Many families and populations use other socio-cultural referents to define age, including family status (e.g., grandparents can be automatically viewed as elderly), physical appearance, or age-related health issues. In the developing countries mean life expectancy are shorter than industrialized western countries (around 10 years), thus 55-60 years of age can be considered as the age limit for being elderly in these regions.

The elderly experience more difficult processes due to physiological changes, disruption of cellular healing mechanisms, comorbidities, polypharmacy and loss of cognitive and functional status, and may be exposed to neglect and abuse. They are more likely to present with 'atypical' or unusual complaints. Therefore, it may be necessary to keep the differential diagnosis lists much wider and to be more aggressive in the treatment. In addition to the high probability of misdiagnosis and delayed diagnosis by the physician, malpractice lawsuits are also a serious problem when the risk of this wrong diagnosis causing direct death in the patient is unacceptably high.

In the EDs, 1 in every 33 adults with an infection is suspected of having severe sepsis. It is estimated that up to 2/3 of the patients who develop sepsis are elderly people [3]. In a cohort study, 45.9% of 1,448 cases with septic shock were septuagenarians and older individuals (70-80 years: 29.4%, ≥ 80 years: 16.5%), and 58.5% of the elderly with sepsis were reported to have come from nursing homes [4].

*Assessment of scores in diagnosis of sepsis*

Organ dysfunction can be defined by an increase of 2 points or more in the "Sequential Organ Failure Assessment" score, known as SOFA. Septic shock, with its severe circulatory, cellular, and metabolic abnormalities, carries a higher mortality risk than sepsis alone. Patients in septic shock are recognized by having a serum lactate level greater than 2 mmol/L or by requiring a vasopressor to maintain mean arterial pressure (MAP) above 65 mmHg after ruling out hypovolemia. This phenomenon represents nearly half of the patients with mortality in hospital [5]. The arterial lactate level is higher in the elderly who died due to sepsis and this predicts mortality independently [6].

Diagnostic system known as "Quick SOFA" (qSOFA) used in the recognition of adult patients with suspected infection, those who have at least two of the criteria of tachypnea (respiratory rate ≥ 22 bpm), altered level of consciousness [Glasgow Coma Scale (GCS) score < 15], or hypotension (systolic blood pressure ≤ 100 mmHg) are sought [5, 7]. The rates of severe sepsis and mortality are expected to be significantly higher in this high-risk group than others. These criteria were thought to be useful for expedient diagnosis of sepsis in the ED. In a prospective study conducted in European EDs, it was reported that qSOFA had a higher predictive value than SIRS or sepsis criteria in mortality estimation in patients admitted to ED with suspected infection [8].

It has also been reported that scoring systems such as Modified Early Warning Score (MEWS) and National Early Warning Score (NEWS) are stronger than qSOFA in terms of predicting death and ICU admission [9]. The study showed that qSOFA had lower sensitivity in predicting premature death than the presence of three or more systemic inflammatory response syndrome (SIRS) criteria [10]. The qSOFA score can be helpful for faster recognition of sepsis outside the ICU (eg, ED or geriatric ward), timely treatment, and better clinical outcome [5]. It would be more appropriate to use the scores by knowing their strengths and weaknesses.

*Differences of clinical course between the elderly and others in disease outbreaks and COVID-19 pandemics*

The pandemic waves have radically changed the global data related to sepsis end infections in general, for almost three years. Both the medical community and ordinary people have focused on COVID-19 in this period and preventive measures such as masks, vaccinations and other practices reduced disease transmission and percentage of symptomatic disease.

It has been reported that clinical and laboratory changes in patients over the age of 65 who died 28 days after the diagnosis of sepsis were brought in response to sepsis are more subtle than those in the middle-aged [11]. Blood and infection site cultures are negative in one-third of the cases [12-14].

Not only COVID-19, but almost all diseases, from heart attack to brain infarction, progress differently in elderly individuals **(Table 1)**. For example, while the mean time from the onset of symptoms to death in the elderly with COVID-19 is 11.5 days, it is 14 days in the young [15].

SARS in 2002, H1N1 (swine flu) in 2009, and MERS in 2012 also had a profound impact on society. However, no different involvement was observed according to age, and they formed an effect in a short time and passed. Their lethality rate was as high as 35% to 10%, much higher than COVID-19, yet the effect size was lower.

The main points that deserve attention are the difficulties in taking the history, more obscure symptoms and findings, the recovery takes longer, and the differences in the effects of the drugs due to the inadequacies in the organ systems. Beyond these, comorbidities directly affect the death rate.

The elderly are more prone to infections due to impaired immunity, as well as COVID-19. They are also slower to heal. Both the complications of the disease and the drug side effects and other treatment complications may

be more frequent and severe in the elderly. If there is smoking, vitamin deficiency, diabetes mellitus, the protacted and difficult recovery will be more pronounced.

In the report published by WHO in relation to COVID-19, the fatality rate was 1.4% in all cases in China, while it was 22% in octogenarians and their elders. In Italy, 23% of the population is 65 years or older, while almost 90% of COVID-19 deaths have been recorded in individuals aged 70 and over [16]. Those over the age of 80 accounted for 58% of the deaths. It is also known that these rates vary according to geography and countries.

Sepsis mortality rates are 10% in children, 26% between the ages of 60-64 and 38% over the age of 85 [12, 17]. In another study, it was reported that the mortality rate due to sepsis was 17.7% under the age of 65, while it was 27.7% over the age of 65 [18]. In a Chinese retrospective study, Jin *et al*. disclosed that age *per se* is not a significant risk factor in predicting death in COVID-19 [19]. Instead, vital sign abnormalities, presentation with dyspnea and certain laboratory and radiological markers have been useful to estimates death in this population. Likewise, mean SOFA, qSOFA, APACHEII and SIRS scores are all significantly different between survivors and nonsurvivors.

In a multicentric USA study (164 EDs across 33 states), Janke *et al*. investigated patterns of ED visit counts for emergent conditions during the COVID-19 pandemic for older adults [20]. There has been a more pronounced and persistent decline in visits to the EDs nationwide for emergent conditions among older adults compared with their younger counterparts, with fewer deaths in ED after the early pandemic period. Across AMI, stroke, and sepsis, the older (75– 84 years of age) and oldest old (85+ years) had the greatest decline in visits during the early pandemic period and the smallest recovery in the post-early pandemic periods.

These findings raise the concern that increased mortality for older adults during the COVID-19 era, especially that occurring outside of ED and inpatient settings, may be related to changes in medical care seeking and warrant investigation and interventions targeting older adult populations at greatest risk.

*Bacterial infections in the COVID-19 era*

The two most frequently healthcare-acquired infections described in patients hospitalized with COVID-19 were bloodstream infection, related or not to catheters, and healthcare-associated pneumonia (HAP). Gram-positive cocci and Gram-negative bacilli in HAP were commonly found in cultures obtained from these patients. The rate of Gram-negative bacilli is particularly high in late-onset ventilator-associated pneumonia, and the specific risk of Pseudomonas aeruginosa-related pneumonia increased when the duration of ventilation was longer than 7 days [21].

**Table 1.** Clinical presentations of sepsis in elderly patients

| Chief complaint in any infection | Findings in specific infection |
|---|---|
| Altered level of consciousness (e.g., delirium/agitation) | **Bacteremia** |
| | Dyspnea, confusion, drop attacks, hypotensive attacks<br>May be afebrile |
| Drop attacks | **Pneumonia** |
| | Tachypnea<br>May be afebrile<br>Cough and sputum may be absent |
| Lethargy | **Intraabdominal infection** |
| | Anorexia<br>May be afebrile<br>Peritoneal findings may be absent/disguised |
| Loss of appetite | **Meningitis** |
| | Confusion, altered mental status<br>Neck stiffness may not be remarkable |
| Growth retardation | **Tuberculosis** |
| | Weight loss, lethargy<br>Growth retardation<br>May be afebrile |
| Change in basal body temperature | **Urinary tract infection** |
| | Dysuria, pollakiuria, flank pain, or fever may be absent. |

*Differences in complaints and findings in the elderly with COVID-19 compared to the young*

*Fever:* Fever is one of the main complaints in young people. Due to the weakening of the immune system and other problems of the elderly, they cannot form the fever response like the young. It has been reported that the fever response was a powerful discriminant between PCR (+) and (-) patients with COVID-19 [22]. In one study, only 1/3 of the elderly was found to be febrile on presentation [23]. The fever limit is considered to be 37.8C in a single measurement or above 37.3C in consecutive measurements.

*Cough:* The elderly may experience chronic cough for different reasons such as long-term smoking and previous or existing lung diseases. Therefore, it can be difficult for them to distinguish cough due to COVID-19 from other causative factors.

*Shortness of breath:* There may be many problems that may lead to shortness of breath in the elderly for reasons similar to the situation in cough. It is difficult to distinguish *de novo* shortness of breath due to COVID-19 from other entities. Senkal *et al*. disclosed that older adults had more prevalent dyspnea than younger patients (72.2% vs. 51.4%, $p$=0.004) [22]. In addition, the development of shortness of breath in the elderly may cause rapid deterioration due to the decrease in other organ capacities.

*Fatigue:* There are many elderly people who have fatigue due to malnutrition, neurological and other chronic diseases.

In brief, there may be delays in the diagnosis and initiation of treatment of COVID-19 as a result of all these difficulties. This may even lead to sudden deterioration and death in the elderly.

*Where does sepsis originate from in a given patient?*

Pneumonia is the most common source of sepsis at any age, and this is followed by intra-abdominal infections and urinary tract infections [12, 24, 25]. The most common foci of infection in elderly patients are respiratory tract and genitourinary infections [7, 15, 18, 26].

During the pandemic period, validity studies of scales were conducted in different cultures regarding sepsis originating from pneumonia. In their Middle East study, Elmoheen *et al*. reported that pneumonia severity index (PSI) can be used to stratify patients with COVID-19 pneumonia and revalidated the tool in predicting 30-day mortality and critical care interventions [27].

**The most commonly isolated in cultures are** Gram (+) pathogens S. aureus and S. pneumoniae, Gram (-) bacteria include E. coli, Klebsiella spp. and P. aeruginosa [14, 28, 29]. Gram (-) bacteria are isolated more frequently in elderly patients than in younger patients [18, 30, 31].

*Why are the elderly more prone to infection and sepsis?* The concept of “immune aging” is important at this point. The immune system of the elderly becomes frail with impaired cellular and humoral immune responses [32]. The good news is that aging and immunodeficiency are not directly related. Phenomena such as nutrition, physical activity, and 'training' immunity with past infections are thought to be effective. Functional changes in cell-mediated immunity and humoral immune responses that ensue with aging contribute to the increase in infection prevalences **(Table 2)**.

**Table 2.** The list of specific changes that occur with aging and the tendency to sepsis [29, 32-36].

- B cell, plasma cell count and T cell production are decreased in the immune system.
- Immunocompetent T cells are reduced in general, and most of the immunocompetent cells are 'memory' T cells.
- Has low IgM production, which results in susceptibility to Gram (-) bacteria and mycotic infection.
- Serum IL-6 levels are higher.
- There is persistent (hyper)inflammation and T cell consumption.
- Sepsis and severe outcomes are associated with high levels of proinflammatory cytokines.
- Major molecular pathways in the elderly are affected during sepsis and worsen outcomes compared to younger patients.
- It has been observed that the elderly have a more exaggerated response to inflammatory and prothrombotic effects, which is associated with organ failure.
- Myocardial depression caused by some compounds such as Myocardial Depressant Factor (MDF) seen in sepsis is effective on mortality rates in the elderly.

*Sepsis risk factors in the elderly*

Comorbidities often accompany increased predisposition to sepsis and organ dysfunction [12, 30, 37-39]. Poor general condition, organ failures, polypharmacy, malnutrition, and living in a nursing home are factors that increase the tendency to sepsis [40].

Advanced age is a risk factor for sepsis tendency due to increased colonization of Gram (-) bacteria with multidrug resistance (MDR) [38]

No reliable biomarker was found for the clinical course of sepsis [41]. SOFA and MEDS scores are strong predictors of ICU admission and mortality in elderly sepsis patients. PCT, IL-10, IL-6 and IL-5 are effective in predicting ICU admission, but not in mortality [42].

*Diagnosis*

In addition to the difficulties of diagnosing sepsis in geriatric cases, diseases such as dementia and delirium render it difficult to take an accurate history. The indistinct and delayed symptoms make the diagnosis of sepsis difficult. Fever response is blunted in most elderly patients. Presence of hypothermia within 24 hours after the first admission may predict the mortality of the elderly individual with sepsis [43] **(Table 3)**.

Elderly patients have lymphopenia more frequently than young people. Leukocytosis is noted in 60% of the elderly; however, the reverse does not rule out infection [44]. Three of the SIRS responses (fever, heart rate, and leukocyte count) are more subtle in the elderly than in the young [3].

In a study published in 2021, it was shown that patients with Troponin I (aTnI) value above 0.31 ng/ml on admission are exposed to a high risk for in-hospital death (OR: 1.834; p: 0.009), and high SOFA (p=0.01) [45]. In addition, it has been reported that the AUC for clinical course increased with the addition of aTnI value to the SOFA criteria ($AUC_{SOFA}$ =0.68; 95% CI 0.64-0.73; $AUC_{SOFA-T}$= 0.71; 95% CI 0.65- 0.76; p=0.0001).

*Use of ischemia-modified albumin (IMA) and procalcitonin in the diagnosis of sepsis*

Findings supportive of IMA were obtained in a retrospective study involving 300 patients in Korea [46]. The AUC for IMA levels was higher for the diagnosis of sepsis than for septic shock (0.729 [(95% CI: 0.667-0.791] vs. 0.681 [0.613-0.824]). IMA cut-off values were used as ≥85.5 U/mL in this study. Of note, AUC values of IMA are higher than procalcitonin (PCT) for the diagnosis of sepsis (PCT cut-off value ≥1.58 ng/mL) (PCT AUC: 0.678 [0.613-0.742]). On the other hand, when IMA and lactate levels were taken together, the AUC was increased: 0.815 (0.762-0.867) for sepsis and 0.806 (0.754-0.858) for septic shock. Likewise, IMA levels can independently predict sepsis (OR, 1.05; 95% CI, 1.00-1.09; p=0.029) and septic shock (OR, 1.07; 95% CI, 1.02-1.11; p=0.002).

PCT is among the most valuable biomarkers for infection and severity in the acute and intensive care settings. Recent studies revealed that baseline PCT levels fails to discriminate those in need of antibiotics in patients with presumptive diagnosis of sepsis [47]. Changes in PCT levels allow us to individualize the duration of antibiotic treatment without negative effect on death rates.

**Table 3.** Diagnostic criteria for sepsis. The presence of the following with proven or suspected infection is suggestive of sepsis

| **General variables/ vital signs** |
|---|
| • Fever (> 38,3$^0$C) |
| • Hypothermia (< 36$^0$C) |
| • Tachycardia (> 90 bpm at rest or 2 SD above the normal value for age) |
| • Tachypnea (> 22 bpm) |
| • Altered mental status (GCS < 15) |
| • Significant peripheral edema or positive fluid balance |
| • Hyperglycemia (random glucose > 140 mg/dL or 7.7 mmol/L) |
| **Inflammatory markers** |
| • Leukocytosis (> 12,000 /μL), leukopenia (< 4000 μL−1), |
| • More than 10% band form (bandemia) with normal WBC count |
| • CRP 2 SD above the normal value |
| • PCT 2 SS above normal value |
| **Hemodynamic variables** |

| |
|---|
| • Hypotension (SBP < 90 mmHg, MAP < 70 mmHg, or SBP decrease > 40 mmHg) or 2 SD below normal value). |
| • In elderly patients, hypotension values may not be in line with expected values due to chronic hypertension. |
| **Organ dysfunction** |
| • Hypoxemia ($PaO_2/FiO_2$ < 300) |
| • Acute oliguria (< 0.5 mL/kg/h despite adequate fluid resuscitation) |
| • Creatinine increase > 0.5 mg/dL |
| • Coagulopathy (INR > 1.5 or aPTT > 60 s) |
| • Adynamic ileus (absent bowel sounds) |
| • Thrombocytopenia (<100,000 µL) |
| • Hyperbilirubinemia (total bilirubin > 4 mg/dL) |
| **Tissue perfusion** |
| • Hyperlactatemia (≥ 2 mmol/L) |
| • Delayed capillary refill (> 2 sec) |

*Prevention from sepsis:* Since there is a tendency to sepsis in the elderly, all risk factors should be counteracted to eliminate. For instance, unnecessary vascular access and urinary catheters should be removed in order to eliminate the risks of catheterization. Solutions such as inhalation of antibiotics may be appropriate. In a meta-analytical study, inhaled antibiotics were shown to be even more effective in preventing exacerbations [48].

*Management principles*

Hyperlactatemia is independently associated with worsening. Lactate clearance is also an independent factor in sepsis mortality. If the lactate clearance is above 10% within 2 hours, it indicates favorable clinical course. Many randomized studies pointed out that lactate-targeted resuscitation has a positive effect on mortality compared to treatment without lactate monitoring [49-52]. In cases with lactate level maintained ≥2 mmol/L despite adequate fluid resuscitation, septic shock should be considered at the forefront and vasopressors should be initiated. Norepinephrine is recommended as the first choice with its vasoconstrictive effect on the arterioles and positive safety profile [53].

*Antibiotics:* Inadequate and delayed antibiotic treatment directly increases the mortality rate [54, 55]. Empirical antibiotic therapy should be initiated within one hour of the diagnosis of sepsis, after blood samples and cultures have been taken from sites of suspected infection. Great care should be taken in the selection of the agent due to the organ failures that may coexist in the elderly.

Unnecessary antibiotic use, which has been increasing worldwide in recent decades, is alarming. It is thought that there will be no effective antibiotics in the near future [56]. Interestingly, there is a higher and unnecessary use of antibiotics in developing and low-income countries than in developed countries. Although important steps have been taken in this regard in some countries, it is clear that more improvements are needed. Continuous training of both the public and health professionals will provide significant progress in the long run.

Elderly patients are in the risk group for prescribing unnecessary antibiotics. In other words, when the patient is old, physicians are more likely to prescribe unnecessary antibiotics [57]. Other risk factors are fever on presentation, male gender, long waiting time before examination, diagnosis of bronchitis, and living in the city center.

In a cohort study, values of electronic alert systems to prevent unnecessary antibiotic prescribing in primary care institutions were assessed. The authors cited that antibiotics were prescribed more rationally in all groups, except young children and the elderly over the age of 84, with this intervention [58]. In other words, there is more resistance in physicians against the prevention of unnecessary antibiotic use in the elderly.

The same study disclosed that the incidence of pneumonia and peritonsillar abscess decreases with antibiotic prescribing, but the rates of mastoiditis, empyema, bacterial meningitis, and intracranial abscess do not change.

The subject is quite complex and difficult. It has been demonstrated that interventions to prevent unnecessary antibiotic use for the elderly in long-term care centers are not effective as expected [59]. On the other hand, Nguyen *et al*. reported that antibiotic use decreased with interventions in nursing homes, but there was no effect on hospitalization rates and clinical course [60].

*Important principles in the management of the elderly with sepsis and septic shock*

1. Identifying sepsis and septic shock in the light of new guidelines.

2. Initiating antibiotic therapy within the first hour of presumptive diagnosis of sepsis or septic shock. Obtaining the necessary cultures prior to this treatment, as well as dissolving the infectious focus without delay.
3. Administration of 30 mL/kg IV crystalloid within the first 3 hours.
4. Since the blood lactate level is a good indicator of hypoperfusion, it should be monitored to evaluate the effectiveness of the treatment.
5. If there is no response to fluid, vasopressors should be used. Norepinephrine is the drug of choice in adults, and should be started with a target MAP of 65 mmHg.
6. If MV is required, tidal volume (TV) is targeted at 6 mL/kg in sepsis-associated ARDS cases.

*Clinical course and outcome*

Geriatric cases have a 2-fold higher risk of sepsis-related death [18]. Mortality increases with age and reaches its highest level in the "elderly old" patient group who are older than 85 years [61-64].

Mortality rates of the elderly in sepsis and sepsis shock reach up to 50-60% [18, 64, 65]. Elderly patients with sepsis also die earlier during their hospitalization when compared to younger age groups [12, 18, 64, 66].

Factors affecting poor outcome include shock, hyperlactatemia, and organ failure [65]. In the long term after recovery from sepsis, CHF, peripheral vascular disease, dementia, and diabetes are the most common entities recorded in the literature [67].

*Final comments*

- Atypical presentations should be emphasized in the training of triage and emergency healthcare workers due to difficulties and pitfalls in diagnostic processes for sepsis. For example, experience will be needed in the interpretation of fever, pulse rate, and shortness of breath in the elderly.
- Elderly people who stay at home, in isolation or in quarantine in cases such as lock-down due to pandemic should be called from the center regularly, and technological tools such as video chats should be activated when appropriate.
- Interactions of drug doses in the elderly, problems in excretion and differences in metabolism should be considered in treatment regimens.
- It should be kept in mind that the vital organ functions of the elderly, who are among the highest risk groups in the management of sepsis, may deteriorate rapidly with very few precursors, and aggressive methods should be used rapidly when necessary.
- Solutions should be sought to eliminate colonization risks such as vascular catheterization, unnecessary vascular access and urinary catheters should be removed.
- Knowing that the psyche of the elderly is fragile besides the severe clinical course, one should be vigilant about issues such as depression and suicidal thoughts, and support from a clinical psychologist or psychiatrist should be sought if necessary.

## CONCLUSION

Symptoms and signs of sepsis in the elderly have unique properties in the routine clinical practice. Atypical presentation is markedly common in the elderly with sepsis and septic shock. This, in turn, mandate tailored approach in the management of these patients. Mortality rates and serious outcomes are substantially higher among elderly patients than younger ones. Organized and aggressive approach can help mitigate the condition and alleviate death toll. Besides timely recognition and admission of these patients, adjusted fluid resuscitation, expedient administration of antibiotics, ventilation management, source control are the minstays of the management. Vasopressors and glucocorticoids are the drugs of choice in selected subgroups. In brief, the key to effective management in the elderly is expedient diagnosis and aggressive resuscitation.

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**REFERENCES**


1. United Nations. World Population Prospects: The 2008 Revision, Highlights, Dept. of Economic and Social Affairs PD; New York: 2009.
2. UNHCR Emergency Handbook. 4th Edition. Available from: https://emergency.unhcr.org/entry/43935/older-persons#:~:text=An%20older%20person%20is%20defined,over%2060%20years%20of%20age.
3. Umberger R, Callen B, Brown ML. Severe sepsis in older adults. Crit Care Nurs Q. 2015;38(3):259-70.
4. Quenot JP, Binquet C, Kara F, Martinet O, Ganster F, Navellou JC, et al. The epidemiology of septic shock in French intensive care units: the prospective multicenter cohort EPISS study. Crit Care. 2013;17(2):R65.
5. Seymour CW, Liu VX, Iwashyna TJ, Brunkhorst FM, Rea TD, Scherag A, et al. Assessment of Clinical Criteria for Sepsis: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016;315(8):762-74.
6. Chen YX, Li CS. Arterial lactate improves the prognostic performance of severity score systems in septic patients in the ED. Am J Emerg Med. 2014;32(9):982-6.
7. 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(8):801-10.
8. Freund Y, Lemachatti N, Krastinova E, Van Laer M, Claessens YE, Avondo A, et al. Prognostic Accuracy of Sepsis-3 Criteria for In-Hospital Mortality Among Patients With Suspected Infection Presenting to the Emergency Department. JAMA. 2017;317(3):301-8.
9. Churpek MM, Edelson DP. Moving beyond single-parameter early warning scores for rapid response system activation. Crit Care Med. 2016;44(12):2283-5.
10. Giamarellos-Bourboulis EJ, Tsaganos T, Tsangaris I, Lada M, Routsi C, Sinapidis D, et al. Validation of the new Sepsis-3 definitions: proposal for improvement in early risk identification. Clin Microbiol Infect. 2017;23(2):104-9.
11. Valencia AM, Vallejo CE, Alvarez ALL, Jaimes FA. Attenuation of the physiological response to infection on adults over 65 years old admitted to the emergency room (ER). Aging Clin Exp Res. 2017;29(5):847-56.
12. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. Crit Care Med. 2001;29:1303-10.
13. Abraham E, Reinhart K, Opal S, Demeyer I, Doig C, Rodriguez AL, et al. Efficacy and safety of tifacogin (recombinant tissue factor pathway inhibitor) in severe sepsis: a randomized controlled trial. JAMA. 2003;290(2):238-47.
14. Ranieri VM, Thompson BT, Barie PS, Dhainaut JF, Douglas IS, Finfer S, et al. Drotrecogin alfa (activated) in adults with septic shock. N Engl J Med. 2012;366(22):2055-64.
15. Wang G, Wu C, Zhang Q, Yu B, LÜ J, Zhang S, et al. Clinical characteristics and the risk factors for severe events of elderly coronavirus disease 2019 patients. Zhong Nan Da Xue Xue Bao Yi Xue Ban. 2020;45(5):542-8.
16. Stancati M. Italy, With Aging Population, Has World's Highest Daily Deaths From Virus. Wall Str J. 2020;9. Available from: https://www.wsj.com/articles/italy-with-elderly-population-has-worlds-highest-death-rate-from-virus-11583785086
17. Adhikari NK, Fowler RA, Bhagwanjee S, Rubenfeld GD. Critical care and the global burden of critical illness in adults. Lancet. 2010;376(9749):1339-46.
18. Martin GS, Mannino DM, Moss M. The effect of age on the development and outcome of adult sepsis. Crit Care Med. 2006;34(1):15-21.
19. Jin M, Lu Z, Zhang X, Wang Y, Wang J, Cai Y, et al. Clinical characteristics and risk factors of fatal patients with COVID-19: a retrospective cohort study in Wuhan, China. BMC Infect Dis. 2021;21(1):951. doi:10.1186/s12879-021-06585-8
20. Janke AT, Jain S, Hwang U, Rosenberg M, Biese K, Schneider S, et al. Emergency department visits for emergent conditions among older adults during the COVID-19 pandemic. J Am Geriatr Soc. 2021;69(7):1713-21. doi:10.1111/jgs.17227

21. Zahar JR, Timsit JF. Risk stratification for selecting empiric antibiotherapy during and after COVID-19. Curr Opin Infect Dis. 2022;35(6):605-13. doi:10.1097/QCO.0000000000000881
22. Senkal N, Bahat G, Medetalibeyoglu A, Cebeci T, Deniz D, Catma Y, et al. Comparison of clinical characteristics and outcome measures of PCR-positive and PCR-negative patients diagnosed as COVID-19: Analyses focusing on the older adults. Exp Gerontol. 2022;170:111998. doi:10.1016/j.exger.2022.111998
23. Lam PP, Coleman BL, Green K, Powis J, Richardson D, Katz K, et al. Predictors of influenza among older adults in the emergency department. BMC Infect Dis. 2016;16(1):615. doi:10.1186/s12879-016-1966-4
24. Lagu T, Rothberg MB, Shieh MS, Pekow PS, Steingrub JS, Lindenauer PK. Hospitalizations, costs, and outcomes of severe sepsis in the United States 2003 to 2007. Crit Care Med. 2012;40(3):754-6.
25. Vincent JL, Rello J, Marshall J, Silva E, Anzueto A, Martin CD, et al. International study of the prevalence and outcomes of infection in intensive care units. JAMA. 2009;302(21):2323-9.
26. Rowe T, Araujo KLB, Van Ness PH, Pisani MA, Juthani-Mehta M. Outcomes of older adults with sepsis at admission to an intensive care unit. Open Forum Infect Dis. 2016;3(1).
27. Elmoheen A, Abdelhafez I, Salem W, Bahgat M, Elkandow A, Tarig A, et al. External Validation and Recalibration of the CURB-65 and PSI for Predicting 30-Day Mortality and Critical Care Intervention in Multiethnic Patients with COVID-19. Int J Infect Dis. 2021;111:108-16. doi:10.1016/j.ijid.2021.08.027
28. Martin GS, Mannino DM, Moss M. Effect of age on the development and outcome with sepsis. Am J Respir Crit Care Med. 2003;167:A837.
29. Opal SM, Girard TD, Ely EW. The immunopathogenesis of sepsis in elderly patients. Clin Infect Dis. 2005;41(Suppl7):S504-12.
30. Girard TD, Opal SM, Ely EW. Insights into severe sepsis in older patients: from epidemiology to evidence-based management. Clin Infect Dis. 2005;40(5):719-27.
31. Kirby JT, Fritsche TR, Jones RN. Influence of patient age on the frequency of occurrence and antimicrobial resistance patterns of isolates from hematology/oncology patients: report from the chemotherapy alliance for neutropenics and the control of emerging resistance program (north America). Diagn Microbiol Infect Dis. 2006;56(1):75-82.
32. Weksler ME. Changes in the B-cell repertoire with age. Vaccine. 2000;18(16):1624-8.
33. Vieira da Silva Pellegrina D, Severino P, Vieira Barbeiro H, Maziero Andreghetto F, Tadeu Velasco I, Possolo de Souza H, et al. Septic shock in advanced age: transcriptome analysis reveals altered molecular signatures in neutrophil granulocytes. PLoS One. 2015;10(6):e0128341.
34. Saito H, Papaconstantinou J. Age-associated differences in cardiovascular inflammatory gene induction during endotoxic stress. J Biol Chem. 2001;276(31):29307-12.
35. Suzuki K, Inoue S, Kametani Y, Komori Y, Chiba S, Sato T, et al. Reduced immunocompetent B cells and increased secondary infection in elderly patients with severe sepsis. Shock. 2016;46(3):270-8.
36. Kumar A, Thota V, Dee L, Olson J, Uretz E, Parrillo JE. Tumor necrosis factor alpha and interleukin 1beta are responsible for in vitro myocardial cell depression induced by human septic shock serum. J Exp Med. 1996;183(3):949-58.
37. Dombrovskiy VY, Martin AA, Sunderram J, Paz HL. Rapid increase in hospitalization and mortality rates for severe sepsis in the United States: a trend analysis from 1993 to 2003. Crit Care Med. 2007;35(5):1244-50.
38. Nasa P, Juneja D, Singh O. Severe sepsis and septic shock in the elderly: an overview. World J Crit Care Med. 2012;1(1):23-30.
39. Walter LC, Brand RJ, Counsell SR, Palmer RM, Landefeld CS, Fortinsky RH, et al. Development and validation of a prognostic index for 1-year mortality in older adults after hospitalization. JAMA. 2001;285(23):2987-94.
40. Ruiz M, Bottle A, Long S, Aylin P. Multi-morbidity in hospitalised older patients: who are the complex elderly? PLoS One. 2015;10(12):e0145372.
41. Chaudhry H, Zhou J, Zhong Y, Ali MM, McGuire F, Nagarkatti PS, et al. Role of cytokines as a double-edged sword in sepsis. In Vivo. 2013;27(6):669-84.
42. Lee WJ, Woo SH, Kim DH, Seol SH, Park SK, Choi SP, et al. Are prognostic scores and biomarkers such as procalcitonin the appropriate prognostic precursors for elderly patients with sepsis in the emergency department? Aging Clin Exp Res. 2016;28(5):917-24. doi:10.1007/s40520-015-0500-7

43. Tiruvoipati R, Ong K, Gangopadhyay H, Arora S, Carney I, Botha J. Hypothermia predicts mortality in critically ill elderly patients with sepsis. BMC Geriatr. 2010;10(1):70.
44. Mouton CP, Pierce B, Espino DV. Common infections in older adults. Am Fam Physician. 2001;63(2):257-69.
45. Tarquinio N, Viticchi G, Zaccone V, Martino M, Fioranelli A, Morciano P, et al. The value of admission Troponin I to predict outcomes in suspected infections in elderly patients admitted in Internal Medicine: results from the SOFA-T collaboration, a multi-center study. Intern Emerg Med. 2021;16(4):981-8. doi:10.1007/s11739-020-02610-x
46. Choo SH, Lim YS, Cho JS, Jang JH, Choi JY, Choi WS, et al. Usefulness of ischemia-modified albumin in the diagnosis of sepsis/septic shock in the emergency department. Clin Exp Emerg Med. 2020;7(3):161-9.
47. Maves RC, Enwezor CH. Uses of Procalcitonin as a Biomarker in Critical Care Medicine. Infect Dis Clin North Am. 2022;36(4):897-909. doi:10.1016/j.idc.2022.07.004
48. Laska IF, Crichton ML, Shoemark A, Chalmers JD. The efficacy and safety of inhaled antibiotics for the treatment of bronchiectasis in adults: a systematic review and meta-analysis. Lancet Respir Med. 2019;7(10):855-69.
49. Jones AE, Shapiro NI, Trzeciak S, Arnold RC, Claremont HA, Kline JA, et al. Lactate clearance vs central venous oxygen saturation as goals of early sepsis therapy: a randomized clinical trial. JAMA. 2010;303(8):739-46.
50. Lyu X, Xu Q, Cai G, Yan J, Yan M. Efficacies of fluid resuscitation as guided by lactate clearance rate and central venous oxygen saturation in patients with septic shock. Zhonghua Yi Xue Za Zhi. 2015;95(7):496-500.
51. Tian HH, Han SS, Lv CJ, Wang T, Li Z, Hao D, et al. The effect of early goal lactate clearance rate on the outcome of septic shock patients with severe pneumonia. Zhongguo Wei Zhong Bing Ji Jiu Yi Xue. 2012;24(1):42-5.
52. Yu B, Tian HY, Hu ZJ, Zhao C, Liu LX, Zhang Y, et al. Comparison of the effect of fluid resuscitation as guided either by lactate clearance rate or by central venous oxygen saturation in patients with sepsis. Zhonghua Wei Zhong Bing Ji Jiu Yi Xue. 2013;25(10):578-83.
53. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. Intensive Care Med. 2017;43(3):304-77.
54. Herring AR, Williamson JC. Principles of antimicrobial use in older adults. Clin Geriatr Med. 2007;23:481-97.
55. Garnacho-Montero J, Garcia-Garmendia JL, Barrero-Almodovar A, Jimenez-Jimenez FJ, Perez-Paredes C, Ortiz-Leyba C. Impact of adequate empirical antibiotic therapy on the outcome of patients admitted to the intensive care unit with sepsis. Crit Care Med. 2003;31(12):2742-51.
56. Klein EY, Van Boeckel TP, Martinez EM, Pant S, Gandra S, Levin SA, et al. Global increase and geographic convergence in antibiotic consumption between 2000 and 2015. Proc Natl Acad Sci U S A. 2018;115(15):E3463-70.
57. Xu KT, Roberts D, Sulapas I, Martinez O, Berk J, Baldwin J. Over-prescribing of antibiotics and imaging in the management of uncomplicated URIs in emergency departments. BMC Emerg Med. 2013;13(1):7.
58. Gulliford MC, Juszczyk D, Prevost AT, Soames J, McDermott L, Sultana K, et al. Electronically delivered interventions to reduce antibiotic prescribing for respiratory infections in primary care: cluster RCT using electronic health records and cohort study. Health Technol Assess. 2019;23(11):1-70.
59. Raban MZ, Gasparini C, Li L, Baysari MT, Westbrook JI. Effectiveness of interventions targeting antibiotic use in long-term aged care facilities: a systematic review and meta-analysis. BMJ Open. 2020;10(1):e028494.
60. Nguyen HQ, Tunney MM, Hughes CM. Interventions to Improve Antimicrobial Stewardship for Older People in Care Homes: A Systematic Review. Drugs Aging. 2019;36(4):355-69.
61. Curns AT, Holman RC, Sejvar JJ, Owings MF, Schonberger LB. Infectious disease hospitalizations among older adults in the United States from 1990 through 2002. Arch Intern Med. 2005;165(21):2514-20.
62. Ely EW, Angus DC, Williams MD, Bates B, Qualy R, Bernard GR. Drotrecogin alfa (activated) treatment of older patients with severe sepsis. Clin Infect Dis. 2003;37(2):187-95.
63. Gavazzi G, Krause KH. Ageing and infection. Lancet Infect Dis. 2002;2(11):659-66.

64. Nasa P, Juneja D, Singh O, Dang R, Arora V. Severe sepsis and its impact on outcome in elderly and very elderly patients admitted in intensive care unit. J Intensive Care Med. 2011;27(3):179-83.
65. Vosylius S, Sipylaite J, Ivaskevicius J. Determinants of outcome in elderly patients admitted to the intensive care unit. Age Ageing. 2005;34(2):157-62.
66. Englert NC, Ross C. The older adult experiencing sepsis. Crit Care Nurs Q. 2015;38(2):175-81.
67. Starr ME, Saito H. Sepsis in old age: review in human and animal studies. Aging Dis. 2014;5(2):126-36.